Oral Chinese Herbal Medicine for Psoriasis Vulgaris

A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

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Declaration

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research program; and, any editorial work, paid or unpaid, carried out by a third party is acknowledged.

Shefton J. Parker

23rd December 2015
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**List of abbreviations**

ACC  acetyl-CoA carboxylase
ANZCTR Australian New Zealand Clinical Trials Registry
AE adverse event
AIx augmentation index
ALP alkaline phosphatase
ALT alanine aminotransferase
AMP antimicrobial peptide
AMPK 5' adenosine monophosphate-activated protein kinas
AP augmented pressure
AST aspartate aminotransferase
ATM ataxia-telangiectasia mutated
ATP adenosine triphosphate
B-cells B-lymphocytes
bid twice per day
BMI body mass index
BSA body surface area
C control
CAM complementary and alternative medicine
cAMP cyclic adenosine monophosphate
CCI4 carbon tetrachloride
CDM Chinese Biomedical Literature
CENTRAL Cochrane Central Register of Controlled Trials
CD cluster of differentiation
cm centimetres
<table>
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<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>CHM</td>
<td>Chinese herbal medicine</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CM</td>
<td>Chinese medicine</td>
</tr>
<tr>
<td>CMG2</td>
<td>capillary morphogenesis gene 2</td>
</tr>
<tr>
<td>CNKO</td>
<td>China National Knowledge Infrastructure</td>
</tr>
<tr>
<td>CONSORT</td>
<td>consolidated standards of reporting trials</td>
</tr>
<tr>
<td>COX</td>
<td>cyclooxygenase</td>
</tr>
<tr>
<td>CRF</td>
<td>case record form</td>
</tr>
<tr>
<td>CQVIP</td>
<td>Chongqing VIP Information Co</td>
</tr>
<tr>
<td>D-B</td>
<td>double blind</td>
</tr>
<tr>
<td>d.f.</td>
<td>degrees of freedom</td>
</tr>
<tr>
<td>d-GalN</td>
<td>d-galactosamine</td>
</tr>
<tr>
<td>DLQI</td>
<td>dermatology life quality index</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DP</td>
<td>diastolic pressure</td>
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<tr>
<td>DPPH2</td>
<td>2-diphenyl-1-picrylhydrazyl</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
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<tr>
<td>EGF</td>
<td>epidermal growth factor</td>
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<tr>
<td>ERK</td>
<td>extracellular signal-regulated kinase</td>
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<tr>
<td>ES</td>
<td>effect size</td>
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<td>ET</td>
<td>endothelin</td>
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<tr>
<td>F</td>
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<tr>
<td>FasL</td>
<td>fas ligand</td>
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<tr>
<td>FOXP3G</td>
<td>transcription factor forkhead box P3 gap</td>
</tr>
<tr>
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<td>Term/Description</td>
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<td>---------</td>
<td>----------------</td>
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<tr>
<td>g</td>
<td>grams</td>
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<tr>
<td>G-A</td>
<td>guanine-adenine</td>
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<td>GGT</td>
<td>gamma-glutamyl transferase</td>
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<tr>
<td>GJIC</td>
<td>Gap junctional communication</td>
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<tr>
<td>GP</td>
<td>general practitioner</td>
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<tr>
<td>GSK-3b</td>
<td>glycogen synthase kinase 3 beta</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>HLA</td>
<td>human leukocyte antigens</td>
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<td>messenger ribonucleic acid</td>
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<td>human neutrophil elastase</td>
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<td>high performance liquid chromatography</td>
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<td>HT</td>
<td>Human colon adenocarcinoma cells</td>
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<td>I</td>
<td>intervention</td>
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<td>heterogeneity</td>
</tr>
<tr>
<td>IBV</td>
<td>influenza B virus</td>
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<tr>
<td>hPIV-1</td>
<td>human parainfluenza virus type-1</td>
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<tr>
<td>ICAM</td>
<td>intercellular adhesion molecule</td>
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<tr>
<td>IgE</td>
<td>immunoglobulin E</td>
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<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
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<td>ILC</td>
<td>innate lymphoid cell</td>
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<td>interferon beta</td>
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IL interleukin
IMPPS Integrative medicine for psoriasis study
iNOS nitric oxide synthase
ITT intention-to-treat
IV intravenous
m months
JAK janus kinase
JNK c-Jun N-terminal protein kinase
kg kilogram
l Paeonia lactiflora
ILFA-3 lymphocyte function associated antigen-3
LPS lipopolysaccharide
M male
MAP mean arterial pressure
MAPK mitogen-activated protein kinase
MCH mean corpuscular haemoglobin
MCHC mean corpuscular haemoglobin concentration
MCP-1 monocyte chemotactic protein-1
MCV mean corpuscular volume
MD mean difference
MeSH medical subject headings
mg milligram
mRNA messenger ribonucleic acid
miRNA micro ribonucleic acid
MTX methotrexate
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<td>once a day</td>
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<td>quality of life</td>
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<td>standard deviation</td>
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<tr>
<td>SF-36</td>
<td>short form health survey</td>
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<tr>
<td>SMD</td>
<td>standard mean difference</td>
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<tr>
<td>SP</td>
<td>systolic pressure</td>
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<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
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<tr>
<td>src.</td>
<td>source</td>
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<td>ST</td>
<td>subtotal</td>
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<tr>
<td>STAT</td>
<td>signal transducer and activator of transcription</td>
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<tr>
<td>T-cell</td>
<td>thymus lymphocyte</td>
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<tr>
<td>TER</td>
<td>total effective rate</td>
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<td>tid</td>
<td>three times a day</td>
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<tr>
<td>TIR8/SIGIRR</td>
<td>toll IL-1R8/single Ig IL-1 related receptor</td>
</tr>
<tr>
<td>TGA</td>
<td>therapeutic good administration</td>
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<tr>
<td>TGF</td>
<td>transforming growth factor</td>
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<tr>
<td>TGP</td>
<td>total glucosides of peony</td>
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<tr>
<td>TH</td>
<td>T helper</td>
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<tr>
<td>TNF-α</td>
<td>tumour necrosis factor alpha</td>
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<tr>
<td>TRAIL</td>
<td>tumour necrosis factor -related apoptosis-inducing ligand</td>
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Tregs regulating T-lymphocytes
UGDH UDP-glucose dehydrogenase
UV ultraviolet
UVA ultraviolet A
UVB ultraviolet B
V *Paeonia veitchii*
VEGF vascular endothelial growth factor
w weeks
WCC white cell count
WHO World Health Organization
y years
εGT ε germline transcript.
Summary

Background: Psoriasis is a common chronic immunological inflammatory skin disease. The most usual phenotype, vulgaris type, has characteristic lesions known as plaques on the surface of the skin. The precise trigger of psoriasis vulgaris is yet to be fully elucidated; however, factors such as an inherited genetic component and smoking increase likelihood of its development. At cellular level, inflammatory factors are present in dermal and epidermal skin layers and excessive skin cell proliferation occurs. Sufferers of psoriasis vulgaris often experience psychological illness, with quality of life (QoL) measures employed along with symptomatic measures to determine disease severity. Recently, psoriasis has been shown to be associated with increased risk of serious co-morbidities such as cardiovascular disease and diabetes.

With no cure available, current recommended therapies only manage symptoms associated with the disease. Although newer biological therapies provide effective symptom management, they are commonly expensive and due to their reduced safety profile, recommended only for severe psoriasis cases. The costs of psoriasis management for individuals and the health system are high. Hence, further effective, and safer therapies are needed. Chinese herbal medicine (CHM) has been utilised for centuries for the management of numerous health conditions including symptoms associated with psoriasis.

Methods: Firstly, two systematic reviews and meta-analyses were conducted to examine published CHM research for psoriasis. 1) Using the Cochrane Library Systematic Review Method, major English and Chinese databases were searched for randomised controlled trials (RCTs) of oral CHM for psoriasis vulgaris compared with placebo. Included studies were pooled for meta-analysis and risk of bias was assessed
using the Cochrane risk of bias tool. Further systematic review using the same rigorous methods was undertaken for RCTs combining oral CHM with conventional therapy for psoriasis vulgaris.

Secondly, *in vitro* and *in vivo* data were reviewed in regard to commonly used CHM formulation of herbal ingredients. This review aimed to evaluate the biological mechanisms of the major constituents of each herb that potentially impact on the molecular pathways of psoriasis. Taking the same methods further, in-depth review was undertaken of the chief ingredient *chi shao* and its simile *bai shao*. Botany and ethnopharmacology of the constituents of botanical species referred to as *chi shao* and *bai shao* were compared to determine the source product for an oral CHM formulation (PSORI-CM01).

From review of RCT data, available CHM treatment guidelines and consultation with experts, an optimised oral CHM formulation (PSORI-CM01) was developed for psoriasis vulgaris. To clinically evaluate the oral CHM formula PSORI-CM01, a pilot RCT was developed based on the methodological strengths and weaknesses of reviewed RCTs and using available trial design recommendations such as pragmatic–explanatory continuum indicator summary, consolidated standards of reporting trials (CONSORT) and the extensions to CONSORT for herbal studies.

**Results:** Literature review indicated mild–moderate psoriasis is currently undertreated, and that topical treatments, while being affordable, have limited efficacy. Systematic review found oral CHM has benefit for psoriasis compared with placebo; however, the effect size is relatively small. Considering this effect was relatively low, a further systematic review was undertaken to evaluate the effects of CHM combined with conventional therapy. Results from this review indicated increased effect for conventional therapies when combined with CHM, and reduced adverse events.
The subsequent pilot RCT is to investigate oral CHM formulation PSORI-CM01 in a mild to moderate psoriasis vulgaris (psoriasis area severity index (PASI) 7–12) population. The pilot study is designed as a double-blinded, randomised, placebo-controlled trial. Thirty participants are to be randomised to receive PSORI-CM01 plus calcipotriol or placebo plus calcipotriol. Eligible participants undergo a two-week run-in phase followed by a 12-week treatment phase and 12-week follow-up phase. The pilot study is to determine the feasibility of the design for an adequately powered RCT, as well as to gather preliminary outcome data for further trial sample size estimation. The primary outcome measure is psoriasis severity (PASI) change (%) and secondary measures are: PASI 75 rate, QoL change using dermatology life quality index (DLQI) and Skindex 29 acceptability of treatment and change to psoriasis-related cytokines (such as TNF-α and IL-23). Safety of oral CHM is also assessed via reporting of adverse events as well as monitoring liver and kidney function via blood pathology changes.

Outcomes are measured at baseline (week 0), mid-treatment (week 6), end of treatment (week 12) and at the end of the follow-up phase (week 24). Between assessments, fortnightly compliance and safety phone calls are conducted, and a daily diary of medication use as well as adverse event reporting is self-completed by participants. Outcome measure data are analysed using the intention-to-treat principle and missing data substituted with the last observation carried forward method. Using SPSS software, tests for equivalence between the treatment and control group are undertaken with P-values <0.05 considered statistically significant. Blood plasma samples are collected at week −2, week 12 and week 24 and concentrations of inflammatory cytokines measured via multi-assay techniques (Bio-Plex® Multiplex System).
Subsequent review of *in vitro* and *in vivo* evidence recognised PSORI-CM01 constituents act on pathways similar to those of conventional drug therapies. Review of botanical species commonly used as primary ingredient *chi shao* recognised it was sourced predominantly from two peony species, *Paeonia lactiflora* Pallas and *Paeonia veitchii* Lynch. A review of the literature indicated that *Radix Paeoniae Rubra* (*chi shao*) included in the formulation was of high quality and contained the required active constituents for psoriasis.

The developed pilot RCT is currently ongoing. Fourteen eligible participants commenced run-in phase; three of these participants withdrew during the run-in phase due to abnormal liver function pathology results. The remaining 11 participants were randomised to treatment at baseline, however two of these dropped out during the treatment phase – one was lost prior to week 12 (end of treatment assessment) and the other withdrew due to time constraints before end of week 6 (mid-treatment assessment). Baseline analysis revealed the mean PASI score of the 11 participants was 9.0±2.4, and DLQI score was 10±7.6. One occasion of serious adverse event was reported with itch requiring medical intervention. Most adverse events were otherwise reported mild and include itch, dizziness, headache and nausea; however, it is not yet known what group these events were reported in. Trial recruitment continues and full data analysis will be conducted when the last recruited participant finishes their follow-up phase.

**Conclusion:** Oral CHM has promising efficacy for psoriasis and enhances the efficacy of conventional treatments when combined. Evidence suggests combined treatment is safe; however, long-term follow-up data are limited. Efficacy of CHM is related to the mechanistic actions of contained constituents, some of which coincide with conventional drug treatment targets. CHM PSORI-CM01 has *in vitro* and *in vivo* evidence
indicating that therapeutic benefit is via modulation of known psoriatic biological pathways. The current pilot study will provide data on the feasibility of a larger-scale study and provide preliminary data for PSORI-CM01 efficacy and safety.

**Publications and Conferences**


Parker S, Zhang AL, Xue CC: Psoriasis: Current treatment patchy at best but Chinese medicine may offer great therapeutic effects. (Poster and oral presentation) In RMIT University HDR Conference; Bundoora, Australia. Oct 2012.


Chapter 1 – General introduction

The suffix of psoriasis, ‘psora’ meaning ‘to itch’, gained its name from Hippocrates (460–377 BCE) (Nickoloff and Nestle, 2004). Historically, psoriasis was mistaken for leprosy, biblical texts detailing the unfortunate and unwarranted isolation of sufferers to avoid spread of what was thought to be a contagious disease (Glickman, 1986). Modern medicine has determined since that psoriasis is a non-communicable disease, with no relationship to leprosy (World Health Organization (WHO), 2013). Today psoriasis is the broad term used for a disease encompassing many phenotypes, each differing in morphology and prevalence. Most commonly psoriasis sufferers present with thickened skin regions, known as ‘plaques’ on the extensor surfaces of arms and legs, however, other body locations can also be afflicted. Psoriasis is understood to develop from hyperactive immune function, with excessive inflammation and the hyper-proliferation of abnormal skin cells in affected areas. The precise trigger is not known, but many aetiological factors have been implicated. Sufferers commonly report physical discomfort such as itching, bleeding and skin irritation. The visual appearance of lesions is unsightly and sufferers commonly experience psychological distress as a result. There is currently no cure for psoriasis and many treatments have limited use due to risk of side effects and/or their high cost. The efficacy of treatments is also limited by the potential development of tolerance and/or resistance to drug therapy.

Although, historically, the use of CHM for psoriasis has been documented to be effective, scientific evidence of its efficacy and safety is inconclusive. Hence, currently no international treatment guidelines recommend CHM for psoriasis.

The aims of this study are to: evaluate available evidence for the efficacy and safety of CHM for psoriasis; evaluate available evidence for the efficacy and safety of combining CHM and conventional pharmacotherapy for psoriasis; develop an evidence-
based CHM formulation for psoriasis; review the potential biological activity of phytochemicals in the CHM formulation for psoriasis; develop the protocol for a clinical trial to investigate the developed CHM formulation; and undertake a pilot study to evaluate the feasibility of the trial design.

This thesis presents: results of associated systematic reviews; explanation of how the evidence-based oral CHM formulation (PSORI-CM01) was developed; investigation of key phytochemicals with potential to act on psoriasis pathogenic pathways; and the protocol design and implementation of a pilot double-blind, randomised, placebo-controlled study ‘integrative medicine for psoriasis study’ ((IMPPS) Australian New Zealand Clinical Trials Registry ACTRN12614000493640). The study includes participants with mild to moderate psoriasis vulgaris severity and is currently ongoing; however, analyses of interim study data are presented.

Chapter 2 explores the aetiology and pathogenesis of the psoriatic disease. A literature review presents the current understanding of psoriasis, citing published scientific research for potential triggers and risk factors of disease development. Chapter 2 also identifies psoriasis research gaps, where further scientific investigation is needed to better understand the development of psoriasis. The chapter then goes on to differentiate between psoriasis phenotypes and reviews the global prevalence, incidence and health cost implications of psoriatic disease. Referring to international treatment guidelines, the significance of disease severity is then explained. For accurate and consistent measure of psoriasis severity, the available psoriasis-specific severity instruments are evaluated, presenting the strengths and weaknesses of their use in clinical study. The impacts of psoriasis on QoL are also discussed, and again relevant instruments are reviewed for their suitability in clinical study.
A number of potential co-morbidities have growing association with psoriasis. Chapter 2 reviews the available evidence for the co-morbidities most often identified. Current first and second line conventional therapy options are then reviewed, exploring where available, their mechanistic actions and any associated physiological risks. Newer ‘third line’ biologic drugs are also described, as are future emerging therapies and the direction of future drug development.

Lastly, the chapter discusses the scientific evidence for herbal psoriasis therapies. Historical use of CHM for psoriasis is described and its potential benefits for modern use are explored.

Chapter 2 defined the characteristics of the population to be targeted in the clinical study; psoriasis type, severity, age group and any excluding factors.

Review in this chapter assisted to determine the conventional therapy utilised in the IMPPS, and guided development of clinically relevant outcome measures for the study, aiding selection of suitable instruments. The chapter also assists identify potential psoriasis-related biological markers for analyte assay of clinical study participant plasma samples.

In Chapter 3 via systematic review of published randomised controlled trials (RCTs) and subsequent meta-analyses of extracted data, the efficacy and safety of oral CHM is evaluated for psoriasis vulgaris compared to placebo. The systematic review also evaluates trial design of previous RCTs to assess their strengths and weaknesses. From the included RCTs, the most common utilised CHM are identified and their phytochemicals are explored for potential psoriasis-related pathway activity. The results of this chapter assist development; of the trial design; of the investigative formulation ingredients, assessment of the general safety of oral CHM and provides insight into potential psoriasis biological pathway targets.
Further review is presented in Chapter 4, which examines the potential add-on effects of oral CHM to conventional therapy. Systematic review and meta-analyses are presented on the safety and efficacy of RCTs integrating oral CHM and conventional therapy for psoriasis vulgaris. Again, trial designs of included RCTs are evaluated and the most commonly utilised CHM again presented for identification of phytochemicals with potential psoriatic activity. This chapter further assists selection of a suitable conventional therapy for the pilot study and confirms the safety of combined therapies for further study.

Chapter 5 utilises data from the previous chapter reviews along with Chinese medicine theory (textbook and recommended treatment guidelines), phytochemical evidence and expert opinion to develop an oral CHM, using an evidence-based approach, for further clinical investigation. Chinese medicine syndrome differentiation in Chinese medicine theory is discussed along with its relevance to selection of herbal ingredients and how such selection may influence treatment outcomes. The chapter then describes early development of a CHM formulation and presents evidence supporting its potential use for psoriasis disease. The ingredients of the final formulation (PSORI-CM01) are then described. The main phytochemicals the early developed and final formulations are also reviewed, briefly presenting, where available, evidence for their biological activity with potential anti-psoriatic action. This chapter primarily describes selection of psoriasis vulgaris targeting CHM formula PSORI-CM01 and provides a review of the key therapeutic phytochemical markers for the final manufactured product. The chapter also describes the development of an instrument, which assesses Chinese medicine syndrome for use in the subsequent study.

Chapter 6 explores PSORI-CM01’s main herbal ingredient, Radix Paeoniae Rubra (chi shao). The chapter reviews the two official botanical sources of Radix Paeoniae
Rubra, comparing their general characteristics as well as their constituent phytochemicals. Review of the published scientific evidence for these phytochemicals presents their potential therapeutic biological activities. Results of this chapter assisted in determining the species to utilise as Radix Paeoniae Rubra for PSORI-CM01. This section also provides a comprehensive review of the phytochemical biological activity of each Radix Paeoniae Rubra species for future investigation.

Chapter 7 describes the development of the clinical study protocol to evaluate PSORI-CM01 for psoriasis. Initially, the pros and cons of pragmatic and explanatory study designs for oral CHM are discussed, compared with pharmaceutical therapies. The chapter also details how the results of previous chapters influenced design of the pilot study. Details of the pilot protocol are presented in full according to the population, intervention, control, and outcomes (PICO) structure. The chapter then goes on to detail the standard operating procedures for the study and strategies employed for advertisement and recruitment. The chapter primarily presents development of the protocols of the pilot and provides justification for the final design.

Chapter 8 presents preliminary results of the pilot study and discusses the progress of the study to date. It summarises current study progress and preliminarily evaluates the strengths and weaknesses of the study design. Study limitations are also discussed and methods are suggested to improve study design for future larger-scale studies. Adverse event data are reported and the feasibility of the trial protocol is preliminarily evaluated.

Chapter 9 presents a summary of the main findings of the thesis. It presents a brief overview of the results of each chapter. This last section identifies the overall significance of the thesis and provides researchers and clinicians with
recommendations for integrating oral CHM and conventional therapy in clinical therapy and research.
Chapter 2 – Psoriasis disease review

This chapter reviews the phenotypes of psoriasis, the aetiology and pathogenesis of psoriasis, the epidemiology and socioeconomic burden of the disease, measurement of psoriasis severity, associated co-morbidities, available therapies based on major therapeutic guidelines and their biological actions on psoriatic disease. It then reviews herbal therapies for psoriasis including CHM.

2.1 The phenotypes of psoriasis

A number of different psoriasis phenotypes have been identified, each with unique visual and symptomatic characteristics. This section differentiates each of the main phenotypes.

2.1.1 Psoriasis vulgaris

Of psoriasis phenotypes, vulgaris is the most common, presenting in about 80% of psoriasis cases (Biondi Oriente et al., 1989). Vulgaris type lesions are predominantly elevated and linear, most commonly on elbows, knees, scalp, hands and feet (Dermatology Expert Group, 2004). Accompanying symptoms may include itching, irritation, stinging and/or pain (World Health Organization (WHO), 2013). The raised red lesions typically have an adherent, thick, silver, scaly appearance from which it derived the more common name 'plaque' psoriasis (Figure 2.1)(Clarke, 2011, Weisshaar, 2012). Although rare for vulgaris type, psoriasis skin surface effects over the entire body can be fatal. Extensive inflammation and peeling of the skin can in turn reduce the skin’s barrier function and subsequently the body is unable to its regulate temperature (Fitzpatrick et al., 2009).
2.1.2 Guttate psoriasis

Red in appearance and typically tear-shaped with central body distribution, guttate psoriasis has the highest incidence in children, where typically it follows bacterial infection, such as streptococcal pharyngitis (Figure 2.2: Guttate psoriasis) (Henley, 2012).

2.1.3 Inverse (flexural) psoriasis

Presenting in flexural folds such as axilla and inguinal regions, inverse psoriasis is also known as flexural psoriasis. Unlike psoriasis vulgaris, its lesions appear shinier and are more moist. As their location is exposed to more sweat and friction, irritation is typical in sufferers (Figure 2.3: Flexural psoriasis) (Syed and Khachemoune, 2011).

2.1.4 Erythrodermic psoriasis

Deemed to be the most severe form of psoriasis, erythrodermic psoriasis sufferers present with diffuse erythema and typically extensive fine scaling over the body. Subsequent inflammation can affect the body's ability to regulate temperature and fluids, where patients risk death from severe fever or infection (Figure 2.4: Erythrodermic psoriasis) (Boyd and Menter, 1989).

2.1.5 Pustular psoriasis

Pustular psoriasis has a number of patterns distinguished by their appearance and development: generalised (or von Zumusch), annular, exanthematic or localised. A key feature is an erythematous area consisting of surface pustules, which may or may not be painful (Figure 2.5: Pustular psoriasis) (Baker and Ryan, 1968).

2.1.6 Further phenotyping

Psoriasis phenotypes may be further classified based on their location, such as the scalp,
genitals, or palms of the hand and soles of the feet (palmoplantar) (Ayala, 2007, Raychaudhuri et al., 2014). Psoriasis location can influence disease severity and in some circumstances, such as palmoplantar, it can be debilitating (Figure 2.6: Acral psoriasis) (Janagond et al., 2013, Ayala, 2007, Burfield and Burden, 2013).

Figure 2.1: Psoriasis vulgaris lesion (DermNet New Zealand Trust, 2014)

Figure 2.2: Guttate psoriasis (DermNet New Zealand Trust, 2014)
Figure 2.3: Flexural psoriasis (DermNet New Zealand Trust, 2014)

Figure 2.4: Erythrodermic psoriasis (DermNet New Zealand Trust, 2014)
2.1.7 Psoriatic arthritis

A common co-symptom found in psoriasis sufferers is arthritis of joints, in which as well as lesion development there is gradual increasing damage to joints from inflammation. The damage leads to associated pain, stiffness and joint deformity, which for some can
be debilitating (Figure 2.7: Psoriasis-associated arthritis). Associated incidence of arthritis is found in 30–40% of psoriasis sufferers (Haroon et al., 2013, Boehncke and Menter, 2013). Over 86% of psoriatic arthritis sufferers report psoriatic lesion development prior to psoriatic arthritis and diagnosis of psoriasis on average precedes the arthritis by 14.6 years (Armstrong et al., 2012).

![Figure 2.7: Psoriasis-associated arthritis (DermNet New Zealand Trust, 2014)](image)

**Figure 2.7: Psoriasis-associated arthritis (DermNet New Zealand Trust, 2014)**

### 2.2 Aetiology and pathogenic mechanisms of psoriasis

Theory of psoriatic aetiology and pathogenesis has guided development of new therapies however there is still conjecture about the precise mechanisms involved. This section reviews the current understanding and evidence for factors affecting psoriatic pathogenesis and aetiology, identifying mechanistic gaps where further research is needed.
2.2.1 A general understanding of psoriasis aetiology

Until recently, scientists believed psoriasis to be a relatively benign disease, with the unsightly appearance and discomfort thought to be the only risks to sufferers. With clinical pathologic and histological study improving over the years, understanding of the pathophysiology of psoriasis has improved significantly (Murphy et al., 2007). Now, researchers understand that psoriasis is likely a systemic disease of the body, with increased risk to a number of associated co-morbidities (Kimball et al., 2008).

The main differences between psoriatic and healthy skin are increased presence of inflammatory cells and increased proliferation of abnormal skin cells. Although the precise cause of psoriasis has not been elucidated, much is known of the psoriasis cellular response and progression once activated. Likely following ‘trigger’ (activation) by an antigen of some type (external or autoimmune), initially CD4+ type T-lymphocyte cells (also known as T-cells) infiltrate, going on to develop into specific T-cell subsets (Korn et al., 2009). One theory is that in some people the skin’s barrier function is reduced leaving them more susceptible to antigen attack and psoriasis development (Feingold, 2014). Research suggests the initial triggers may vary, as they are shown to be inconsistent for psoriasis development. Another plausible, yet unsubstantiated, theory suggests genetic immune system mutation potentiates psoriasis (Fry et al., 2014). Research indicates that further investigation of psoriasis triggering antigens is needed as well as how they might link to genetic polymorphisms (Ryan et al., 2013). However, substantial research has been carried out on the biological processes, which follow the onset of psoriasis.

Looking at the visual features of psoriatic skin under a microscope and recognising the physiological changes occurring, can identify the stage of lesion development. Early dermal changes see an increase of T-cell infiltrate, neutrophils, activated mast cells and
plasmacytoid dendritic cells. Identified as important in subsequent upstream development of psoriasis lesions, the plasmacytoid dendritic cells produce key psoriasis related cytokine, interferon-α (IFN-α). Later, plasmacytoid dendritic cells differentiate into dendritic cells (DCs), and it has been proposed that drug development should target this phase, preventing IFN-α release for earlier treatment and/or preventing psoriasis (Nestle et al., 2005).

Dendritic cells are antigen detection and presenting cells originating from bone marrow. In psoriasis they circulate in the bloodstream and migrate to peripheral tissues where they process antigens and present them to circulating T-cells and B-lymphocytes (B-cells), further triggering psoriasis immunological response (Boehncke et al., 2010, Bowcock and Krueger, 2005). Likely acting as auto-antigens, research has shown that adenosine triphosphate, induced by an antimicrobial peptide known as LL37 and receptor P2X7, further increases DC maturation and inflammation (Killeen et al., 2013, Lande et al., 2014). Interestingly, in psoriatic patients, DCs located at psoriatic regions are stronger stimulators of T-cell proliferation than DCs derived from non-psoriatic peripheral blood or skin (Nestle et al., 1994). The DCs also secrete known psoriasis-associated cytokines, such as tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and interleukins 12, 23 and 15 (IL-12, IL-23 and IL-15). These cytokines then further stimulate and proliferate T-cells, likely locally maintaining the initial triggered response. Development of lesions likely then ensues due to continued dermal inflammation and epidermal hyperplasia (Boyman et al., 2007).

Keratinocytes secreting various cytokines likely recruit T-cells for activation in affected areas (Jariwala, 2007). Stimulated T-cells then release TNF-α, IFN-γ and other cytokines that induce further downstream gene responses and activate further signal pathways. This leads to migration of leukocytes to inflammatory regions and
subsequent vasodilation representing the common erythema characteristic of psoriatic skin (Chamian and Krueger, 2004). Conventional treatments such as cyclosporine and alefacept were developed to act on these T-cell pathways, while other therapies such as infliximab and etanercept are TNF-α antagonists, aimed at decreasing pro-inflammatory cytokines and reducing infiltration of characteristic psoriasis cells (see 7.6.8 Cytokine concentrations) (Boyman et al., 2007).

In psoriasis, IFN-γ production decreases expression of enzymes required for production of ultra-long-chain ceramides. Found in the stratum corneum, these ceramides play a key role in maintaining the skin’s permeable barrier (Feingold, 2014). Despite a host of available anti-TNF-α drugs to treat psoriasis, drugs aimed at IFN-γ have not proven to be efficacious (Harden et al., 2014).

Like T-cells, mast cells infiltrate early in psoriatic plaque development, peaking at around 14 days, before more T-cells infiltrate followed closely by macrophages. These lead to large production of TNF, IFN-γ, IL-8 and mediators, such as vascular endothelial growth factor (Ghoreschi et al., 2007, Toruniowa and Jablonska, 1988). Contributing to this, dendritic cells are also known to secrete psoriasis-active cytokines (TNF-α, IFN-γ, IL-12, IL-23 and IL-15)(Lowes et al., 2007). Contrasting with the apparent contributing effect of dendritic cells on psoriasis, it seems in vivo, antigen-presenting cells (Langerhans cells) suppress psoriasis severity (Glitzner et al., 2014). During psoriasis development, antigen-presenting cells and T-cells continue to interact, forming surface complexes known as lymphocyte function-associated antigen-1 (LFA-1). These bind to adjacent cells, such as keratinocytes, via intercellular adhesion molecule 1 (ICAM-1). This ICAM-1 is another common drug target for psoriasis. When such adhesion is prevented, this further prevents T-cell activation and release of inflammatory cytokines,
chemokines and growth factors known to be implicated in development, proliferation and altered differentiation of psoriatic keratinocytes (Boehncke et al., 2010).

Acting as the first line of defence against pathogens, cathelicidin, S100 proteins and defensins are also implicated in psoriasis pathogenesis, evidenced to aid in the recruitment and attraction of chemokines identified as key to pathogenesis of psoriasis (Batycka-Baran et al., 2014).

Found predominantly in the upper dermis of psoriatic skin, research indicates that CD4+ T-cells are mostly involved in early psoriasis pathogenesis. In the epidermis, CD8+ cells are more predominant and their influx corresponds with latter psoriatic lesion progression (Nickoloff and Wrone-Smith, 1999, Paukkonen et al., 1992). It is suggested that fluctuation in levels and ratios of CD4+ and CD8+ T-cells reflects patterns of acute psoriasis exacerbation and subsequent remission (Gudjonsson et al., 2004). While T-cell processes occur, mast cells of the upper dermis continue to be activated, continually producing inflammatory cells and assisting with lesion perpetuation (Harvima et al., 2008).

Regulating T-cells (Tregs) have been identified as important in suppressing inflammation processes and maintaining homeostasis. Although Treg levels are found to be raised in psoriatic skin, it has been recognised that people with psoriasis have reduced ability to suppress and inhibit immune response against self-antigens (Sugiyama et al., 2005, Mattozzi et al., 2013). The decreased expression of transcription factor forkhead box P3 (FOXP3) likely decreases development and differentiation of these Tregs, which reduces their function. People with psoriasis have increased expression of microRNA (miRNA) miR-210 in CD4+ cells, which is implicated in this decrease (Zhao et al., 2013). Subsequently, there has been an increase in research on the development of miRNA-targeted therapies (Guinea-Viniegra et al., 2014). Newer
biologic drugs elevate Treg subsets, which may contribute to their therapeutic effects for psoriasis (Figure 2.8) (Quaglino et al., 2009).

Figure 2.8: Biological activation and pathological pathways of psoriasis (Adapted from (Nickoloff and Nestle, 2004, Kaffenberger et al., 2014))

The triggered immune response in psoriasis is understood to follow the T helper type 1 (Th1) cell-mediated delayed hypersensitivity pathway. This differs from other common dermatological conditions such as atopic dermatitis, which follow the T helper type 2 (Th2) pathway (Uyemura et al., 1993). Interesting research shows allergic contact dermatitis reaction is delayed in people with psoriasis, peaking in intensity around day 7, compared with the typical 3–5 day peak of non-psoriatic people. However, the clinical course of psoriasis following a dermatitis trigger does not change (Quaranta et al., 2014).

More recently, innate lymphoid cells (ILCs) such as natural killer (NK) cells that are non-antigen specific, have been implicated in psoriasis. An increased proportion of NCR+ ILC3 is present in the affected skin and peripheral blood of people with psoriasis.
compared with non-psoriatic people. This NCR+ ILC3 produces IL-22, indicated as important in epidermal thickening of psoriasis lesions (Teunissen et al., 2014). The level of ILCs is shown to decrease after treatment with anti-TNF-α therapy. Interestingly, drugs targeting IL-22 likely also reduce ILC3, yet clinically they have not been shown to improve psoriasis symptoms (Ward and Umetsu, 2014).

Another key pathway relatively unique to psoriasis is that of the Th17 cell line (stimulated by transforming growth factor (TGF)-β1, IL-6, IL-23 and IL-15), which is involved in clearance of pathogens undetectable to Th1 and Th2 (Michalak-Stoma et al., 2013, Asarch et al., 2008). Interestingly, T-cells extracted from psoriatic skin lesions are predominantly of this Th17 phenotype (Pene et al., 2008). Leading to production of key chemokines, IL-17, IL-17F and IL-22, which further activate inflammatory pathways and mediate other known psoriatic cytokines such as IL-23 (Lowes et al., 2008, Zheng et al., 2007). Th22 line cytokines are now also implicated in psoriatic development and express distinctive chemokine receptors compared with Th1 and Th2 lines (Michalak-Stoma et al., 2013) (Pene et al., 2008).

Despite evidence that psoriasis follows Th1 and Th17 pathways, research suggests there are decreased levels of IgM, IgA and IgG against Candida species C. albicans. This may indicate psoriatic people have a reduced humoral immune response to Candida (Taheri Sarvtin et al., 2014).

Following such immune response dilated and elongated blood capillaries form (angiogenesis) within dermal papillae, along with mild dermal oedema and spongiosis. At this time, T-cells and/or neutrophil invasion of the epidermal layer (exocytosis) is rare (Albanesi, 2014, Creamer et al., 2002). Lymphatic system remodelling sees their increased permeability yet in contrast to capillaries, lymphatics constrict in their diameter (Meier et al., 2013) (Moustou et al., 2014). The increased angiogenesis is
linked to an increase in vascular endothelial growth factor (VEGF). However, the impact of such increase for psoriasis needs further investigation, as it may assist in the development of new drugs (Man et al., 2008, Ryan et al., 2013).

As lesions develop further there is slight psoriasiform (regular) epidermal hyperplasia, with greater neutrophil exocytosis and development of parakeratosis containing neutrophils. When psoriasis is fully developed, clinical plaques show marked epidermal hyperplasia with characteristic features, including regular elongation and ‘clubbing’ (widening of the deep portion) of epidermal rete. The dermal papillae become elongated, containing dilated and twisted capillaries and the epidermis covering these papillae becomes progressively thinner. In addition, superficial epidermal layers show pallor, while increased keratinocyte proliferation thickens other epidermal areas. This reflects increased mitotic activity of basal and suprabasal layers (Murphy et al., 2007). Further aggravating this thickening are inflammatory mediators such as IL-15, which increase apoptotic resistance of abnormal keratinocytes (Ruckert et al., 2000, Wrone-Smith et al., 1997).

At the epidermal layer, presence of both orthokeratosis and horizontally confluent parakeratosis suggests fluctuations in epidermal growth of lesions and hyperkeratosis is more obvious (Murphy et al., 2007). For lesioned areas, keratinocyte proliferation increases substantially, where up to 100% of keratinocytes are in a proliferating state and cell cycle time reduces from around 13 days to just 36 hours (Weinstein et al., 1985). When compared with normal skin, psoriatic lesions are shown to be 27 times more mitotically active and have a 12-fold decrease in cell cycle time of basal and suprabasal keratinocytes. There is also more than a 7-fold increase in epidermis turnover time (\(\sim 7\) days in psoriatic skin vs. \(\sim 56\) days in normal skin) (Murphy et al., 2007). Such altered growth reflects the complexity of involved immunological pathways,
where lesions are characterised by presence of both neutrophilic and mononuclear infiltrates, signalling that both acute and chronic inflammatory responses are occurring. As a result, psoriasis vulgaris treatments need to target both chronic and acute inflammatory cells for optimum effect. The specificity of many psoriasis pharmaceuticals could explain why some drugs such as TNF-α blockers (thought to be active mainly on innate immunity) are only 75% effective, or why response to topical corticosteroids can differ within the same psoriatic lesion (chronic inflammatory areas respond well and acute areas are more resistant) (Griffin et al., 1988).

Interestingly, identified as activated in psoriasis, the Th1 pathway is evidenced to be triggered by Th1-type immunity drugs, such as IFN-α or imiquimod (a Toll-like receptor agonist that triggers production of IFN-α by plasmacytoid dendritic cells), and has been shown to exacerbate psoriasis (Toichi et al., 2000, Ketikoglou et al., 2005). Furthermore, in vivo blocking of IFN-α or prevention of its production from plasmacytoid dendritic cells prevents development of psoriasis (Nestle et al., 2005). Theory suggests that plaque presence may correspond with neutrophil and lymphocyte levels, where decreasing neutrophil levels subsequently reduces lesions, and following cessation of neutrophil-specific treatment lesions return as the neutrophil level raises (Toichi et al., 2000).

Despite obvious aspects of hyper-immune system function in psoriasis, research indicates that psoriasis-affected people have impaired immune reactivity to common bacterial and viral infections (Henseler and Christophers, 1995). The cause of such immune dysfunction is contentious. Research suggests it is associated with an imbalance in the numbers of Th1 and Th2 cells. However, therapies have targeted Th cells, raising Th2 type cell levels in an attempt to recalibrate ratios of Th1 to Th2 cells without obvious psoriasis effect (Nickoloff and Nestle, 2004). DNA has also been
implicated in immune dysfunction, yet investigation into cytokine gene polymorphism indicates local inflammatory factors and antigen presence are more likely to be relevant than genotype (Craven et al., 2001, Romagnani, 1997).

As they normally provide an important role in inflammatory response, the potent ability of Th17 line cytokines to induce tissue inflammation has implicated them as key in development of autoimmune diseases and inflammatory conditions such as psoriasis (Korn et al., 2009). Produced by multiple lineages of leukocytes and stromal cells, the regulatory cytokine TGF-β has been identified as a fundamental precursor for the development of naïve T-cells into Th17 cells (Korn et al., 2009). Interestingly, dendritic cells are believed to have an essential role in raising the level of TGF-β (transforming growth factor beta) in the affected area and contributing to the psoriasis inflammatory loop (Travis et al., 2007).

Continued Th17 cell response after initial induction requires continued presence of IL-23. Limiting the availability of IL-23 subsequently impairs Th17 immune and inflammatory responses (Veldhoen et al., 2006). Discovery of the beneficial effects of limiting IL-23 has seen development of newer biologic drugs such as etanercept. These IL-23 target drugs aim to reduce inflammatory dendritic cell products driving Th17 cell proliferation and in turn reduce downstream secretion of psoriasis inflammatory cells and the chronic psoriasis loop (Zaba et al., 2007). Despite the major role Th17 plays in psoriasis, evidence suggests regulation of Th1 cells may also be required for complete disease resolution and may explain why even high efficacy biologics are still not 100% effective (Zaba et al., 2007).
2.2.2 Other potential evidence for pathogenesis of psoriasis

A study of psoriatic-like mice (triggered by either chemical Aldara or cytokine-induced models) identified that deficiency of toll IL-1R8/single Ig IL-1 related receptor (TIR8/SIGIRR) leads to development of more severe psoriasis (Russell et al., 2013). The TIR8/SIGIRR has been shown to decrease expression of IL-17A and IL-1R1–driven proliferation of Th17 (Russell et al., 2013). In mouse models of inflammation triggered by IL-23, when toll like receptors (7, 8 and 9) are targeted by antagonists there is decreased expression of the IL-17 pathway (Suarez-Farinas et al., 2013).

Comprehensive research indicates that people with psoriasis have decreased melanin production in lesion-affected areas, which is likely related to increased production of TNF-α and IL-17. After treatment with anti-TNF-α and anti-IL-17 therapies, melanocytes increase, with subsequent basal cell hyperpigmentation and elongation of rete ridges. This may explain why psoriasis sufferers have lower incidence of skin cancer, but more research is needed (Di Cesare et al., 2015).

The functional protein caveolin-1 decreases considerably in psoriasis vulgaris (Campbell et al., 2002). Caveolin-1 inhibits associated kinase activity of pathways involved in cell differentiation and proliferation by modulating signal transduction (Zhang et al., 2014c). Further, caveolin-1 likely sensitises cells to apoptosis through inhibition of anti-apoptotic kinases, suggesting low levels of caveolin-1 may contribute to increased proliferation in psoriasis (Liu et al., 2001).

Oxidation has also been implicated in the development and severity of psoriasis, including increased oxidant levels in people with psoriasis (Pujari et al., 2014). Such increase in oxidants leads to development of reactive oxygen species ROS, which are known to release superoxide anions that mediate dermal tissue damaging interleukins such as TNF-α (Fuchs et al., 2001).
MicroRNAs are small non-coding RNA molecules that modulate gene expression at post-transcriptional level. Laser capture micro-dissection followed by next-generation sequencing has identified deregulated miRNAs in psoriatic skin (Lovendorf et al., 2014). There is evidence that these miRNAs are involved in proliferation and differentiation of keratinocytes; however, more research into their specific role in psoriasis is needed (Lovendorf et al., 2014). The proliferation of keratinocytes and lack of apoptosis in psoriasis also implicates mitogen-activated protein kinases p38 (p38 MAPKs) in its development. Understood to be important for the differentiation of cells p38 MAPKs, an increase in cell differentiation activity has been found in psoriatic compared with unaffected skin (Mavropoulos et al., 2013).

Natural killer cells regulate immune cells and cause secretion of cytokines, thus they have also been implicated in the development of psoriasis. A unique function of NK cells is their ability to kill T-cells and antigen-presenting cells, subsequently down-regulating the inflammatory response and the psoriasis inflammatory cascade. Likely due to competitive binding by another receptor cell (NKG2A), the NK receptor cell NKG2C is reduced in people with psoriasis. The subsequent imbalance reduces activation of NK cells, allowing T-cells to propagate uncontrolled. Similarly, another theory suggests that when NKG2A is bound to HLA-E it competes with HLA-Cw* 0602, subsequently protecting against psoriasis. With a decrease in NKG2A there is less bound to HLA-E, and development of psoriasis increases (Patel et al., 2013).

2.2.3 Known contributing factors to psoriasis pathogenesis

In an attempt to explain why and how psoriasis is initiated and sustained, extensive research into the biological mechanisms of psoriasis continues. Although active pathways for psoriasis sufferers are identified, the initiating and/or triggering factors
vary considerably. Preventable lifestyle factors such as cigarette smoking, alcohol consumption and stress have been linked with psoriasis development. Genetics have also been linked to increased psoriasis risk. For some people, use of various pharmaceuticals also increases the risk of psoriasis. The variety of triggers and their inconsistency in psoriasis development contributes to difficulty understanding the precise pathogenesis of psoriasis. This section discusses the main known external and internal triggers or aggravators known to induce and/or exacerbate psoriasis.

*Pharmaceutical drug psoriasis inducement and/or aggravation*

Some pharmaceutical drugs have been reported to trigger or exacerbate psoriasis in both the genetically susceptible and those without a family history of psoriasis. Drugs have been implicated with psoriasis in four ways: (1) precipitating psoriasis de novo in predisposed and non-predisposed individuals; (2) exacerbating pre-existing psoriatic lesions; (3) inducing lesions in clinically normal skin areas of patients with psoriasis; and (4) developing treatment-resistant psoriasis (Tsankov et al., 2000). It is likely that biological mechanisms of implicated drugs trigger or induce psoriasis, or in psoriasis sufferers aggravates the psoriatic inflammatory cascade, amplifying symptoms (Dika et al., 2006). Drugs commonly administered for non-psoriasis related conditions that have been implicated for psoriasis include lithium, beta-adrenergic receptor blocking agents (β-blockers) and antimalarials. This section discusses these known drugs and their potential psoriatic biological activity.

*β-blockers*

Used predominantly for cardiovascular conditions, β-blockers such as practolol have been known to trigger psoriasis. As a result of this and other side effects, practolol has since been withdrawn (Basavaraj et al., 2010). The psoriasis-activating pathway is likely
to be from the presence of β-adrenergic receptors in the skin, with β-blockers preventing binding to β-agonists. Such binding is necessary for increases in secondary messenger, cellular cyclic adenosine monophosphate (cAMP), which stimulates skin cell differentiation and inhibits their proliferation. For some, this lack of binding results in keratinocyte proliferation and skin appearance symptoms the same as psoriasis (Basavaraj et al., 2010, Tsankov et al., 2000). Such lesion development usually appears 1–18 months after β-blocker use (Heng and Heng, 1988).

**Lithium salts**

Prescribed for psychological and urology management, a common unwanted side effect of lithium salts is the triggering or exacerbation of psoriasis (Albert et al., 2014). The prevalence of cutaneous skin disorders including psoriasis may be as high as 45% in lithium users (Yeung and Chan, 2004). Interestingly, psoriasis sufferers without a history of lithium use have greater serum lithium concentration than people without psoriasis (Hanada et al., 1987). The precise mechanism through which lithium induces psoriasis is unknown; however, evidence suggests lithium affects cAMP levels, inhibiting inositol-1-phosphate and by subsequently lowering the intracellular levels of calcium, alters cellular transduction signals (DiGiovanna et al., 1981, Skoven and Thormann, 1979). This leads to reduced keratinocyte differentiation and increased proliferation, while chemotaxis and phagocytic activity of polymorphonuclear leukocytes is enhanced (Bloomfield and Young, 1983). In psoriatic patients, levels of inositol are typically low following lithium treatment and supplementation has shown reduction of psoriatic symptoms and overall severity (Allan et al., 2004). Studies also report increased IL-2 and TNF-α production following lithium therapy. This increase may assist development of psoriasis supported by the efficacy of TNF-α inhibitors such
as etanercept in lithium-triggered psoriasis (Fry and Baker, 2007) (Wachter et al., 2007). Psoriasis typically subsides when lithium therapy stops and returns when it is recommenced (Skoven and Thormann, 1979).

**Synthetic antimalarial drugs**

In approximately 18% of psoriasis sufferers, synthetic antimalarial drugs such as chloroquine, hydroxychloroquine, primaquine and meflo-quine have been found to exacerbate psoriasis symptoms (Gravani et al., 2013). Synthetic antimalarial drugs are not thought to induce psoriasis in previously unaffected people, yet in the susceptible, psoriasis retrigger is common and reported to occur quicker than with other drugs (Namazi, 2008). Psoriasis symptoms subside after the drug is ceased in only 30% of cases. The mechanism is not well understood, however, theory suggests keratinocytes inhibit transglutaminase activity and/or cholesterol biosynthesis, causing breaks in epidermis barrier function so the epidermis responds to repair and restore the break (Namazi, 2008, Basavaraj et al., 2010, Wolf and Lo Schiavo, 1997).

**Antibiotics**

There is limited evidence that antibiotics induce psoriasis, although the relationship is uncertain and it is possible the underlying infection the antibiotics were administered to treat is actually the psoriatic trigger. Among antibiotics, tetracyclines are most likely to cause or exacerbate psoriasis due to their ability to cause photosensitisation and reduction in cAMP (Wright and Colver, 1988, Kim and Del Rosso, 2010).

**Non-steroidal anti-inflammatory drugs**

Limited evidence indicates non-steroidal anti-inflammatory drugs can both induce and exacerbate psoriasis (Basavaraj et al., 2010). Indomethacin has been implicated, although incidence of psoriasis from its use is relatively low (Lazarova et al., 1989).
Non-steroidal anti-inflammatory drugs inhibit metabolism of arachidonic acid via the cyclooxygenase pathway, leading to accumulation of leukotrienes known to aggravate psoriasis (Lammers and van de Kerkhof, 1987).

**Biological drugs**

New-onset psoriatic lesions and exacerbation have been described after treatment with biologics for multiple sclerosis, mainly interferon-beta (INF-β) or natalizumab (Gkalpakiotis et al., 2014). Similarly, psoriasis has been induced after treatment with an antibody targeting CD20, rituximab, for immunological diseases such as rheumatoid arthritis. The CD20 antigen is found on mature B-cells (Ozen et al., 2013, Fiorillo et al., 2014). Due to action on the Th1 pathway, interferon has been implicated in psoriasis activation in a hepatitis C patient (Nestle and Gilliet, 2005, Kim et al., 2013b). Imatinib is a first line therapy for newly diagnosed chronic myeloid leukaemia patients, and patients with no previous history of psoriasis have also been reported to develop psoriasis after its administration (Atalay et al., 2013). Contrary to their common administration as treatments for psoriasis, biologics ustekinumab and adalimumab as well as other TNF-α blocking biologics also risk onset and/or exacerbation of psoriasis (Borras-Blasco et al., 2008, Ko et al., 2009, Sanso Sureda et al.).

**Interferon-β**

A drug utilised for multiple sclerosis, interferon-β may aggravate or induce psoriasis. It is unclear whether immunomechanisms of multiple sclerosis and psoriasis are similar although, interestingly, both multiple sclerosis and psoriasis respond to treatment with fumaric acid esters (Fellner et al., 2014) (Zecca et al., 2014).
**Thalidomide**

Possibly related to its effects on TNF-α, immunomodulator thalidomide was reported to trigger psoriasis in a person without previous psoriatic history (Ferrazzi et al., 2014).

**Granulocyte-macrophage colony-stimulating factors**

Used for treatment of myelodysplasias and after chemotherapy, there is clinical evidence suggesting granulocyte-macrophage colony-stimulating factors can exacerbate psoriasis symptoms, though more research is needed to clarify a direct link (Kelly et al., 1993).

**Angiotensin-converting enzyme inhibitor**

Utilised for hypertensive patients, angiotensin-converting enzyme (ACE) inhibitor use in people with familial history of psoriasis and specific ACE genotype exhibiting low enzyme activity are more susceptible to developing psoriasis (Chang et al., 2007).

**Other**

Drugs with limited evidence for exacerbation or development of psoriasis include interferon, gemfibrozil, iodine, digoxin and chlonidine (Milavec-Puretic et al., 2011). There are also reports of incidents in which vaccinations, such as the H1N1 vaccine, trigger psoriasis. Although the risk is typically low it is interesting to note that the majority who develop psoriasis from vaccinations tend to present a mixture of vulgaris and guttate types (Sbidian et al., 2014). As mentioned previously, guttate psoriasis typically develops after infection (Henley, 2012). A clinical case study reports psoriasis onset after administration of a purified protein derivative, which was part of a negative Mantoux test for tuberculin (Khanna et al., 2014).
Although psoriasis may be an unwanted side effect of some drug treatments, there are also some drugs in development designed to trigger psoriasis. Such psoriasis-inducing drugs are intended to assist laboratory exploration of psoriasis pathogenesis, help understand its development and aid drug development for future treatments (Vinter et al., 2014).

**Genetics and psoriasis**

Research has long indicated a genetic psoriatic predisposition and significant evidence now indicates genetics as one of the strongest factors determining psoriasis development in a person, and its age of onset (Elder et al., 2001). If either parent suffers from psoriasis, the incidence in their children is increased by 14%. If both parents are afflicted with psoriasis, then the reported incidence rises to 41% in their children (Andressen and Henseler, 1982). More recent studies have confirmed such parental ‘transmission’ of disease with 59% of psoriasis-affected people reporting at least one relative with psoriasis (Di Lernia et al., 2014).

A genetic basis of psoriasis is also supported by studies of monozygotic (identical) twins, with similarity in age of onset, distribution of disease and severity (Duffy et al., 1993). Early studies of twins with psoriasis revealed higher concordance in monozygotic twins than dizygotic (non-identical) twins (Farber et al., 1974, Duffy et al., 1993).

Susceptibility to psoriasis has been linked to specific genetic markers known to increase the probability of psoriasis development in carriers. However, not all people with the psoriasis-promoting gene markers will develop the disease, and others without positive genetic markers may still develop psoriasis (Barker, 2001). Thus, genetics is not considered to be the sole determining factor in psoriasis development, and research
indicates environmental factors also play a significant role (Szczerkowska-Dobosz, 2005).

Despite their varied role, genetic markers may still assist researchers in future drug development. One promoter region highly likely to be related to psoriasis is an increased production of IL-22, which increases the risk of psoriasis in children (Nikamo et al., 2014). As discussed previously, TNF-α production is key to psoriasis development and progression. Produced by keratinocytes, dermal dendrocytes, macrophages, mast cells and activated T-cells the production of TNF-α is then further increased by subsequent intervention of other cytokines (Bonifati and Ameglio, 1999). There is plausible research indicating that increased TNF-α gene promoter polymorphism confers higher risk of early-onset psoriasis (Zhuang et al., 2013). A recent review evaluated the two most evidenced TNF-α gene polymorphisms implicated in development of psoriasis, with both polymorphisms at guanine-adenine (G-A) transitions, one at position 308 and the other at position 238. Interestingly, people with the TNF-α308 G-A polymorphism have a decreased risk of psoriasis, while those with TNF-α 238 G-A have an increased risk of psoriasis (Zhuang et al., 2013).

Genome-wide linkage scans have identified 20 possible susceptible loci on 15 different chromosomes. These loci have been designated as PSORS 1 to PSORS 6 with others also identified (PSORS 7 and PSORS 9). Active genome sequences likely impact on the IL-23 and Th17 pathways, significant pathways in the susceptibility of people to psoriasis development (Yin et al., 2014).

A mapped genetic region known as PSORS1, has been associated with presence of psoriasis in 60–65% of psoriasis sufferers. (Barker, 2001, Jordan et al., 2012, Bowcock, 2004, Duffin and Krueger, 2009). It consists of a region on the 6p chromosome
containing the major histocompatibility complex and is the location of genes for human leucocyte antigens (Barker, 2001).

Several human leukocyte antigens (HLA), classes I and II, associated with psoriasis vulgaris have been investigated. Presence of antigens produced in this region such as the HLA-Cw6 antigenic peptide have been linked to both earlier onset of psoriasis (<40 years) and positive family history (Tiilikainen et al., 1980). Around 66% of people with psoriasis have the HLA-Cw6 allele and are identified as type I (Gudjonsson et al., 2004, Cassia et al., 2007). Those positive to HLA-Cw6 have more severe psoriasis, more extensive plaques and higher incidence of Koebner’s phenomenon (skin lesions appearing along lines of trauma) (Gudjonsson et al., 2002). On the other hand, type II psoriasis is associated with HLA-Cw2 and HLA-B27, which is correlated with later psoriasis onset (>40 years) and a negative family history (Lebwohl, 2007, Bahcetepe et al., 2013). Atypical cases that fit neither type I nor type II led to further classification of types Ia, Ib, IIa and IIb where ‘a’ types are associated with HLA-Cw6 and ‘b’ types are not (Fry et al., 2006).

Despite extensive research it is possible there is linkage disequilibrium between HLA-Cw6 and other genes also affecting the development of psoriasis. The mechanism is likely to be an antigen bound to either HLA class I or HLA class II, which interacts with T-cell receptors via peripheral tissue dendritic cells, which migrate, mature and activate T-cells (Cassia et al., 2007). The triggering antigen remains unknown, however excessive production of non-antigen specific, innate antimicrobial peptides and proteins (AMPs or alarmins) are characteristic of psoriasis.

The absence or presence of some single nucleotide polymorphisms (SNPs) has been associated with psoriasis. Specifically, absence of HLA-Cw6 and presence of IL12B SNP and IL6 SNP decreases psoriasis risk by 96% (Boca et al., 2013). Although
substantial research indicates Cw6 is related to development of psoriasis, Cw6 is not present in all people with psoriasis (Fry et al., 2006).

Difference in genetic susceptibility is also evidenced among different races. Chinese psoriatic populations with SNPs of the IL-15 gene have been associated with psoriasis, but Caucasian populations from the UK, Germany and the US do not show the same association (Smith et al., 2008). Research in Han Chinese of other polymorphisms such as those that regulate epidermal growth factor receptors implicates further SNPs in the development of psoriasis (Zhang et al., 2014d). Further, in the Han Chinese polymorphisms such as rs610604 have been implicated in increasing psoriasis severity (Zhang et al., 2014a). On the other hand, European populations with primary SNPs IL-23R and IL-17 show association with psoriasis, yet they are polymorphic in the Chinese (Li et al., 2014, Ellinghaus et al., 2010). In a Spanish population, genetic variation in IL12B, IL23R and IL23A increased risk of psoriasis development and severity, and also increased risk of developing the metabolic disorder type II diabetes (Eiris et al., 2014).

Although genetics likely play a substantial role, it should be highlighted that ethnic differences exist in the location of such susceptible genes, and further difference is likely between genders of the same ethnicity (Haase et al., 2014, Mabuchi et al., 2014). Such genome location variation has implications for biological drug efficacy and adverse events as they target specific genes for psoriasis treatment. Prior to market release, it could be argued that, to ensure sufficient safety of biologic drugs, each biologic should be tested in a wide range of ethnicities prior to therapeutic approval by governing bodies.

Thanks to genome-wide association studies, upwards of 36 genes have been linked to psoriasis and researchers have developed a complex model of psoriasis pathogenesis. This complex model consists of theory involving irregular skin barrier
function, innate immunity and adaptive immunity (Tsoi et al., 2012, Mahil et al., 2015). The only well-recognised protective allele against psoriasis is present in less than 3% of the population: IL23R SNP impairs the IL-23-induced Th17 effector response (Di Meglio et al., 2011). An area of the major histocompatibility complex, with glutamine at position 45 has recently been identified as likely linked to susceptibility of more severe arthritic phenotypes of psoriasis (Eder et al., 2015).

Future of genetics research for psoriasis

Numerous genetic factors may be involved in psoriasis, and understanding how each of these factors relates to its development is becoming more and more complex. Considering such complexity, researchers are developing new technology allowing correlation of multiple genetic factors with psoriasis. Such technology may in the future lead to specific clinical testing to evaluate susceptibility to psoriasis and could eventually lead to development of personalised psoriasis drug treatments (Climer et al., 2014). Further genetic research is needed to determine how genotype differences impact on development of the various psoriasis phenotypes and should further explore differences in molecular pathways between psoriasis phenotypes (Ryan et al., 2013).

Lifestyle and other external factors in psoriasis

A number of lifestyle and non-genetic factors have been implicated in development and exacerbation of psoriasis. This section discusses such factors, reviewing the evidence for pregnancy and hormonal change, cigarette smoking, sunlight, and bacterial or viral infection.

Pregnancy and hormonal change

Research has revealed links between hormonal changes, such as that evidenced in stress, and improvement or worsening of psoriasis symptoms. Commonly people with
Psoriasis indicate worsening (flare-up) of their symptoms during stressful events (Xhaja et al., 2014). It has been theorised that altered hypothalamic-pituitary-adrenal response from higher circulating levels of hormones, such as corticotrophin-releasing hormone, may be associated with these flares; however, more research is needed (O’Kane et al., 2006, Richards et al., 2005). Conversely, in pregnant psoriatic women, higher levels of oestrogen correlate with improvement in psoriasis symptoms (Murase et al., 2005). Anti-psoriatic action may be due to the ability of oestrogen to inhibit key psoriasis cytokine TNF-α (Ceovic et al., 2013). As oestrogen and progesterone levels fall in women during puberty, post-partum or menopausal stages, the opposite often ensues and psoriasis symptoms increase.

**Cigarette smoking**

Found to be an independent risk factor for psoriasis in men and women, cigarette smoking correlates with increased incidence of psoriasis. As smoking duration increases so does the risk to psoriasis development; for instance, risk is highest among smokers of 65 or more cigarette packs per year for 30 or more years. In turn, psoriasis risk reduces with time since smoking cessation (Li et al., 2012c, Setty et al., 2007). The interaction between cigarette smoking and psoriasis is most likely due to the immune-suppressing effects of the chemical constituents of cigarettes, as well as the increase in oxidative stress (Sopori, 2002, Attwa and Swelam, 2011). In addition to acting as a trigger, smoking can also exacerbate psoriasis symptoms, perhaps owing to higher level of circulating Th17 in smokers, a pathway well evidenced in the inflammatory loop of psoriasis (Torii et al., 2011).
Sunlight

Evidence indicates that sunlight exposure can improve psoriatic plaque symptoms. Conversely, lack of sunlight is known to aggravate psoriasis plaques. The therapeutic relationship between sunlight and psoriasis is related to the beneficial production of vitamin D, where ultraviolet radiation (UV) is necessary for basal epidermal vitamin D synthesis (Ryan and Menter, 2012) (Holick, 1981). Promoting keratinocyte differentiation, the action of vitamin D on psoriasis is likely related to its ability to act as an anti-inflammatory and anti-angiogenic (Oikawa et al., 1990). Vitamin D level concentration in psoriatic people tends to be lower than in healthy controls (El-Moaty Zaher et al., 2013). Therapies such as UVB phototherapy aim to enhance vitamin D production to reduce psoriasis plaque severity. Vitamin D analogues are commonly used topically (e.g. calcipotriol) and are understood to emulate vitamin D by reducing Th17 pathways and other key chemo-attractants. Without regulation these would otherwise signal cytokine production by keratinocytes, amplifying the psoriasis immune response (Hegyi et al., 2012).

Bacterial or viral infection

Psoriasis development has been linked to bacterial and viral infection, with reports indicating they may trigger and/or exacerbate psoriasis symptoms (Travers et al., 1999). Most likely, bacterial and viral impacts on psoriasis pathogenesis are due to previous antigen presentation in pathogenic tissues (e.g. throat) and subsequent production of pathogenic T-cells. These T-cells migrate to the skin dermis and are presented to antigen-presenting cells (APCs), triggering or contributing to epidermal and dermal inflammation (Valdimarsson et al., 2009). Staphylococcal exotoxin is commonly found
on the surface of psoriasis-affected skin, although its part, if any, in psoriasis pathogenesis is unclear (Leung et al., 1993).

Likely related to lymphatic function and formation of antigens, reports identify higher prevalence of psoriasis (most typically guttate type) after throat infection by b-haemolytic streptococci (tonsillitis), and it is known these infections exacerbate psoriasis symptoms (Whyte and Baughman, 1964, Telfer et al., 1992, Fry et al., 2006, Horiuchi et al., 1998, Gudjonsson et al., 2003, Wardrop et al., 1998). Controversial yet significant evidence suggests that tonsillectomy after streptococcal infection is an effective treatment for psoriasis (Wu et al., 2013). However, evidence should be evaluated with caution, more long-term controlled studies are needed to evaluate true risks and benefits of tonsillectomy intervention (Rachakonda et al., 2014).

Viral diseases such as herpes zoster, hepatitis C virus and chickenpox have also been implicated with the development and/or exacerbation of psoriasis (Blanco Gonzalez et al., 2000, Failla et al., 2012, Veraldi et al., 2009, Gabr et al., 2014). Indeed, people with hepatitis C typically have more severe psoriasis than those without (Taha et al., 2014). The human immunodeficiency virus (HIV) has also been connected with psoriasis, likely due to an immunodeficiency drop in CD4+ lymphocyte (Montazeri et al., 1996).

*Helicobacter pylori* bacterial infection has been implicated with increased severity of psoriasis (higher PASI than non-*H. pylori* psoriatic cases). There is also a subsequent greater improvement in symptoms when such cases are concurrently treated for *H. pylori* and psoriasis rather than anti-psoriatic alone (Onsun et al., 2012). The precise involvement of *H. pylori* in psoriasis, however, is still unknown.
Other factors

The Koebner phenomenon, in which lesions appear along a site of injury, can ensue in people with psoriasis following localised trauma such as from tattoos, burns, animal and insect bites, skin grafts, and surgical incision, but is less frequent in those without previous psoriasis (Zitelli and Lucky, 2013).

2.2.4 Summary of aetiology and pathogenesis for psoriasis

Various triggers and aggravators of psoriasis have been identified, and it is likely that many others remain undiscovered. Evidence suggests psoriasis pathogenesis and aetiology have genetic components that may be complicated or exacerbated by external factors. In the future, treating physicians may need to identify psoriasis triggers for each patient to decide which therapy should be administered. While it is possible to reduce known risk factors that trigger or exacerbate psoriasis, future immunising drug therapies may be developed to protect high-risk patients against development of psoriasis. New research techniques with the ability to screen for psoriasis indicators at the genome level may provide such immunisation opportunities and lead to development of a range of pharmaceuticals that target known psoriasis sequences. It is clear that understanding the pathogenesis and aetiology of psoriasis is paramount for the eventual discovery of a cure for psoriasis.

2.2.5 Exploring potential biological marker targets for psoriasis

Part of the hunt for a psoriasis cure involves identification of psoriasis-related biological markers. Such markers may also aid in the diagnosis and/or monitoring of psoriasis and its treatment. Recently, promising research has emerged indicating that such psoriasis-specific markers do exist, such as neutrophil to lymphocyte ratios (Ataseven et al., 2014). Although as yet no single determinant marker has been identified, many
cytokines are recognised to be involved in psoriasis pathogenesis, and changes in their concentrations can assist with diagnosis, evaluate the efficacy of treatment or correlate directly with psoriasis severity (Bonifati and Ameglio, 1999). Unfortunately, despite identification of such cytokines none have yet proven to be reliable and consistent markers for such symptom clearance and subsequently are insufficient on their own to evaluate the clinical benefit of a given therapy or indicate when it should be changed or ceased (Griffiths and Barker, 2007).

To further explore therapeutic impacts on biological concentrations of various cell types, the current pilot study collected plasma samples of participants at various time points to evaluate changes in a number of inflammatory factors. For further details on the inflammatory factors that have been implicated in psoriasis see Chapter 7 (Development of a pilot randomised, placebo-controlled parallel design study).

2.2.6 Research gaps of psoriasis aetiology and pathogenesis

Despite available evidence for psoriasis pathogenesis and key identification of many key cytokines in psoriasis, researchers have identified a number of knowledge gaps. While some biological markers may help evaluate treatment response, such markers are not specific to psoriasis. Discovery of a new subset of CD4+ cells known as follicular helper T-cells provides promise that psoriasis-specific markers may be identified in the future (DaErme et al., 2014, Niu et al., 2015). Encouragingly, recent research has also identified entire pathways that are more active in severe than mild psoriasis (Nikamo et al., 2015).

There is a push from research experts for further large, broad, longitudinal studies investigating further in areas such as: the natural history of psoriasis; genetic factors that influence clinical phenotypes; severity trends in incidence over time; prevalence of
associated co-morbidities; and the spontaneous remission of psoriasis (Ryan et al., 2013). Such research will assist in progression towards a cure for psoriasis.

2.3 The epidemiology and socioeconomic burden of psoriasis

Psoriasis is distributed relatively equally between males and females, with mean age of psoriasis development calculated to be 33 years of age. For the majority of psoriasis cases onset occurs between 11 and 20 years old, with 75% of cases developing before age 46 (Nevitt and Hutchinson, 1996). Research generally suggests increasing psoriasis incidence with increasing age. Adolescents tend to have a low prevalence (0.5–2%), however, as is found in other age groups they most commonly present with the vulgaris phenotype (74%). Interestingly, children with childhood asthma have increased risk of developing psoriasis (Parisi et al., 2013, Tollefson et al., 2010).

With figures varying among population demographics, ethnicity has been clearly indicated as a factor that determines incidence of psoriasis. Higher psoriasis incidence is reported in Caucasians than Asians or people of African descent (Boehncke et al., 2010). There has been no reported incidence of psoriasis in the Australian Indigenous population, suggesting they are not genetically susceptible to its development (Green, 1984). Australia’s psoriasis prevalence has been estimated to be between 3.5 and 6.6%, but no health cost has yet been applied to this figure (Plunkett et al., 1999, Kilkenny et al., 1998). Considering many psoriatic therapies are subsidised in Australia through Medicare (e.g. acitretin 25mg pack of 100 reduced from $334.55 to $36.90 for the consumer), new interventions that provide substantial savings would be welcome (Australian Government - Department of Health, 2014).

Globally, the prevalence of psoriasis varies considerably. A large telephone survey involving both the US and a number of European countries estimated global prevalence
to be between 1.4% and 3.3% (Lebwohl et al., 2014). In the US, prevalence is between 1.2% and 5.1% (Lima et al., 2012, Stern et al., 2004, Kurd and Gelfand, 2009). In Malaysia, psoriasis incidence was calculated at 9.5%, however, the study was conducted in a dermatological outpatient clinic so results would be expected to be higher than in the general population (Sinniah et al., 2010). Studies conducted in the UK report psoriasis prevalence of between 1.3% and 1.9% (O’Neill and Kelly, 1996) (Seminara et al., 2011). In Europe, there is substantial variation in reported incidence of psoriasis, including: Croatia 1.5% (Barisic-Drusko et al., 1989); Denmark 2.5% for women and 3.2% for men (Brandrup and Green, 1981); France 5.2% (Wolkenstein et al., 2009); and Norway between 4.8% and 8.5% (Bo et al., 2008, Kavli et al., 1985). More research is needed to examine the incidence disparities between age and race groups, and may provide further insight into psoriasis aetiology and pathogenesis (Ryan et al., 2013).

In the United States of America in 2011, annual healthcare costs related to psoriasis were estimated at US$11.3 billion and by 2013 this had risen to $11.8 billion (Staidle et al., 2011, Vanderpuye-Orgle et al., 2015). Related losses in productivity are more difficult to estimate, but estimates tend to be well over $10 billion (Mustonen et al., 2015, Brezinski et al., 2015). Given the increasing cost of psoriatic treatments, as new drugs such as biologics enter the market, this figure will continue to rise (Schmitt and Ford, 2006).

Further research into employment and income availability of sufferers would help evaluate the socioeconomic impacts of the disease (Ryan et al., 2013). Introduction of new expensive psoriasis drugs, such as biologics, require both direct and indirect cost evaluation along with clinical efficacy assessment to assist clinicians and governments develop cost-effective treatment guidelines (Ryan et al., 2013). Further, comparative
studies between different drugs may help determine intervention superiority relative to their efficacy and cost (Conway and Clancy, 2009).

2.4 Disease differentiation of psoriasis vulgaris

Currently, no specific diagnostic tests for psoriasis exist; however, tests (e.g. biopsy and microscopic examination) can be performed to differentiate psoriasis from diseases that are visually similar (such as seborrheic dermatitis, lichen planus and sub-acute cutaneous lupus erythematosus) (World Health Organization (WHO), 2013). A lack of diagnostic tests requires clinicians to visually diagnose psoriasis, using presentation of key characteristic features and clinical progression. This requires the physician to inspect the affected skin area, review the patient’s medical history and evaluate possible precipitating causes (Callen et al., 2003).

The lesioned areas of typical psoriasis vulgaris present silver (grey) or white flaking, which may be thicker than unaffected skin, with lesions individual or merged into larger plaque areas (Dermatology Expert Group, 2004). As a result of blood profusion from increased angiogenesis, affected areas may present with erythema (redness) and can be accompanied by pruritus (itching) (Figure 2.1: Psoriasis vulgaris lesion) (Burden et al., 2010). A key feature of psoriatic skin, often diagnostic, has long been the Auspitz sign, where slight abrasion (e.g. scratch) to an affected skin area leads to pinpoint bleeding. Unfortunately, the Auspitz sign alone is not sufficient to diagnose psoriasis, as is not specific to psoriasis and is not present in all psoriasis cases (Bernhard, 1990). In some psoriasis cases fingernail changes such as pitting, onchylosis (detachment of the nail) and/or subungual hyperkeratosis (excessive nail proliferation) may help diagnose psoriasis (Figure 2.9) (Cohen et al., 2012).
Figure 2.9: Characteristic pitting, onychlosis and subungual hyperkeratosis of psoriatic nails (DermNet New Zealand Trust, 2014)

As diagnosis requires a reasonable degree of physician experience and judgement, psoriasis may be mistaken for other dermatological conditions, such as eczema, fungal infection or skin cancer. Patients presenting to general practitioners (GPs) may be referred to a dermatologist for definitive diagnosis, or a skin biopsy may be taken to be viewed under a microscope to detect key histological characteristics. Under dermoscopy, for instance, psoriatic scales are typically white whereas those of eczema are more commonly yellow (Xu et al., 2014). Compared with normal skin (Figure 2.10), psoriatic skin has marked histological difference, with obvious inflammatory signs such as lymphocyte and neutrophil infiltration, thickening of dermal (acanthosis) and epidermal (keratosis) layers, increased vascularity and, due to incomplete cell differentiation, keratinocyte cells show presence of nuclei (parakeratosis) (Figure 2.11) (Menter et al., 2008). Increased vascularity is likely due to increased levels of vascular endothelial growth factor (VEGF) receptors on keratinocytes (Man et al., 2008).
**Figure 2.10:** Histologically normal skin appearance (DermNet New Zealand Trust, 2014)

**Figure 2.11:** Histologically psoriatic appearance skin (Adapted from: (DermNet New Zealand Trust, 2014))
More recently, the dermoscopy techniques reflectance confocal microscopy and confocal laser scanning microscopy have shown possible usefulness in diagnosis and monitoring progression of psoriasis plaques (Hui and Ai, 2013). Such advanced dermoscopy techniques can reveal micro-morphological aspects such as epidermal spongiosis not evident in histopathological examination (Caruntu et al., 2014). Following successful treatment and macro-improvement of psoriasis lesions, skin samples show histopathological evidence of decreased parakeratosis, Munro’s micro abscesses, acanthosis, pustules of Kogoj, lymphocyte and neutrophil infiltration, granular layer reduction, spongiosis and angiogenesis (Ozkanli et al., 2014). With further research and validation, more non-invasive techniques may be employed in the future to diagnose and assess progression of psoriasis (Lacarrubba et al., 2015).

2.5 Measuring psoriasis severity

Clinically, psoriasis severity is typically determined via visual assessment of skin lesions and evaluation of the size of the surface area involved. While many different methods have been proposed for severity measurement, the most well-known measure is the psoriasis area severity index (PASI)(Cabrera et al., 2015). Despite common global usage, since its inception, variation in classifying severity has persisted, due largely to the subjective decision-making required by assessors (Finlay, 2005). Typically, psoriasis is divided into three classifications: mild, moderate or severe. However, determining where PASI scores for each rating should start and finish has also been contentious. As a result of this inconsistency, a European consensus was developed by a group of specialists to standardise classifications for severity of psoriasis and provide guidelines for measuring improvement (Mrowietz et al., 2011).
Even after development of these guidelines, researchers and clinicians continue to search for new instruments that are effective, suitable for all degrees of psoriasis, simple to conduct and reflect both psoriasis severity and QoL (Gottlieb et al., 2014). International health bodies now recognise that psoriasis severity measures should not only be based on symptom severity, but also should consider QoL measures, both physical and psychological. This adds another level of complexity to discussion surrounding suitability of psoriasis severity measurement instruments (Kimball et al., 2005) (Magin et al., 2011). Researchers have attempted to reduce confusion by developing protocols and guidelines aimed to simplify severity assessment, such as the rule of tens, which proposes psoriasis is classified ‘severe’ if body surface area (BSA) coverage is >10%, psoriasis area severity index (PASI) score >10 or dermatology life quality index (DLQI) score >10, although uptake of such protocols by clinicians has not been consistent (Finlay, 2005). This section describes available severity instruments and QoL measures for psoriasis and discusses their strengths and weaknesses.

2.5.1 Common psoriasis severity measures

**Body surface area**

Rarely utilised alone to assess severity, body surface area (BSA) only measures surface area coverage of psoriatic lesions. Instead, BSA is typically combined with specific psoriasis symptoms such as erythema and scaling in order to get a clinically meaningful measure of severity. Considered a beneficial measure for treatment selection and monitoring treatment change, BSA change or lack of change can signal whether therapy should be altered or continued (i.e. when a treatment has substantially reduced erythema and induration, yet BSA has not changed, a different type of therapy may be substituted to enhance effect) (Van Voorhees and Fried, 2009).
Psoriasis area and severity index (PASI)

In use for over 30 years, the PASI is the most well-known psoriasis-specific instrument and its reliability and validity has been well evaluated (Mrowietz et al., 2011, Spuls et al., 2010, Fredriksson and Pettersson, 1978, Cabrera et al., 2015). Calculated using a somewhat complex formula, the PASI first involves estimation of the affected skin surface area, dividing the body into four regions and assigning a percentage BSA to each: head (10%), upper extremities (20%), trunk (30%) and lower extremities (40%). The lesion area for each division is then allocated a score between 1 and 6 (where 1 is <10% BSA affected, 2 is 10–29% BSA, 3 is 30–49% BSA, 4 is 50–69% BSA, 5 is 70–89% BSA and 6 is 90–100% BSA). After surface involvement evaluation, the degree of erythema (redness), desquamation (scaling) and induration (thickness) of the psoriatic plaques is assessed. For each symptom a score of 0–4 is given: 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe. The figures are then applied to a mathematical formula and a total score result is produced ranging from 0 to 72, with higher scores representing greater severity of disease (Table 2.1).
### Table 2.1: Psoriasis area severity index (PASI) score calculation

<table>
<thead>
<tr>
<th>Plaque characteristic</th>
<th>Rating</th>
<th>Body region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Head</td>
</tr>
<tr>
<td>Erythema</td>
<td>0=none</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1=slight</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2=moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3=severe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4=very severe</td>
<td></td>
</tr>
<tr>
<td>Thickness</td>
<td>0=none</td>
<td></td>
</tr>
<tr>
<td>Scaling</td>
<td>4=very severe</td>
<td></td>
</tr>
</tbody>
</table>

Add each of the three scores together for each body region giving four separate subtotals

<table>
<thead>
<tr>
<th>Sub totals</th>
<th>A1=</th>
<th>A2=</th>
<th>A3=</th>
<th>A4=</th>
</tr>
</thead>
</table>

Multiply each subtotal by amount of body surface area represented by that region i.e. A1×0.1 for head, A2×0.2 for upper limbs, A3×0.3 for trunk, A4×0.4 for lower limbs

<table>
<thead>
<tr>
<th>Degree of involvement of each body region affected (0–6)</th>
<th>0=none</th>
<th>1=1–9%</th>
<th>2=10–29%</th>
<th>3=30–49%</th>
<th>4=50–69%</th>
<th>5=70–89%</th>
<th>6=90–100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1=</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2=</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B3=</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B4=</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

For each body region multiply B1, B2, B3 and B4 by the % body region affected (0–6) to give subtotals for each body region

<table>
<thead>
<tr>
<th></th>
<th>B1×score=C 1</th>
<th>B2×score=C 2</th>
<th>B3×score=C 3</th>
<th>B4×score=C 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1=</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2=</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3=</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4=</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Final PASI score=sum of C1+C2+C3+C4  
PASI (0–72)=

(Adapted from severe chronic plaque psoriasis initial PBS authority application, Australian Government, Department of Health & Ageing, Medicare Australia, 2005)

Using the PASI for severity assessment helps ensure psoriasis severity measurement is similar between cases. Combining lesion size, location and appearance of lesions calculates severity with a relative weighting applied to key symptoms of psoriasis. Therefore, temporary, inconsequential environmental reactions affecting one aspect of the PASI, for example, erythema will have an effect on the final score.

Often reported by clinical trials as overall mean percentage PASI improvement, trials may also add a responder analysis, with responders being defined as those
patients who have reached a predetermined percentage PASI improvement, for example, PASI 50 (the percentage of patients who have reached a level of 50% PASI reduction from baseline). Responder analyses permit intention-to-treat analysis of the percentage of patients who achieve a predetermined level to be considered treatment success (Weisman et al., 2003). The highest typically reported responder outcome for psoriasis is PASI 90, well above most guideline recommendations for evaluating effectiveness of a therapy (commonly PASI 50 or 75), it is most commonly utilised for strong action pharmaceutical trials such as those investigating the use of biologics for psoriasis (Reich et al., 2012, The Australian Government, 2004, Food & Drug Administration, 1998).

It should be noted that following treatment, if BSA of lesions does not change, but erythema, induration and scaling do then PASI 75 is not achievable. Similarly, PASI 75 cannot be reached if there is dramatic reduction in BSA, but no change to erythema, induration and scaling of remaining plaques. Thus, guidelines sometimes consider PASI 50 a suitable outcome measure when assessing clinical efficacy of an intervention (Carlin et al., 2004).

Despite its popularity, the PASI still has limitations. It has been argued that the PASI is not comprehensive enough, ignoring symptoms such as itching (pruritus) and pain, which can play significant roles in the personal experience of psoriasis severity (Nast and Schmitt, 2013). The PASI has also been criticised for a lack of sensitivity in milder conditions, although researchers have recently modified the PASI to improve its sensitivity (Kolios et al., 2015). As the PASI requires subjective estimation based on visual appearance, assessor variation may affect its accuracy and consistency. Furthermore, the possible variation in induration, scaling and erythema over a single plaque makes standardisation of PASI measurement more difficult.
**Self-administered PASI**

The self-administered PASI has been developed to utilise the patient’s own observations of disease severity. The instrument is designed for the patient to give an objective score, independent of their subjective impression of their ‘overall’ disease severity. This method is more suitable to large epidemiological studies where the PASI may not be feasible to collect in person. A silhouette of the body is given to participants to shade in the affected areas and a visual scale to rate and record the erythema, induration, and scaling of an average lesion. Test–retest reliability of the self-administered PASI is quite good, with variability of less than 2%; validity has been also been demonstrated (Weisman et al., 2003).

**2.5.2 Other psoriasis severity measures**

Ongoing research to improve specificity and relevance of available psoriasis symptom measure instruments continues, as does research developing entirely new enhanced instruments. Over 50 different psoriasis measurement instruments have been identified, each with its own inherent strengths and weaknesses, and none yet has been proven to be without fault (Spuls et al., 2010). Subsequently, further instruments have been developed to meet specific needs of researchers or clinicians and as such many are not intended for universal use for psoriasis. Research instrument selection should consider the outcome researchers seek and should reflect some degree of clinical relevance if assessing treatment (Gottlieb and Armstrong, 2013). This section briefly discusses some of the less commonly used severity measures for psoriasis.

**Physician’s global assessment and physician’s static global assessment**

The physician's global assessment (PGA), otherwise known as the investigator’s global assessment, is often considered the next best alternative to the PASI, and some have
suggested it should be utilised more in clinical trials in collaboration with the PASI (Nast and Schmitt, 2013). The PGA and PASI are evidenced to closely correlate in clinical trials investigating moderate to severe psoriasis, although the PGA is not as well validated as the PASI (Robinson et al., 2012). The PGA was primarily designed to show improvement compared with baseline disease severity, quantified on a scale (for example, from 1 to 6). Selection of scales for PGA varies considerably, from 2-point scales up to 11-point scales, however the 6-point scale is the most commonly utilised (Langley et al., 2013). However, this approach is limited to the investigator’s ability to remember the disease severity observed at the previous visit, with photographs often used to assist recollection. A strength of the PGA is its relevance to clinical practice but the degree of assessor subjectivity is a weakness (Weisman et al., 2003).

More recently, the PGA has been further developed so assessment is a measurement made at a single moment in time, without need for comparison with previous results, known as the physician’s static global assessment (or physician’s static global response). This method uses, for example, 0=all clear, 1=nearly clear, 2=mild, 3=moderate or 4=severe.

Lattice system physician’s global assessment

Based on the PGA, the lattice system physician’s global assessment allows quantitative measurement of disease severity by integrating involved BSA range (%) and overall plaque morphology using a 4-point scale (none to marked) (Langley and Ellis, 2004). One benefit of the lattice system PGA is that rather than apply equal weighting to key psoriasis symptoms it applies more weight to plaque elevation than to scale or erythema. It does this because the degree of scale typically varies with hydration or emollients, as can the degree of erythema. Plaque elevation is also related to both characteristic psoriasis processes of inflammation and proliferation (Langley and Ellis,
The same level of experience needed to ensure consistent reproducible PASI scores is not necessary for the lattice system PGA, which appears to be far more reliable and with reduced inter-rater variation (Langley and Ellis, 2004). Results are entered into a computerised lattice algorithm, hence its name, where clinically meaningful improvement is more clear than that of PASI (Chow et al., 2015). It has proven to have greater construct validity and correlation, with DLQI than the physician’s static global assessment (Simpson et al., 2015).

**Psoriasis disability index**

First developed around 30 years ago, the psoriasis disability index has since been improved and now consists of 15 questions, scored along either a visual analogue scale (1–7) where scores range from 15 to 105, or via tick box selection (0–3), with a final score between 0 and 45 (Finlay and Kelly, 1987). Regardless of scale type, an increase in score signals increasing disability, or severity. An advantage of the psoriasis disability index is that it is based on actual psoriasis patient feedback, and so might be a more acceptable measure for psoriasis sufferers (Lewis and Finlay, 2005). However, differences in scale options makes pooling of results between studies difficult and can create confusion between clinicians. Thus, to ensure consistency between studies and simplify clinical assessment, recent recommendation is to use only the tick box scale. Another benefit of the psoriasis disability index is its assessment of psoriasis symptoms as well as QoL impacts. However, it assesses neither exceptionally well, for instance, it does not include questions on emotions, which are deemed to be an important aspect for assessing QoL (Lewis and Finlay, 2005).

**Psoriasis symptom inventory**

A relatively new developed instrument, the psoriasis symptom inventory is an eight-item patient-reported outcome measure for assessing psoriasis symptom severity
Developed in conjunction with the US Food and Drug Administration (FDA), and designed to fulfill insufficiencies of other instruments, it was intended to provide information centered on patient-reported outcomes. Unfortunately, the psoriasis symptom inventory is currently only rated as highly acceptable for psoriasis vulgaris. However, it does provide more outcome detail than the PASI, making it potentially useful for clinical trials (Bushnell et al., 2012).

**National psoriasis foundation psoriasis score**

The national psoriasis foundation score is another instrument intending to encompass both QoL as well as symptom severity in order to calculate a simplified assessment of severity for psoriasis. The national psoriasis foundation score was originally designed by dermatologists to measure disease severity endpoints, which were relevant to clinically significant improvement in psoriasis (Gottlieb et al., 2003). Its scoring system combines five primary endpoints: (1) assessment of induration of two target lesions, rated from 0 (clear) to 5 (severe); (2) change in BSA coverage of disease relative to baseline, expressed as a percentage from 0%=0 (clear) to 100%=5 (no change or worse); (3) physician’s static global assessment, from 0 to 5; (4) patient’s global assessment, from 0 (clear) to 5 (worst the psoriasis has ever been); and (5) itching graded numerically from 0 (clear) to 5 (severe). The score can be reported as a total from 0 to 30 or as individual scores (Weisman et al., 2003). Despite its apparent appropriateness as a measure and its correlation with the PASI and PGA, uptake of its use has been low, with most published trials using the PASI, PGA or other instrument outcome measures.

**Reflective evaluation of psoriasis efficacy of treatment and severity**

A more recently developed instrument, the reflective evaluation of psoriasis efficacy of treatment and severity has the potential to fill deficiencies of other instruments. Consisting of 29 categorised items related to either psoriasis severity or treatment...
efficacy, the reflective evaluation of psoriasis efficacy of treatment and severity was designed to measure perceived disease severity and treatment efficacy. Within the severity category three sub-dimensions exist: disease course, symptoms and the impact of psoriasis. Each item is scored from 0 to 100, with higher scores indicating greater severity or more effective treatment. Internal reliability and validity of the instrument are good, as is the response to change. Furthermore, it measures joint pain in arthritis sufferers, which the PASI does not. Although a promising instrument, it was initially validated in a French population so future translation and validation is still needed in other populations (Gilet et al., 2014).

2.5.3 Quality of life measures commonly utilised for psoriasis

As mentioned previously, early treatment goals centred solely on improving the symptomatic appearance of psoriatic lesions, however as psoriasis research has expanded, the importance of QoL impacts has gained significant weight. Considerable research highlights the importance of emotions and the psychological wellbeing of people with psoriasis (Dalgard et al., 2014). Such aspects impact on the daily life of many sufferers and in turn affect their routine activities or in some cases may prevent activity entirely (Dubertret et al., 2006). A survey by the national psoriasis foundation reported psoriasis has a negative effect on the life of around 79% of sufferers (Krueger et al., 2001). Recently, international treatment guidelines have placed QoL measures on equal or almost equal footing as symptom measures when evaluating psoriasis severity and/or selecting treatment. Improvements in QoL are hence viewed as an important measure for treatment outcomes. As such, counselling or other psychological therapies are often advised in conjunction with psoriasis-specific therapy (World Health
Organization (WHO), 2013). This push by governing bodies has also generated an increased emphasis on monitoring QoL in clinical trials (Basra and Hussain, 2012).

**Dermatology life quality index**

First developed in the 1990s for daily clinical practice, the dermatology life quality index is generated by a compact questionnaire and has gained prominent use in clinical trials. Reliability and validity have been established, with greater severity of disease positively associated with higher scores (Weisman et al., 2003). The questionnaire consists of 10 questions, each with four or five tick box response options: ‘very much’, ‘a lot’, ‘a little’, ‘not at all’, and for questions 3–10 ‘not relevant’. Each selection corresponds to a score from 0 (not at all or not relevant) to 3 (very much). In addition, question 7 asks if work or study was prevented due to disease, where the value of ‘yes’ is 3. The highest potential total score of 30 indicates most severe QoL impact (Finlay and Khan, 1994). The dermatology life quality index has been translated into over 20 languages and has a separate instrument for children (Lewis and Finlay, 2004). It is still not without fault, some suggesting it requires improvement, as some items are ill fitting. The instrument has also been accused of not being sensitive enough to measure mild illness change (Twiss et al., 2012). In addition, while providing good insight into QoL for sufferers, the dermatology life quality index is insufficient for calculation of treatment cost effectiveness, requiring it to be combined with further generic QoL measures, such as the EuroQol 5D, to provide more clinically relevant results (Norlin et al., 2012).

**Skindex**

Some researchers for its reduced floor effect favour the Skindex instrument, that is, it has a greater reliability and sensitivity to lower limit data compared with other QoL measures, such as the dermatology life quality index. Another advantage of the Skindex is its high cross-cultural validity, beneficial for use in large international studies.
(Bronsard et al., 2010). Designed to compare QoL differences between different dermatological diseases and provide data on their change over time, the Skindex is also sensitive to severity change in milder conditions (Fernandez-Penas et al., 2012). Originally containing 61 items, to improve ease of administration and construct validity it has since been refined to 17-item and 29-item Skindexes (Chren et al., 1996, Chren et al., 1997, Chren et al., 2001).

Each item in the Skindex has five response options – ‘never’, ‘rarely’, ‘sometimes’, ‘often’ or ‘always’ – which correspond to scores from 1 (never) to 5 (always). These scores are then transferred to a linear scale between 0 and 100 (0=never, rarely=25, sometimes=50, often=75 and always=100) (Chren, 2012). Instrument items can then be further classified (grouped) into scores for different domains: degree of symptoms, psychosocial functioning or emotional status. This unique strategy allows an overall mean score to be calculated, as well as separate construct group scoring, which provides opportunity for comparison between domain groups.

2.5.4 Other psoriasis quality of life measures

Numerous other QoL instruments exist, some specific to dermatology, providing more comprehensive assessment than generic QoL instruments, but many are not suitable for psoriasis. For instrument selection, it is important for researchers to consider the nature of the data being collected and intended statistical analyses techniques. For instance, the QoL instrument selected should be sensitive enough for the targeted psoriasis severity population, or if socioeconomic impacts such as productivity are central to study outcomes, then an instrument that enables such calculation should be utilised. Generic instruments, although often less sensitive, can provide beneficial data to compare psoriasis to other diseases, which can be useful for informing health policy
(Weiss et al., 2002). Such research need has seen development of QoL mixed measure instruments, consisting of both specific and generic items (Bhosle et al., 2006). This section discusses other QoL instrument measures utilised for evaluating psoriasis QoL change.

Dermatology quality of life scale

Derived from real patients, the dermatology QoL scale assesses the psychological and daily activity impacts of dermatological disease. Although when initially developed and validated it was not psoriasis-specific, the majority of original test participants were suffering from psoriasis. Consisting of 29 questions relating to psychosocial state (n=17) and daily activities (n=12), each is rated on a 5-point Likert scale (‘very slightly or not at all’, ‘a little’, ‘moderately’, ‘quite a bit’ or ‘extremely’). It further groups items into subscales similar to the Skindex, but is more specific: ‘psychosocial’ despair, irritableness and distress; and summer, social and sexual ‘activities’ (Morgan et al., 1997). With good construct validity, the instrument has had greater uptake in clinical trials than in general practice (Bronsard et al., 2010).

Psoriasis index of quality of life

While being psoriasis-specific for QoL, unlike other QoL measures, the psoriasis index of quality of life bases assessment around a needs model for the impact psoriasis has on QoL. Again, an instrument derived from patient response, the psoriasis index of quality of life was created under the premise that QoL is reduced when needs are not met. Consisting of 25 items validly developed using Rasch modelling, the maximum score of 25 indicates greatest possible life impairment (McKenna et al., 2003). Despite the psoriasis index of quality of life focusing on the needs of people with psoriasis it has experienced low uptake in clinical trials (Bronsard et al., 2010).
**EuroQol 5D**

A generic instrument, the EuroQol 5D was designed for use in large population health surveys. The first of three components assesses health state over five criteria: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each criterion has three response options: ‘no problem’, ‘some problem’ or ‘extreme problem’. The second component classifies each person into one of 243 distinct health statuses. The third component uses a visual analogue scale to self-rate health status (0 equals ‘worst imaginable health state’ and 100 equals ‘best imaginable health state’)(EuroQol Group, 1990). While not being specific for psoriasis, it has often been utilised for psoriasis as it provides data that are helpful for cost–benefit analysis (Norlin et al., 2012).

**Short form health survey (SF-36)**

Another generic instrument, the short form health survey (SF-36) is one of the most widely used generic instruments for assessing health and life quality in disease. With 36 items it covers eight different domains: physical activities, social activities, usual physical role activities, bodily pain, general mental health, usual emotional role activities, vitality, and general health perception. Unlike other instruments it uses a mixture of different rating scales where a higher score indicates improved QoL (Ware and Sherbourne, 1992). The SF-36 has successfully shown the significance of psoriasis disease, where its impact has been rated similar to that of severe community diseases (e.g. cancer, chronic lung disease or depression) (Rapp et al., 1999).

**Psoriasis life stress inventory**

Designed to assess stress in people with psoriasis, the psoriasis life stress inventory was developed based on clinical experience and then tested in a psoriasis population. The psoriasis life stress inventory is a very specific scale and so is not widely used in trials. Consisting of 15 items rated on a four-point scale of frequency of experience (0=‘not at
all’ to 3=’a great deal’), the total score can be between 0 and 45 (Gupta and Gupta, 1995). The psoriasis life stress inventory asks for each item to be rated over the previous four weeks, so it may not be sensitive to acute exacerbations as short-term reassessment in follow-up sessions i.e. weekly or fortnightly becomes redundant. Such deficiencies contribute to a lack of flexibility for use, hence in most cases where general QoL measures are needed other instruments provide a better option, however it is worth considering for stress-specific impacts (Fortune et al., 1997).

Health assessment questionnaire

Assessing health quality across five domains – disability, pain, medication effects, costs of care and mortality – the health assessment questionnaire can also be administered in a shorter two-page version that only measures disability and pain (Bruce and Fries, 2005). If subjects lack significant pain or disability, the domains have limited applicability to psoriasis; however, it may be a useful instrument for psoriasis complicated by arthritis. The constructs have more focus on severe conditions and would probably not be sensitive enough for mild conditions of psoriasis.

Koo–Menter psoriasis instrument

Specifically designed for measuring QoL prior to determining if systemic treatment is warranted, the Koo–Menter psoriasis instrument is more an aid to physicians than a viable instrument for clinical trial use. The instrument combines QoL questions with psoriasis severity assessment and records BSA. The outcome of the instrument determines whether a patient is a suitable candidate for systemic therapy (Feldman et al., 2005).

Impact of psoriasis questionnaire

The impact of psoriasis questionnaire was originally developed as part of a study investigating a cohort of psoriasis patients receiving psoralen plus ultraviolet light
therapy. The questionnaire originally consisted of 16 items based on questions used in another instrument, the medical outcomes study short form general health survey. Items are rated on a 5-point ordinal scale (1='none', 2='some', 3='moderately', 4='quite a bit' and 5='extreme'), further grouped as either physical, psychological or social with a final score ranging from 0 to 64 (McKenna and Stern, 1997). Since inception it has undergone further refinement using Rasch analysis and the number of items has reduced to 11 (Nijsten et al., 2006). Since refinement there has been little uptake in psoriasis trials despite evidence it has reasonably good reproducibility and acceptability (Bronsard et al., 2010).

**Psoriasis family index**

A novel psoriasis-specific QoL instrument, the psoriasis family index, measures QoL of family members and partners of psoriasis patients. Item were created based on interviews at a dermatology outpatient clinic, with validation into a 20-item instrument (Eghlileb et al., 2009). Further testing of the instrument to assess its reliability is needed and as yet the instrument has not had significant uptake.

**Salford psoriasis index**

Assisting clinicians to manage the care of psoriasis patients, the Salford psoriasis index is a 3-component system consisting of current psoriatic extent score (based on PASI banding and valued from 0 to 10), psychosocial impact score and a severity score for historical disease. For the psychosocial section patients mark on a visual analogue scale the extent that psoriasis impacts on their everyday life (0='not at all affected' and 10='completely affected'). The historical severity score is based on treatment history of the patient. Each score is reported separately (e.g. 5:5:0) so clinicians can quickly assess patients and choose appropriate treatments. A benefit of the Salford psoriasis index is that it combines comprehensive physician and patient input, as well as an objective
view of disease history, to give insight into difficulties of psoriasis treatment (Weisman et al., 2003, Kirby et al., 2000). Recently, the Salford psoriasis index has been modified further into two versions with strong reliability: a professional version designed for completion by health professionals and a patient self-assessment version (Chularojanamontri et al., 2013). The relevance and design of the Salford psoriasis index is more suited to clinical settings than research trials.

2.5.5 Summary of assessment measures

With a variety of available instruments and conjecture about their use for psoriasis, determining which instrument to use in clinical studies requires consideration of psoriasis type, target population, required degree of sensitivity to change and ease of use (Ryan et al., 2013). For research, it is advised to use common validated instruments with proven reliability. The PASI and various forms of the PGA are most commonly utilised for psoriasis severity and should continue to be utilised until more suitable methods are developed. For QoL a number of instruments have been validated in a psoriatic population and researchers should consider the population type and intended outcomes when choosing an instrument. The DLQI is most often utilised however due to lack of sensitivity in mild cases the SKINDEX can supplement QoL data.

Selecting these instruments enables data from previous and future studies to be statistically pooled and/or compared. Many available instrument measures are not ideal for psoriasis, lacking key factors known to be significant for sufferers. Newer instruments aim to address deficiencies, but as yet none have had significant uptake. Unfortunately, as yet there is no worldwide consensus on a severity measure for psoriasis; however, the World Health Organization (WHO) suggests that further clinician education and support may lead to eventual development of universal severity
guidelines appropriate for all aspects of psoriasis (World Health Organization (WHO), 2013). Researchers are encouraged to include, where possible, newer psoriasis instruments in their research design along with more traditional measures, so newer instrument data can be further compared and further improvements made.

2.5.6 Chinese medicine theory for psoriasis measurement

While validated and reliable conventional instruments exist for measurement of psoriasis symptoms and QoL, there is yet no widely accepted instrument that considers Chinese medicine theory in psoriasis assessment. While lesion changes are an important aspect for management and treatment of psoriasis, Chinese medicine assesses psoriasis beyond the appearance of the disease when determining cause and progress of disease. In Chinese medicine, features of the tongue and pulse assist in differentiation of syndrome type and guide selection of treatment (Mei, 2011).

Unlike conventional therapy, Chinese medicine treatment prescription is not determined predominantly by severity and location of lesions, but instead considers Chinese medicine concepts such as yin, yang and meridians. Thus, two people with identical conventionally diagnosed psoriasis may be considered to have two very different syndromes in Chinese medicine (Lu et al., 2014a). Differentiation uses inspection, assessment and Chinese medicine enquiry techniques. Once diagnosed, Chinese medicine therapy consists of treatments such as acupuncture and/or CHM, among other options. Syndrome differentiation instruments have been designed for Chinese medicine with some level of validation and reliability for some health conditions, but there is no known specific instrument for psoriasis (Grant et al., 2013, Schnyer et al., 2005). Given this, a unique instrument was developed for the current
study based on Chinese recommended guidelines for psoriasis to classify study participants (China Academy of Chinese Medicine, 2011) (Appendix 1)

2.6 Co-morbidities associated with psoriasis

Evidence indicates an increased likelihood of various co-morbidities in psoriasis sufferers. Likely as result of such co-morbidity risk, the life expectancy of people with psoriasis is around 3–4 years lower than people without the disease (Gelfand et al., 2007). Metabolic disorders are the most frequent co-morbidities reported and pose risk to liver and/or kidney disease (Svedbom et al., 2015). Other significant diseases have been associated with psoriasis including hypertension, obesity, restless legs syndrome, bowel disease, lymphoma, depression, diabetes, cancer, Crohn’s disease, liver disease, infections, dyslipidaemia, osteoporosis and lymphoma (Schell et al., 2015, Gelfand et al., 2003) (Gottlieb et al., 2008b, Bernstein et al., 2005, Schmitt and Ford, 2007, Zanni, 2012).

Available evidence for these potential co-morbidities varies, with some such as metabolic disorders attracting far more interest than others. It has been proposed that rather than psoriasis leading to these co-morbidities, in fact there is a genetic predisposition in people with psoriasis that leads to co-morbidity development (Koch et al., 2015). Indeed, paediatric research supports such a genetic link, in which risk of developing hyperlipidaemia, obesity, hypertension, diabetes mellitus, rheumatoid arthritis and Crohn’s disease is increased around 2-fold for children diagnosed with psoriasis (Augustin et al., 2010).

This section discusses the most commonly reported co-morbidities associated with psoriasis, detailing their prevalence and reviewing evidence of their relationship to psoriasis.
2.6.1 Cardiovascular disease

Mortality from cardiovascular disease is increased by 57% in people with psoriasis, although there is conjecture surrounding the precise mechanistic relationship between the two. Genetic polymorphisms in psoriatic people is a growing area of research, where data are emerging from genome-wide association studies indicating existence of common genetic variants predisposing people to increased risk of dyslipidaemia, hypertension and coronary artery disease (Lu et al., 2013). However, recent research identifies no increased risk of cardiovascular events following adjustment for cardiovascular disease risk factors (Aldeen and Basra, 2011) (Parisi et al., 2015).

A key inflammatory mediator in the development and progression of psoriasis, TNF-α is also understood to be important in cardiovascular disease. Despite TNF-α polymorphisms being found to increase incidence of psoriasis, research suggests these same polymorphisms have no impact on development of coronary artery calcification (Zhuang et al., 2013) (Torres et al., 2014). With TNF-α unlikely to be the genetic cause of cardiovascular disease development, research has focused on other elevated inflammatory factors of both conditions, such as vascular endothelial growth factor, IL-12, monocyte chemotactic protein-1 (MCP-1) and circulating IL-17A, among others (Wang et al., 2012e).

Of these, IL-17A shows the most promising evidence for involvement (Golden et al., 2013). Found in blood, plasma C-reactive protein is typically high in inflammatory disease and has been implicated in both cardiovascular disease and psoriasis. For people with moderate and/or severe psoriasis, greater levels of C-reactive protein have been reported than for milder conditions (Beygi et al., 2013). An overall increase in the prevalence of metabolic syndromes in people with psoriasis is likely to be the key
precursor to development of cardiovascular disease in this population, and with suitable preventive therapy this risk may be reduced (Voiculescu et al., 2014).

2.6.2 Diabetes

Similar to cardiovascular disease, genetic indicators found in people with psoriasis are also known to increase risk of diabetes (Koch et al., 2015). For people with psoriasis who develop diabetes, there is an increase in micro-vascular and macro-vascular complications compared with non-psoriatic diabetics (Armstrong et al., 2015). Incidence of insulin resistance is also higher in psoriatic people, providing some insight into how diabetes may develop (Gyldenlove et al., 2015). Similarly, risk of diabetes is likely related to a coinciding increased incidence of obesity in psoriatic people (Tobin et al., 2014).

Research indicates decreasing obesity of sufferers correlates with reduced psoriasis severity, although again the mechanism is unclear. Indeed, paediatric research confirms concomitant obesity in children is common with psoriasis, supporting a possible genetic link (Solomon, 2014, Mahe et al., 2014). Obesity also affects metabolism and the effectiveness of treatments; for instance, obesity may reduce the success of drug treatment for psoriasis (Carrascosa et al., 2013). Despite apparent metabolic risk and an increased risk of diabetes, dispute remains among researchers – no direct link was detected in a US population, while a Dutch study concluded there was a link (Casagrande et al., 2014, Khalid et al., 2013). Clearly more research is needed to evaluate if there are indeed any links between diabetes and psoriasis.

2.6.3 Psychological impacts of psoriasis

The degree to which psychological state impacts on psoriasis symptoms is arguable. Regardless, the statistics are alarming, indicating 20% of people with psoriasis may
experience suicidal ideation (Dermatology Expert Group, 2004) (Bhosle et al., 2006). Such research does highlight the importance of psychological effects on people with psoriasis, likely owing to the physical appearance of lesions, often amplified by their location. Lesions on exposed areas of the body, such as the face, can cause significant reductions in QoL (Heydendael et al., 2004), triggering shame, anger and worry, further contributing to difficulties undertaking daily activities and impacting on social life.

Sufferers also feel stigmatised by the common misconception that psoriasis is contagious (Donigan et al., 2015), leading to an increase in stress, poor self-image and embarrassment (Kimball et al., 2005). These emotions can lead to depression and/or anxiety disorders (Sampogna et al., 2012). If combined, such factors can diminish QoL so substantially that people with psoriasis have reported reduced QoL comparable to people with severe diseases such as cancer, ischaemic heart disease, diabetes and chronic obstructive pulmonary disease (Rapp et al., 1999).

Going beyond the psychological and emotional impacts of psoriasis, many patients (both male and female) can go on to manifest physical dysfunction, such as sexual impairment (Sampogna et al., 2007, Turel Ermertcan et al., 2006, Goulding et al., 2011). Erectile dysfunction is a common manifestation in psoriatic men, with high disease severity correlated with increasing dysfunction. Such sexual dysfunction is predominantly reported as a psychological disorder, however evidence suggests it may also be physiological, with reductions in testosterone levels and increases in estradiol shown in psoriatic men (Cemil et al., 2015). Depression can also have physiologically implications, increasing risk of atrial fibrillation and stroke in psoriasis sufferers (Egeberg et al., 2015).

With greater importance placed on improving QoL as well as psoriasis symptoms, during treatment the provision of psychological support and therapy is as important as
addressing psoriasis symptoms. This is especially important in cases where anxiety and fear of relapse continue even after psoriasis lesions have cleared (Rapp et al., 1999). Unfortunately, identification of psychological disorder in people with psoriasis is low (Richards et al., 2004). Left untreated, psychological distress can impair treatment; for instance, clearance rates of treatments such as psoralen plus ultraviolet light therapy and photochemotherapy are reduced in patients with psychological distress (Fortune et al., 2003).

2.6.4 Other potential psoriasis-related co-morbidities

Another co-morbidity associated with psoriasis is sarcoidosis, an inflammatory disease that affects multiple organs in the body, but predominantly the lungs and lymph glands. In particular it has been related to pulmonary sarcoidosis, possibly linked via the Th17 pathway (Wanat et al., 2013). Psoriasis has also been implicated in an increased likelihood of other autoimmune diseases (Wu et al., 2012). Although unclear why, coeliac disease has shown more positive IgA antigliadin antibodies in psoriasis sufferers than healthy controls (Bhatia et al., 2014). Evidence also suggests that psoriasis may increase risk of complications during pregnancy (Ben-David et al., 2008).

2.6.5 Co-morbidities summary

Psoriasis imparts a significant burden on a sufferers’ health. A survey of psoriasis sufferers found 46% of respondents felt it would be better or the same to have diabetes instead of psoriasis, and 99% of respondents said they would be prepared to spend two or three hours each day on therapy, if it might result in normal skin for the rest of the day (Palotai et al., 2010).

A health-related QoL study describes reduction in physical and mental function of psoriatic people as comparable to that seen in cancer, arthritis, hypertension, heart
disease, diabetes and depression (Rapp et al., 1999). Growing co-morbidity evidence has led to a push from clinicians to assess and appropriately treat co-morbidity risks, such as cardiovascular disease and diabetes (Ryan and Kirby, 2015). The impact of psoriasis is now understood to be far greater than just the affected skin's appearance, with links to systemic disease patterns increasing mortality and psychological disorder risk. Researchers investigating psoriasis treatment should, where possible, also investigate changes in related co-morbidity risk through suitable testing such as blood glucose and blood lipid levels.

2.7 Conventional treatments for psoriasis

The degree of psoriasis severity has important implications in treatment selection. Appropriate selection of therapy maximises therapeutic outcomes while minimising unwanted effects for patients. Approximately 80% of all psoriasis cases are considered as mild to moderate in severity (Menter et al., 2009). Guidelines typically recommend milder therapies (e.g. topical steroid creams) for lower severity psoriasis, while increasingly stronger therapies (e.g. biological drugs) are administered as psoriasis severity increases.

Historically, with little known about their precise therapeutic mechanism, psoriasis treatments were discovered largely via trial and error. As psoriasis research techniques have improved so too has the biological understanding of psoriasis. When excessive proliferation of keratinocytes was scientifically recognised in psoriasis, a significant period of drug development followed. Since cyclosporine A first successfully showed anti-psoriatic effects, irregular immune function has been considered central to understanding psoriasis. Subsequent drug development has endeavoured to produce
new immune-based drug therapies that are less toxic than cyclosporine A (Micali et al., 2014, Van Joost et al., 1988).

Current drug development research, such as into targeted biologics, predominantly focuses on specific immune pathway activity, reducing likelihood of unwanted widespread systemic effects (Nickoloff and Nestle, 2004). Unfortunately, many effective modern drugs, including biologics, still have drawbacks, such as high retail costs and the risk of potentially severe side effects (Ryan and Menter, 2012). Recent drug development has primarily targeted severe and/or unresponsive psoriasis cases, so for the majority of milder psoriasis cases available therapies remain quite limited. Psoriasis sufferers with mild disease are commonly directed towards less effective and inconvenient therapies, such as topical creams, which show low adherence (Storm et al., 2008) (Zschocke et al., 2014, Reich and Dauden, 2014).

In accordance with treatment guideline recommendations, this section reviews conventional treatment options for psoriasis (Dermatology Expert Group, 2004, Mrowietz et al., 2011, Excellence, 2012, Menter et al., 2008). Therapies are each reviewed to explain their potential biological mechanisms relevant to psoriasis and their safety.

2.7.1 Background of therapeutic guideline treatment recommendations

Documented therapeutic guidelines for psoriasis differ around the world regarding measure of severity and selection of treatment. Most well-known and referred guidelines are from the United States of America (Menter et al., 2008), United Kingdom (Excellence, 2012) and Europe (Pathirana et al., 2009, Nast et al., 2015a). Australia has developed its own guidelines based on those internationally available (Dermatology Expert Group, 2004). Guidelines aim to ensure patients are consistently managed and
cost–benefit typically strongly influences local therapeutic guidelines. Unfortunately, global variation in guidelines limits analyses of pooled data. To assist data pooling, consistent use of outcome measures and therapies needs to be reported. Global data pooling may assist in development of international standardised guidelines to support global treatment outcome optimisation.

The potential benefits of standardisation have led to recent discussion, cooperation and consensus between various chief health bodies, and the gradual development of wider region guidelines (Mrowietz et al., 2011). Such international co-operation recently culminated in development of a resolution for psoriasis, put forward by the WHO, which resulted in subsequent release of key actions to improve care of people with psoriasis (World Health Organization (WHO), 2013). A published WHO report describes psoriasis as a “chronic, non-communicable, painful, disfiguring, and disabling disease for which there is no cure”. Furthermore, the psychological impacts of psoriasis have been acknowledged and the elevated risk of serious co-morbidities, such as cardiovascular disease, diabetes and metabolic syndrome, has been recognised (World Health Organization (WHO), 2013).

When assessing psoriasis to determine suitable treatment prescription (drug and dosage selection), it is now widely accepted that both psoriasis symptoms and QoL should be evaluated (Samarasekera and Smith, 2014). Guidelines commonly divide treatment into first, second and third line therapies. First line therapies are targeted at milder or newly presenting moderate cases of psoriasis. Typically, first line therapy consists of mild-action topical drugs, such as vitamin D analogues. Second line therapies typically consist of stronger topical drug such as moderate- to high-strength corticosteroids, phototherapy and non-biological systemic treatments such as methotrexate and cyclosporine A. Second line therapies are recommended for moderate
to severe disease or mild psoriasis cases unresponsive to first line therapy (Samarasekera et al., 2012). Third line therapies are typically prescribed when first and second line therapies are unsuccessful, or in cases of very severe psoriasis requiring immediate and drastic symptom reduction. Third line therapy consists predominantly of biologics such as TNF antagonists (e.g. adalimumab and etanercept) or IL-17 inhibitors (e.g. Brodalumab) (Samarasekera and Smith, 2014).

Guidelines also recommend addition of concomitant therapies such as emollients for people experiencing pruritus (itching) (Excellence, 2012, Menter et al., 2009). Interestingly, no one treatment has proven to have superior efficacy for pruritus in controlled trials (Reich and Szepietowski, 2014).

This section discusses the various treatment options available. Conventional therapies are grouped with other therapies with similar indicated use and/or mechanism in psoriasis: topical therapies, systemic drugs, other conventional therapies, novel and emerging therapies. The known mechanisms of these drugs are reviewed then associated risks and limitations discussed.

### 2.7.2 Conventional topical therapies for psoriasis

Given the majority of psoriasis cases (80%) are mild to moderate in severity, topical drugs are the most commonly prescribed therapy (Menter et al., 2009).

**Topical steroidals**

Understood to inhibit synthesis of some regulatory proteins while inducing synthesis of others, the corticosteroids known as glucocorticoids are shown to inhibit psoriasis pro-inflammatory cell TNF-α (Bos and Spuls, 2008). As glucocorticoids act on multiple pathways, physicians commonly prescribe them for psoriasis. It has been shown that
glucocorticoids have anti-inflammatory, anti-proliferative, anti-pruritic and vasoconstrictive activity (Humbert and Guichard, 2015).

Corticosteroids are rated as mild, moderate, potent or very potent, with increasing potency providing greater efficacy, but also increasing risk of side effects. Regardless of origin, treatment guidelines tend to advocate and encourage the use of topical steroidals as a first line therapy in psoriasis. The benefits of topical steroidals for psoriasis are clear, however with the development of newer drugs with far greater efficacy, glucocorticoid use is starting to be questioned (Samarasekera et al., 2013).

Despite the common use of topicals, adherence is typically low. Patients prefer gels to ointments yet ointments show greater effect (Bewley and Page, 2011). Furthermore, extensive or persistent use of glucocorticoids should be avoided due to risk of tachyphylaxis (severe flare-up when steroid is stopped plus poor response when restarted), skin atrophy, Cushing’s and risk of suppression of the hypothalamic-pituitary-adrenal axis (Clarke, 2011, Humbert and Guichard, 2015).

**Vitamin D analogues**

Vitamin D analogues decrease proliferation, induce differentiation and induce apoptosis of psoriatic keratinocytes (Tiberio et al., 2009). They reduce expression and/or protein levels of inflammatory factors IL-2, IL-6, IL-8, IFN-γ and GM-CSF, which are likely involved in the proliferation of T-cells in psoriasis (Nagpal et al., 2001). Thoroughly investigated for its involvement in psoriasis, the Th-17 inflammatory pathway is reduced by vitamin D analogues (Hegyi et al., 2012). With reduced risk of side effects, yet similar efficacy, vitamin D analogues may in fact be superior to corticosteroids as topical anti-psoriatics (Soleymani et al., 2015). Early animal studies of Vitamin D analogues showed they reduced angiogenesis however can be calcemic (Oikawa et al., 1990). Calipotriol however has shown to be as
effective as other vitamin D analogues without being as calcemic. Left/right comparative study indicates calcipotriol (50gm) to be effective and safe for psoriasis vulgaris when compared to vehicle ($p<0.001$) (Dubertret et al., 1992).

**Other**

Another topical is tar, which despite widespread usage increases risk of spontaneous abortion in pregnant women (Bae et al., 2012). Tacrolimus is a topical immunosuppressive drug that also carries some risk for pregnant women, with potential for lower birth weight, premature birth and substantial levels found in breast milk, posing further risk to the infant (Jain et al., 2003). Keratolytics such as salicylic acid, lactic acid and urea are used typically as adjunct therapies, to remove thick scaling, and are not typically prescribed as a sole treatment (Tollefson, 2014).

**2.7.3 Conventional systemic therapies for psoriasis**

**Systemic corticosteroids**

Having similar action to topical corticosteroids systemic forms are orally ingested and metabolised through the GI tract, as such GI related side effects can ensue. Oral forms also carry greater risk to pregnant women, with low foetal weight and a reported increase in the incidence of cleft pallet (Chi et al., 2011, Edwards et al., 2003).

**Methotrexate**

An immunosuppressant, methotrexate is a folic acid antagonist, acting by competitively inhibiting the enzyme dihydrofolate reductase, which is needed in the synthesis of folate and subsequent DNA, RNA and protein synthesis (Ho et al., 2009). Its therapeutic mechanism is also a potential risk for people with folic acid deficiency, and can lead to adverse effects requiring folic acid supplementation to relieve them (Whittle and Hughes, 2004). The dosage of such supplementation requires further research, as too
high a dosage has been shown to reduce methotrexate efficacy, thus requiring a careful balance (Baran et al., 2014). Use of methotrexate is further limited by other potential side effects including increased risk of pulmonary complications, myelosuppression, hepatotoxicity and haematological toxicities (Barrera et al., 1994). Consequently, to monitor hepatic and haematological parameters, strict laboratory monitoring, including a liver biopsy is essential after administering a total cumulative dose of 1.5g of methotrexate (Kovesdy and Kalantar-Zadeh, 2012, Staidle et al., 2011).

Considering the increased prevalence of alcohol use and co-morbidities such as obesity and diabetes in people with psoriasis, the risk of liver fibrosis is also greater, and as such restricts use of methotrexate in some cases (Montaudie et al., 2011). Methotrexate can also cause severe teratogenicity such as mental retardation and craniofacial defects in pregnant women so use should be avoided in women considering pregnancy. Emerging evidence suggests low dose methotrexate use may reduce risk of cardiovascular disease events, although the mechanism behind this is still unclear (De Vecchis et al., 2015).

**Acitretin**

Shown to decrease the expression of chemokines in peripheral blood of people with psoriasis, acitretin is an oral retinoid that acts by binding to nuclear transcription factors (Dai et al., 2014a). Binding induces keratinocyte differentiation and reduces epidermal hyperplasia, however at higher doses side effects can arise, including itchy dry skin, dry mucus membranes and joint pain. Another concern of oral retinoids is their highly teratogenic nature, so it should be avoided in women of childbearing age (Bae et al., 2012). Reports suggest avoiding pregnancy for at least two years following the cessation of oral retinoid use (Staidle et al., 2011). Acitretin is a useful option for psoriasis patients in which immunosuppression is contraindicated.
Calcineurin inhibitors

Derived from soil fungi, cyclosporine A is the most well-known calcineurin inhibitor for psoriasis vulgaris. Calcineurin is a key molecule in inducing transcription factors of potential cytokines. When administered, cyclosporine A reduces numbers of epidermal and dermal T-cells and inhibits mast cell activity (Boyman et al., 2007, Oran et al., 1997). Evidenced to reduce production of TNF-α and IL-2 it is also understood to reduce helper T-cells, regulatory T-cells, NK cells and block the activation of monocytes, all assisting to reduce inflammation of psoriasis (Akcali et al., 2014). Although cyclosporine A can suppress psoriasis symptoms, resolved plaques still often show regenerative keratinocytes, indicating its actions do not reverse psoriasis inflammatory pathways (Guttman-Yassky and Krueger, 2007).

Long-term use of cyclosporine A is associated with nephrotoxicity, thus monitoring of renal function and blood pressure is recommended. As such, cyclosporine A is best avoided in the elderly and is typically only prescribed in short courses for acute flare-ups (Grossman et al., 1996). Following remission or control, cyclosporine A therapy should cease and patients changed to other forms of systemic therapy safer for long-term maintenance (e.g. acitretin) (Staidle et al., 2011). As cyclosporine A is understood to cross the foetal blood barrier, it should be avoided in pregnant patients (Lamarque et al., 1997). Similar calcineurin inhibitors have also been developed include sirolimus, pimecrolimus and racrolimus, with the latter being 50–100 times more potent than cyclosporine A (Reitamo et al., 2001, Rappersberger et al., 2002, Reynolds and Al-Daraji, 2002).

Tumour necrosis factor alpha inhibitors

Anti-tumour necrosis factor therapies work against psoriasis by decreasing Th17 pathway cells (Zaba et al., 2007). While effective, they are not without risks, including
subsequent development of serious infections and malignancy (Staidle et al., 2011). Further risk of spontaneous abortion is linked to administration of TNF-α inhibitors before and after conception in women (Verstappen et al., 2011). Although TNF-α inhibitor drugs show strong efficacy in psoriasis, due to progressive formation of antibodies against them, subsequent immunogenicity can considerably reduce long-term efficacy (Baert et al., 2003). In contrast to its therapeutic use for psoriasis, anti-TNF-α drug use in people without psoriasis may actually trigger psoriasis lesions (Pugliese et al., 2015). A few of the more common anti-TNF-α drugs are now discussed in more depth.

**Etanercept**

Known to suppress Th17 pathway cytokines that inhibit psoriasis-related pathways, etanercept prevents excess TNF from binding and interacting with cell-bound receptors by competitively inhibiting TNF-mediated activity (Wang et al., 2012b). Significant adverse effects noted with etanercept therapy include temporary injection site reactions, exacerbation of congestive heart failure (although rare) and bone marrow suppression during therapy. Users are also at increased risk of antinuclear antibody development, but only in rare cases do patients develop any clinical manifestations. There are extremely rare yet severe reports of central nervous system demyelinating disease associated with etanercept, and a small number of lymphoma cases reported following induction of etanercept (Staidle et al., 2011).

**Adalimumab**

A fully human monoclonal antibody, adalimumab binds to TNF-α, blocking its interaction with TNF cell-surface receptors. Common side effects associated with adalimumab include upper respiratory infections and nasopharyngitis. Disseminated
and extra pulmonary infections have also been reported, most commonly in patients treated with doses of adalimumab higher than recommended. Like other TNF-α inhibitors, the main concerns associated with adalimumab therapy, aside from infection, are malignancy and development of antinuclear antibody positivity (Staidle et al., 2011).

**Infliximab**

A chimeric monoclonal antibody, infliximab binds specifically to soluble and membrane-bound TNF-α. Administered by intravenous (IV) infusion, the most common adverse events are infusion reactions, headache, itching and myalgia. Rare incidents of latent tuberculosis reactivation have occurred with infliximab as well as T-cell lymphoma (Staidle et al., 2011).

**Alefacept**

A CD2-binding fusion protein combining a portion of human IgG and binding site of lymphocyte function associated antigen-3 (LFA-3), alefacept reduces infiltrating T-cells, activated dendritic cells and inflammatory genes of psoriasis. Given intramuscularly, symptom reduction has been proposed to be via depletion of T-cell surface CD2, thereby inhibiting memory T-cell activation and proliferation (e.g. lesional T-cells and dendritic cells) (Boyman et al., 2007, Chamian et al., 2005). Risk of lymphopenia, malignancy and serious infections due to T-cell reduction has led the US FDA to recommend monitoring CD4+ and CD8+ T-cell counts on a weekly basis (Staidle et al., 2011).

**Interleukin-12 and interleukin-23 inhibitors**

**Efalizumab**

A human monoclonal antibody, efalizumab is directed against LFA-1 adhesion to endothelial cells, blocking interaction in infiltrated T-cells and the intercellular adhesion
molecule-1 (ICAM-1) on dendritic cells, which consequently reduces dendritic cell numbers (Boyman et al., 2007, Ghoreschi et al., 2007). Efalizumab is known to prevent movement of T-cells from circulation to psoriasis plaques through blockage of LFA-1, however usage is restricted and it was removed from the US market by the US FDA in 2009 (Jullien et al., 2004).

**Ustekinumab**

A fully human monoclonal antibody, ustekinumab seems to be the most favourable biologic in terms of cost per PASI 75 response in psoriasis treatment (Terranova et al., 2014). Ustekinumab acts by binding to the p40 subunit shared by pro-inflammatory cytokines IL-12 and IL-23, thereby neutralising their activity and blocking interactions with related receptors and associated T-cells producing IL-17 (Croxtall, 2011). The most commonly reported adverse events include nasopharyngitis, upper respiratory tract infection and increased incidence of malignancy, although long-term safety data are unknown (Staidle et al., 2011).

**Tazarotene**

With similar action to other retinoids, tazarotene also has potential teratogenic effects, causing post-implantation loss in animal studies, and so is usually avoided in pregnant women (Bae et al., 2012).

2.7.4 Other conventional therapies for psoriasis

**Psoralen and ultraviolet A**

Psoralen is often utilised along with ultraviolet treatment (320nm–400nm) to decrease numbers of lesional dendritic cells and epidermal T-cells (Boyman et al., 2007). When psoralen is exposed to UVA it enters an excited state, cross-linking with DNA and inhibiting DNA replication. Treatment risk includes those associated with significant
exposure to UV such as melanoma and non-melanoma skin cancer. Ultraviolet A patients may also experience acute phototoxicity, which is considered more severe than the risk in ultraviolet B therapy (UVB) (Staidle et al., 2011).

*Narrow-band ultraviolet B phototherapy*

Applied in broadband (280nm–315nm) or narrow-band (311 nm) form, UVB acts as an immunomodulator to cause cytopathic and delayed immunosuppressive effects. Narrow-band UVB appears to be more effective than broadband UVB despite the broader safety profile of broadband UVB. Risks associated with use of UVB include acute skin reactions, similar to sunburn, and a small increased risk of skin cancer with long-term use (Staidle et al., 2011). Therapy response is often quick, although after a number of weeks or months relapse often ensues, likely due to UVB’s lack of sensitivity in keratinocytes. Following this treatment there is likely gradual dendritic cell replenishment to the area by blood, only epidermal CD8+ T-cells are evidenced to be reduced long term (Gudjonsson et al., 2004). The relatively low risk of UVB combined with significant efficacy and reasonable cost has established it as the most cost-effective psoriasis therapy available (Miller and Feldman, 2006).

2.7.5 Novel and emerging therapeutics for psoriasis

Significant effort is currently going into development of biologic and small molecule drug treatments, such as promising janus kinase (JAK) inhibitors for psoriasis (Kwatra et al., 2012). Growth in the biologic sector of the psoriasis pharmaceutical industry is due to clearer identification of immunological activities and pathophysiological pathways involved in psoriasis (Krueger, 2002, Krueger and Bowcock, 2005). The use of biologics has not only improved psoriasis symptoms, but also enhanced QoL, for example, seen in decreasing DLQI scores (Basra and Hussain, 2012).
Despite their strong efficacy, biologics are disconcerting to some psoriasis sufferers, as typically they require IV injection. To increase usage and allow oral administration there has been recent development of small molecule medicines with trial results indicating lesion clearance rates approaching those of IV biologics. However, ingestible versions do carry risks, typically of gastrointestinal side effects, so small molecule drugs are being further refined into topical forms (Han, 2014).

The benefits of target-action pharmaceuticals and growing evidence of genetic alleles has seen gradual increase in development of pharmacogenomics, in which markers predicting response to treatment are being investigated (Menter and Griffiths, 2015). Commonly known as personalised or stratified medicine, such research has potential to target people with specific alleles with corresponding biologics known to benefit that group (Foulkes and Warren, 2015). Already, evidence has emerged in identification of polymorphisms, which influence outcomes of anti-TNF-α treatment (Julia et al., 2013). Assisting this progress is research analysing clinical transcriptomics data set to further identify novel drug targets, not just psoriasis-specific transcriptomics (Qu et al., 2014). Current evidence suggests that biologics are more effective than traditional systemic treatments, although their recent introduction limits prediction of their long-term safety profile (Sandoval et al., 2014).

*Interleukin-17 (IL-17)*

Treatments targeting IL-17 have been shown to suppress expression of psoriasis-related genes, and a number of newer drugs now target this pathway (Russell et al., 2014) (Chiricozzi and Krueger, 2013). For example, secukinumab is a fully human monoclonal antibody that binds and neutralises IL-17A, and in a phase II trial proved to be superior in achieving PASI 75 and PASI 100 compared with placebo (Rich et al., 2013, Leonardi et al., 2012, Edson-Heredia et al., 2015). While secukinumab neutralises IL-17,
brodalumab, a human monoclonal antibody that antagonises IL-17RA receptors, decreases downstream effects of IL-17. Subsequently, brodalumab inhibits binding of IL-17 subtypes (IL-17A, IL-17F and IL-17E) to their receptor (Gisondi et al., 2014) (Coimbra et al., 2014). In clinical trials a decent proportion of participants using brodalumab achieved clearance of PASI 90 and PASI 100 (Papp et al., 2012b).

Of the experimental drugs targeting IL-17 and undergoing phase III trials for psoriasis, phase II results show brodalumab has the greatest potential efficacy, which suggests blocking of IL-17RA receptors is superior to neutralising IL-17. Interestingly, there is evidence these drugs may also reduce associated cardiovascular plaque formation, likely owing to reduction of IL-17 and the subsequent inflammatory pathways that lead to plaque formation. Adverse events caused by drugs targeting IL-17 include nasopharyngitis, upper respiratory infections, injection site reactions and, less frequent but more concerning, reduction in neutrophils with potential neutropenia (Brown et al., 2014).

**Interleukin-23 (IL-23)**

Geuselkumab and tildrakizumab are human monoclonal antibodies that target and neutralise IL-23 and prevent downstream production of cytokine IL-17. It is unclear if it is safest and most efficacious to targeting IL-23 or its downstream cytokine IL-17 and further comparison research is needed (Yiu and Warren, 2015). Recent research does, though, show strong efficacy of tildrakizumab with promise in moderate to severe psoriasis (Kopp et al., 2015).

**MicroRNA (miRNA)**

Although not yet established in human studies, locked nucleic acid-modified anti-
miRNA-21 compounds have shown to be effective treatments in mouse models of psoriatic disease (Guinea-Vinniegra et al., 2014).

**Tumour necrosis factor alpha (TNF-α)**

In phase II studies, a new anti-TNF-α agent, certolizumab pego, has caused improvement in psoriasis following 12 weeks of treatment (Reich et al., 2012).

**Janus kinase (JAK)**

Of the JAK targets, JAK1/3 has proven to be the most effective, with late phase trials continuing (Kaffenberger et al., 2014, Papp et al., 2015). Small molecule tofacitinib inhibits JAK1/3, leading to down-regulation of systemic levels of IL17, IL-22, IL-23 and TNF-α (Chang et al., 2009, Papp et al., 2012c, Mamolo et al., 2013). Baricitinib and ruxolitinib are also JAK inhibitors undergoing further research for psoriasis. Ruxolitinib has been developed into a topical drug with improvements seen in erythema, induration and scaling of psoriatic lesions (Punwani et al., 2012).

**Cyclic adenosine monophosphate (cAMP)**

Preventing activation of transcription factors, apremilast is understood to decrease production of pro-inflammatory cytokines through blocking of phosphodiesterase-4 and degradation of cAMP (Conti et al., 2003). A low dose (10mg) efficacy study indicated no difference to placebo, but PASI 75 has been achieved in 40% of users when dose is increased to 30mg (Papp et al., 2012a).

**Kv1.3**

Applied topically in psoriasis, the protein Kv1.3 targets voltage-gated potassium channels, preventing Ca²⁺ influx in T-cells. In vitro it appears to target memory T-cells while not affecting immune-affected conditions with naïve T-cells (Kundu-Raychaudhuri et al., 2014).
Vascular endothelial growth factor (VEGF)

As mentioned previously, increased levels of VEGF are found in psoriasis sufferers. Research into VEGF therapies is limited; however, there is some evidence of anti-VEGF treatment being effective for psoriasis, such as inflammatory skin conditions in *in vitro* mice study (Halin et al., 2008). A human case has also been reported in which the anti-VEGF bevacizumab was utilised in colon cancer with subsequent remission in coexisting psoriasis (Akman et al., 2009).

2.7.6 Combined therapies for psoriasis

Research indicates that combining therapies for psoriasis increases efficacy of common monotherapies such as corticosteroids, vitamin D analogues and UV therapy (Bailey et al., 2012). Calcipotriol plus betamethasone dipropionate has been commercially developed due to proven increased efficacy in clinical trials compared with each utilised alone (Stein Gold, 2014). Application options for betamethasone dipropionate now range from creams, ointments and gels to, more recently, aerosols, which improve ease of application and provide greater efficacy (Queille-Roussel et al., 2015). It should be noted that although efficacy may increase with combined therapy, there is also increased risk of side effects, for instance, polypharmacy use of biologics and methotrexate can increase risk of the herpes simplex virus (Shalom et al., 2015).

2.7.7 Limitation of conventional therapies

Risks vary depending on treatment type; typically, mild–moderate action therapies carry low risk of side effects and those of stronger action, including many newer drugs, tend to have greater risk of side effects. Unfortunately for biologic users it has recently been evidenced they lose efficacy over time with continued use (Levin et al., 2014). This commonly results in dosage escalation over time, and physicians switching between
biologics in search of efficacy (Feldman et al., 2015). To minimise risk of infection after surgery, people with psoriasis are advised to stop taking biologics between two and twelve weeks prior and recommence following recovery (Smith et al., 2009, Ledingham and Deighton, 2005). In some people biologics cause a tendency to weight gain, increasing risk of cardiovascular disease in a population already at increased risk (Ross et al, 2015). There is well-documented evidence of anti-TNF-α therapy increasing risk of tuberculosis in people with latent psoriasis (Ergun et al., 2015).

2.7.8 Summary of conventional therapy for psoriasis

Most commonly prescribed psoriasis medications have side effects and some degree of risk associated with them. In some instances side effects of therapies can be more severe than the condition itself, which can limit psoriasis treatment options and frustrate both treating physicians and sufferers. A survey in Europe reported 53% of dermatologists were dissatisfied with their patients’ treatments (Palotai et al., 2010). In almost all of these patients, physicians considered changing treatments. Indeed, on average, people change treatment once a year (Palotai et al., 2010, Anderson and Feldman, 2015). An earlier study in Europe found over 70% of people with psoriasis rated available therapies as having moderate to low effect, indicating general dissatisfaction with the treatment options available (Dubertret et al., 2006). In a survey of psoriasis patients receiving oral or biologic therapy, 57% and 45%, respectively discontinued therapy, most often for safety or tolerability reasons, and lack or loss of efficacy (Lebwohl et al., 2014). For patients receiving topical therapies, 51% are reported to change therapies, and although reasons for a switch are unclear it is likely that lack of efficacy is a factor (Neri et al., 2014).
Biologic research studies are still on the increase, which provides good news for moderate to severe psoriasis sufferers, but provides little hope for people with milder conditions or for groups in which biologic use is contraindicated (Manalo et al., 2015). Despite new psoriasis drug successes, treatment options in vulnerable populations such as children, pregnant women and the elderly are unfortunately still limited. Risks and side effects are reported in even mild action drugs such as corticosteroids (Fotiadou et al., 2014, Edwards et al., 2003, Chi et al., 2011). These issues indicate a need for further discovery and development of safe and effective treatments for use in wider populations. Such a need has seen interest in non-drug interventions such as the WHITE Holographic Bioresonance method, although research into this approach is still limited (Del Giudice et al., 2015).

Efficacy of therapeutic intervention varies, perhaps reflecting variation in pathogenic stage and inflammatory activity at the time of administration (Albanesi, 2014). For instance, TNF-α blockers are thought to be active mainly on innate immunity, which may explain why they are effective in only 75% of cases. In addition, new research has found greater efficacy in patients with the Cw6-positive polymorphism than those without (Batalla et al., 2015). Such differences may explain why response to topical corticosteroids can differ within the same psoriatic lesion, with chronic areas responding well to therapy while areas characterised by acute inflammation are more resistant.

The complex pathogenic pathways and biological activity involved makes psoriasis a difficult disease to decipher. While genetic factors are likely involved they are yet inconclusive. Much of the psoriasis pathogenic pathway knowledge has come from previous demonstrated biological action from efficacious drug exploration (Christophers, 1996). Even without treatment, plaque symptoms can mysteriously
disappear (such spontaneous remission occurs in around 25% of psoriasis sufferers), but can resurface again years later (Griffiths and Barker, 2007, Nevitt and Hutchinson, 1996). The complex pathogenic pathways that contribute to psoriasis, along with psoriasis-specific symptoms, co-morbidities and psychosocial impacts, make management and treatment of the condition difficult (Martin et al., 2011). Such disease complexity has led clinical experts to develop more multi-disciplinary approaches for psoriasis management (Prignano et al., 2015).

Physicians are aware of conventional treatment limitations and there has been discussion that an individualised approach may help improve adherence, outcomes and QoL for patients with psoriasis. This is the fundamental philosophy behind CHM treatment and may be one reason why patients turn to it for treatment (Bewley and Page, 2011).

**2.8 Complementary and alternative medicine therapies for psoriasis**

As societal interest in ‘wellness’, complementary and alternative medicine (CAM) has become increasingly mainstream, use has increased substantially in recent years (Steinberg, 2007, Frass et al., 2012, Xue et al., 2007a). Widespread interest in CAM may, in part, be due to the offer of holistic nonsurgical treatments for conditions that may otherwise involve invasive medical procedures or administration of pharmaceuticals with potential side effects (Wardle et al., 2012, Astin, 1998, McLaughlin et al., 2012). In a UK hospital survey, 81% of respondents indicated their main problem had improved since commencing CAM and 61% of those surveyed who were taking prescription medication had reduced or stopped medication use since commencing CAM (Sharples et al., 2003). While this raises concerns over patient safety around ceasing prescribed pharmaceuticals it also indicates the confidence patients have in CAM.
This growing popularity in CAM and its perceived benefits has encouraged Australian private health insurance companies to increase their cover and access to therapies including CAM. In the June 2015 quarter, over $12 million was charged in acupuncture and natural therapy fees through private health and, of this, only $87,128,018 was covered by their entitled benefits (Australian Prudential Regulation Authority (APRA), August 2015). Reimbursements for private health cover members who use CAM reduces out of pocket expenses for patients which may also contribute to the growing popularity of CAM. In 1995, 31% of the population had general private health cover, which had risen to over half the population by 2015 (56%) (Australian Prudential Regulation Authority (APRA), June 2015). Cost does not appear to be a great concern for psoriasis patients when seeking treatment and a study reported 71% of respondents would pay $1500 or more for a cure for their psoriasis (Finlay and Coles, 1995). This section discusses some of the key herbal and dietary therapies used for psoriasis.

2.8.1 Chinese medicine

Chinese medicine treatment may consist of a variety of modalities including acupuncture, Chinese herbal medicine, tui na (Chinese massage) and gua sha (scraping of the skin with an instrument to induce redness), amongst others. Chinese medicine usage in Australia increased significantly from 1993 to 2000 (MacLennan et al., 2002). In 2004, an Australian survey indicated of those surveyed who had used a form of complementary and alternative medicine, 7% had visited a CHM practitioner in the previous 12 months (Xue et al., 2007b). Of surveyed Australian GPs, 50% rated CHM as effective; however, 66% also consider CHM to be potentially harmful (Cohen et al., 2005). (MacLennan et al., 2002, Fuhrmann et al., 2010)
With the inclusion of Chinese medicine in the Australian Health Practitioner Regulation Agency's regulated professions in 2012, use of CHM is likely to increase further. Improvements in regulation to ensure safety of patients could also increase consumer confidence. Specific risks to people with psoriasis include the usual risks associated with acupuncture and cupping, in addition to an increased risk of further induction of lesions (Koebner phenomenon) [Vender and Vender, 2015]. To inform healthcare professionals and policymakers, CHM clinical research monitoring Chinese medicine and concomitant drug therapy, reporting on population patterns of Chinese medicine use and any significant harms or risks is needed.

Herbal medicine has a long historical usage for psoriasis, predating scientific investigative procedures. Key texts recommend numerous herbs for psoriasis based on past usage; however, scientific evidence for use of herbs in psoriasis is relatively low. However, treatment guidelines available from China recommend various herbal medicine therapies based on the presenting patient’s symptoms (discussed further in Chapter 5) [China Academy of Chinese Medicine, 2011].

To develop a CHM formula for psoriasis vulgaris, historic CHM use should be considered, as well as modern research techniques and available treatment guidelines. Investigation into CHM formulations should consider clinical evidence, scientific evidence, relevant guideline recommendations and specialist opinion. Chinese herbal medicine formulations should be evaluated using the gold standard for testing, that is, via double blind, randomised placebo controlled trial. Chapters’ three to seven describe the process of developing and investigating a CHM formulation for psoriasis.
2.8.2 Diet therapy for psoriasis

Nutritional supplementation may provide a viable treatment alternative for patients with psoriasis. There have been positive effects of vitamin B₁₂, selenium, retinoic acid metabolism-blocking agents, and a gluten-free diet on psoriasis (Ricketts et al., 2010). As discussed previously, obesity can exacerbate psoriasis, so dietary changes along with exercise that reduce obesity can consequently improve psoriasis (Jensen et al., 2013, Naldi et al., 2013). Fasting periods, low-energy diets, vegetarian diets and diets rich in omega-3 polyunsaturated fatty acids from fish oil have improved psoriasis symptoms (Wolters, 2005). For psoriasis sufferers with coeliac disease, a gluten-free diet can reduce IgA anti-gliadin antibody values as well as PASI score (Bhatia et al., 2014).

2.8.3 Other herbal therapies for psoriasis

A herbal-marine origin drug, HESA-A (Osveh Drug Co.), has reported positive results for psoriasis; however, all trials were carried out by the same research group, which raises potential bias concerns (Ahmadi et al., 2008). Furthermore, HESA-A has been indicated for macular degeneration and metastasis in breast cancer, raising query around the specificity of the product (Ahmadi et al., 2009, Ahmadi et al., 2005). Aloe vera appears to be largely safe, with drying of the skin the most common side effect; however, efficacy in psoriasis is uncertain and more high-quality studies are needed (Miroddi et al., 2015, Paulsen et al., 2005).

2.9 Summary of psoriasis disease and its treatment

Psoriasis vulgaris is the most common psoriasis phenotype and the aetiology and pathogenesis of its development is multi-factorial. Genetic factors are the most likely determinant of psoriasis development, but limiting external risk factors, such as cigarettes, are also recommended for susceptible people (Di Lernia et al., 2014, Ryan et
Psoriasis does not appear to discriminate between age and sex; however, there do appear to be geographical areas with higher prevalence of psoriasis, which is likely due to genetic factors.

Psoriasis severity varies considerably; lesions can be small and indiscriminate or large and widespread across multiple surfaces of the body. Those with mild conditions can still experience reduced QoL depending on the location of the lesion and their emotional and psychological perspective of the disease. It is important that QoL instruments are utilised along with symptom measures when evaluating severity of psoriasis and monitoring response to treatment. The severity of psoriasis determines therapy selection and helps physicians calculate dosage as well as decide when to change therapies.

It is clear there is link between psoriasis and a number of serious co-morbidities, yet it is still unclear how direct the relationships are and what specific biological pathways link them. More research is needed to investigate the biological relationship between psoriasis and co-morbidities, and evaluate the potential of current psoriasis therapy for reducing co-morbidity risk. Further research of co-morbidities may lead to the development of new or novel therapies for psoriasis based on newly identified common pathway activity.

Psoriasis therapies generally aim to reduce inflammation and decrease irregular skin cell proliferation (Mrowietz et al., 2011). Available therapies range from topical and oral drugs to light therapy. There is general consensus about the complex inflammatory pathways involved in psoriasis, which has led to development of new therapies such as biologics; however, these are expensive and their long-term safety profile is still unclear. Traditional oral therapies also carry risks, such as liver damage, so some drugs need to be avoided by immune-compromised sufferers. Furthermore,
rebound, relapse, tolerance and resistance are all potential limitations to pharmaceutical therapies for psoriasis (Gottlieb et al., 2008a). For mild–moderate severity psoriasis there is currently a lack of low cost and safe oral therapeutic options.

Complementary and alternative therapy for psoriasis is increasing in popularity, but there is little data available for their efficacy and safety. Historical evidence suggests CHM has potential for treating psoriasis, however scientific evidence is relatively low. As such, treatment guidelines do not yet recommend CAM therapies for psoriasis and more research is needed. Textbooks and published data, however, do indicate likely efficacy of some CAM therapies such as CHM. Considerably more research into the safety and efficacy of CHM for psoriasis is needed.

The next chapter presents systematic review of RCT evidence for efficacy and safety of oral CHM compared with placebo and evaluates potential mechanisms of common phytochemicals found in utilised CHM.
Chapter 3 – The efficacy and safety of oral Chinese herbal medicine compared with placebo for psoriasis vulgaris: A systematic review

This chapter presents systematic review data of RCTs of oral CHM for psoriasis vulgaris compared to placebo. It evaluates published efficacy and safety evidence for oral CHM and assesses the quality of published RCTs to date based on Cochrane risk of bias. Characteristics of the studies are compared and the CHM intervention ingredients are reviewed to identify the most common utilised herbs and potential psoriatic biological activity of their phytochemicals.

3.1 Background, rationale and objectives

Review of psoriasis aetiology, pathogenesis and treatment indicates psoriasis vulgaris is common and mild-moderate disease is often poorly managed. Traditional Chinese medicine has a long history of treating psoriasis, with previous reviews identifying 174 different herbs that have been used for psoriasis (Huang et al., 2012, Zhang et al., 2014b, Yu et al., 2013b). Comprehensive evaluation of oral CHM for psoriasis has not been published so recommendation for its use cannot be confidently given. Evaluation of clinical evidence from RCTs is recognised as the most rigorous method to evaluate an intervention.

This chapter consists of a systematic review of databases for RCTs of human subjects with psoriasis vulgaris receiving oral CHM compared with placebo groups. The systematic review aims to evaluate the efficacy and safety of oral CHM for psoriasis and recommend future trial improvements. Most common CHM utilised in RCTs are also detailed along with available evidence for their biological activity in psoriasis. Trial designs are compared to assist development potential for further CHM RCTs.
3.2 Methods

The review method was based on the Cochrane Handbook for Systematic Reviews of Interventions (Higgins J, 2011). Outcome measure data for symptom severity were extracted from identified studies. Study data for QoL, syndromes and adverse events were also extracted to evaluate potential future use of oral CHM for psoriasis. Ingredients of CHM of each included study were investigated for frequency of use and constituent compounds with anti-psoriasis activity.

3.2.1 Search strategy

To identify relevant studies both Chinese and English databases were searched. The English databases searched were the Cochrane Central Register of Controlled Trials (CENTRAL), Embase and PubMed, which were pre-assessed as the most likely to have inclusions that fit the eligibility criteria. CINAHL was also searched using the option ‘exclude Medline results’, as PubMed covers Medline; however, none of the 136 title results in CINAHL matched the inclusion criteria, and so were not included in the review. Four Chinese databases were searched, Wanfang, Chinese Biomedical Literature (CBM), China National Knowledge Infrastructure (CNKI) and Chongqing VIP Information Co. (CQVIP), which were pre-assessed as the most extensive and applicable to our criteria.

The chosen databases were searched from their inception to June 2015. Search terms were grouped into three search blocks: condition (psoriasis vulgaris), CHM intervention and study design (RCT), and synonyms of each (see below). Selection of search terms was individualised for each database. For ‘condition’ and ‘study type’ previously published Cochrane review protocols were screened to ensure a comprehensive list of search terms. These terms were then combined with medical subject headings (MeSH) terms as well as source and map terms for each criterion of the
databases. The list of search terms was then modified specific to the search functions of each database.

*Cochrane search term development*

Since the focus of the Cochrane Library is clinical trials and systematic reviews of clinical trials the group of search terms for ‘study type’ was not used for this search. The two groups and subgroups of terms are listed below. These were entered into the advanced search bar and the ‘all text’ search option was selected.

*Condition*

Psoriasis or psoriases or psoriasiform or parapsoriasis or psoriatic or skin diseases, papulosquamous or palmoplantar pustulosis or "pustular psoriasis of palms and soles or pustulosis palmaris et plantaris.

*Intervention*

(a) Chinese medicine, traditional or medicine, Chinese traditional or Chinese traditional medicine or traditional Chinese medicine or medicine, traditional or medicine, oriental traditional or medicine, Chinese traditional or tcm or t.c.m. or medicine, Tibetan traditional or medicine, Mongolian traditional or medicine, east asian traditional or alternative medicine or complementary medicine or complementary therapies or medicine, ayurvedic.

(b) Chinese drugs, plant or drugs, Chinese herbal or Chinese herbal drugs or ethnopharmacology or ethnomedicine or ethnobotany or medicine, kampo or kampo or phytotherapy or medicine, herbal or herbology or plants, medicinal or plant preparations or plant extracts or materia medica or single prescription or herbs or herbal medicine.
The subgroups of group 2 were combined with ‘OR’ then groups 1 and 2 were combined with ‘AND’. The sub-databases for ‘clinical trials’ and ‘Cochrane reviews’ were searched and the results were downloaded to a dedicated EndNote library.

*Embase search term development*

The ‘multi field search’ tab option was selected and each of the three criteria was entered into separate fields selecting ‘all fields’ as a search method.

*Condition*

(a) Psoriasis or psoriasiform or psoriatic or psoriases or erythematous squamous skin disease or parapsoriasis.

(b) Palmoplantar pustulosis or pustulosis palmaris et plantaris or acrodermatitis continua or impetigo herpetiformis or pustulosis palmaris et plantaris or palmoplantaris pustulosis.

(c) Pustulosis of palms and soles.

(d) Pustular psoriasis of palms and soles.

*Intervention*

(a) Medicine, traditional or oriental traditional medicine or traditional medicine or medicine, Chinese traditional or tcm or t.c.m. or medicine, ayurvedic or alternative medicine or complementary medicine or complementary therapies.

(b) Ethnopharmacology or ethnomedicine or ethnobotany or medicine, kampo or kampo or phytotherapy or medicine, herbal or herbology or plants, medicine or drugs, Chinese herbal or materia medica or single prescription or herbal medicine or herbs or Chinese medicine herb.
Study type
Clinical trial or clinical study or controlled trial or controlled study or random! control! trial or random! control! study or multicentre study or meta-analysis or random allocation or double-blind or single-blind or comparative study or evaluation study or follow-up study or prospective study or research design or control group or placebo control or dummy control or blinding or clinical research or medical trial or in vivo study or case control study or case study or intervention study or longitudinal study.

The results of the search were downloaded to a dedicated EndNote library using the ‘export citation(s)’ function and the ‘complete reference’ option.

PubMed search term development
Search terms were mapped to MeSH headings. Using the ‘advanced’ search option each of the developed criteria was entered into the ‘builder’ in separate fields and ‘title/abstract’ selected.

Condition
Psoriasis or psoriases or psoriasiform or parapsoriasis or psoriatic psoriasis arthropathica or psoriasis, arthritic or skin diseases, papulosquamous or palmoplantar pustulosis or pustular psoriasis of palms and soles or pustulosis palmaris et plantaris or pustulosis of palms and soles or acrodermatitis continua or impetigo herpetiformis.

Intervention
Traditional Chinese medicine or Chinese traditional medicine or Chinese herbal drugs or Chinese drugs, plant or medicine, traditional or ethnopharmacology or ethnomedicine or ethnobotany or medicine, kampo or kampo or tcm or t.c.m. or medicine, ayurvedic or alternative medicine or complementary medicine or phytotherapy or herbology or plants, medicinal or plant preparations or plant extracts
or plants, medicine or materia medica or single prescription or acupuncture or meridians or electroacupuncture or moxibustion or auriculotherapy or catgut embedding or herbs or Chinese medicine herb or herbal medicine.

**Study type**

Clinical trial or clinical study or biomedical research or controlled trial or controlled study or random* control* trial or random* control* study or multicentre study or meta-analysis or random allocation or double-blind or single-blind or comparative study or evaluation study or follow-up study or prospective study or research design or control group or placebo control or dummy control or blinding or clinical research or medical trial or *in vivo* study or case control study or case study or intervention study or longitudinal study.

The three main groups were combined with ‘AND’ and the results downloaded to a dedicated EndNote library.

**Chinese database search**

Due to language restrictions, Chinese database searching was conducted by a colleague. The method for the development of search terms and conditions of the search is detailed and described in Chinese in appendix 2.

**3.2.2 Study screening and data extraction**

Trial selection was based on the Cochrane Handbook for Systematic Reviews of Interventions (Higgins J, 2011). The results of each of the three databases were exported to separate EndNote files, which were then combined to form a comprehensive library. Duplicates were removed using the ‘remove duplicates’ function. The researchers then visually scanned the remaining list and excluded obvious duplicates. The remaining records were then screened via title and or/abstract to
exclude articles that did not meet all three initial search criteria. Thus, the exclusion criteria were:

1. Duplication
2. Condition – not specifically investigating psoriasis
3. Intervention – not CHM oral form
4. Study type – not RCT
5. Publication language – not English or Chinese
6. Subjects – not human
7. RCT – not for investigating the efficacy of oral CHM
8. RCT – not CHM and conventional medicine administered together compared to conventional medicine alone

Randomised controlled trials in which oral CHM was the intervention were included. Condition was limited to psoriasis vulgaris type of any stage, severity or duration. Only trials published in English or Chinese were included with no limitations on age or gender. Journal articles, conference proceedings and theses were eligible for inclusion. Multiple arm studies were considered if one of the control arms was placebo. Studies investigating psoriasis type other than vulgaris or utilising CHM in a form other than orally were excluded. Any RCTs involving use of a conventional therapy along with CHM were also considered, providing the control group (placebo) received the same conventional therapy and the therapy was recommended by international guidelines.

Data were extracted from included studies to an Excel spread sheet, including: author, year, country, trial design, number of participants, treatment duration, intervention, methodological quality, outcome measures, study results and adverse
events. In situations of missing data, attempts were made to contact authors to attain the information.

3.2.3 Risk of bias assessment

Risk of bias was assessed according to the Cochrane Collaboration’s tool for items of: sequence generation, allocation concealment, blinding of participants and practitioner, blinding of outcome assessors, incomplete data, selective outcome reporting and other bias (if any) (Higgins J, 2011). For each domain two reviewers assessed bias risk as low, high or unclear. Where two different judgements were made, the two researchers discussed the case and continued disagreement was resolved by a third reviewer. Where information was not sufficient to make judgement, attempt was made to contact authors for further information and an unclear rating was judged for that domain.

3.2.4 Meta-analyses

Data for primary outcomes were entered into RevMan 5.2 for analysis. If there were more than two clinically homogeneous studies, such as multiple studies reporting PASI outcome, they were pooled together for meta-analysis. The variation in oral CHM intervention did not affect how data were pooled and specific formulation data were sufficient to perform any subgroup analysis based on heterogeneous intervention. For dichotomous data, relative risk (RR) and 95% confidence interval (CI) were reported, while mean difference (MD) and 95% CI was reported for continuous data. Statistical heterogeneity was explored through sensitivity and subgroup analyses where the $I^2$ statistic was >50%. Where $I^2$ remained >50% a random effects model was employed.

3.3 Results

The initial database search identified 16,020 records. After removal of duplicates and screening titles and abstracts, 1014 full-text articles were screened for inclusion. Seven studies
from eight publications were included in the final review (Figure 3.1), two articles referred to data from the same study (Chen, 2005, Wang, 2003) and one study was excluded from meta analyses as it did not use PASI as an outcome measure (Tan, 2008).

**Figure 3.1:** PRISMA flowchart detailing study selection for analysis

CHM, Chinese herbal medicine; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PT, pharmacotherapy; RCT, randomised controlled trial
3.3.1 Description of the included studies

Out of the seven included studies, six were conducted on hospital outpatients and the seventh did not state location (Dai et al., 2014b). Five studies were published in Chinese and undertaken in China and the other two were published in English, one conducted in China (Dai et al., 2014b) and the other in Hong Kong (Ho et al., 2009). The earliest study was published in 1999 (Zhang et al., 1999) and the most recent in 2012 (Zhou et al., 2012a). Two studies had a third arm (control other than placebo), but these arms of data were not included in this review (Ho et al., 2009, Tan, 2008). One study stratified participants into one of three groups based on Chinese medicine syndrome type, but all groups received the same treatment (Table 3.1)(Dai et al., 2014b).

3.3.2 Participants

The total number of included participants in the seven studies was 569, but 31 were reported as either dropouts or lost to follow-up, so the remaining 538 were included in assessed data (Table 3.1). In four studies the participants had progressive stage psoriasis and the remaining studies did not state stage (Dai et al., 2014b) (Ho et al., 2009, Tan, 2008). For baseline severity, one study described participants as mild, moderate or severe (Su et al., 2010b), another included participants with body surface area (BSA) greater than 20% (Ho et al., 2009), while the remaining five did not state initial severity. Mean psoriasis duration ranged from 3.3 (Wang, 2003) to 8.9 (Dai et al., 2014b) years in the intervention group and 3.3 (Wang, 2003) to 6.45 (Dai et al., 2014b) years in control groups (Table 3.1), but was not reported by Ho (2009).
<table>
<thead>
<tr>
<th>First author; publication year; country; setting</th>
<th>Study design; blinding; number of arms</th>
<th>Treatment duration; follow-up duration</th>
<th>Stage; severity and duration of condition</th>
<th>No. of participants randomised/assessed; dropouts</th>
<th>Age (mean (SD) or range); gender (M/F)</th>
<th>Intervention</th>
<th>Control 1</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dai; 2014</td>
<td>RCT; NS; 4</td>
<td>8w</td>
<td>I¹: NS, NS, 9.62(5.33)y</td>
<td>I¹: 30/30; 0</td>
<td>I¹: 38.7(11.8); 12/18</td>
<td>Yinxieling decoction and cod liver oil ointment</td>
<td>N/A</td>
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<td></td>
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<td>I²: NS, NS, 8.51(7.69)y</td>
<td>I²: 30/30; 0</td>
<td>I²: 36.48(12.34); 11/19</td>
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<td>I³: NS, NS, 8.59(5.4)y</td>
<td>I³: 30/30; 0</td>
<td>I³: 36.3(12.7); 13/17</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>C: NS, NS, 6.45(8.15)y</td>
<td>C: 30/30; 0</td>
<td>C: 37.39 (13.04); 14/16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ho; 2009; Hong Kong; hospital outpatient</td>
<td>RCT; S-B; 3</td>
<td>6m; 0</td>
<td>I: NS; &gt;20%BSA; NS</td>
<td>I: 21/14; 7</td>
<td>I: 48.5; 14/7</td>
<td>Wen tong hua yu fang</td>
<td>Placebo capsule</td>
<td>Methotrexate and folic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C1: NS; &gt;20%BSA; NS</td>
<td>C1: 20/17; 3</td>
<td>C1: 43.5; 18/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C2: NS; &gt;20%BSA; NS</td>
<td>C2: 20/19; 1</td>
<td>C2: 38.5; 18/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Su; 2010; China; hospital outpatient</td>
<td>RCT; NS; 2</td>
<td>12w; 0</td>
<td>I: progressive stage; mild; moderate and severe; 11.7 (3.5)y</td>
<td>I: 35/35; 0</td>
<td>I: 48.8 (18.1); 28/7</td>
<td>Ke yin he ji</td>
<td>Placebo (Starch pill);</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: progressive stage; mild; moderate and severe; 11.4 (4.0)y</td>
<td>C: 35/35; 0</td>
<td>C: 52.2 (16.1); 26/9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First author; publication year; country; setting</td>
<td>Study design; blinding; number of arms</td>
<td>Treatment duration; follow-up duration</td>
<td>Stage; severity and duration of condition</td>
<td>No. of participants randomised/assessed; dropouts</td>
<td>Age (mean (SD) or range); gender (M/F)</td>
<td>Intervention</td>
<td>Control 1</td>
<td>Control 2</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Tan; 2008; China; hospital outpatient</td>
<td>RCT; S-B; 3</td>
<td>NS; 0</td>
<td>I: NS; NS; 6.3 (3.4)y</td>
<td>I: 49/49; 0</td>
<td>I: 30.3 (7.23); 31/18</td>
<td>CHM (unnamed formula)</td>
<td>Placebo</td>
<td>Diyin tablet</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C1: NS; NS; 7.8 (4.7)y</td>
<td>C1: 40/40; 0</td>
<td>C1: 31.6 (7.3); 27/13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C2: NS; NS; 7.3 (3.8)y</td>
<td>C2: 47/47; 0</td>
<td>C2: 33.3 (6.4); 31/16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang; 2003; China; hospital outpatient</td>
<td>RCT; D-B; 2</td>
<td>4w; 0</td>
<td>I: progressive stage; NS; 56.7 (40)m</td>
<td>I: 27/25; 2</td>
<td>I: 26.7 (12.3); 16/9</td>
<td>Fu fang qing dai jiao nang</td>
<td>Placebo</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: progressive stage; NS; 61.2 (40)m</td>
<td>C: 32/27; 5</td>
<td>C: 28.6 (14.2); 20/7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang; 1999; China; hospital outpatient</td>
<td>RCT; D-B; 2</td>
<td>4w; 0</td>
<td>I: progressive stage; NS; 56.7 (40.1)m</td>
<td>I: 29/25; 4</td>
<td>I: 26.7 (12.3); 16/9</td>
<td>Lei gong teng jiao nang</td>
<td>Placebo capsule</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: progressive stage; NS; 61.2 (39.6)m</td>
<td>C: 32/27; 5</td>
<td>C: 28.6 (14.3); 20/7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhou; 2012; China; hospital outpatient</td>
<td>RCT; D-B; 2</td>
<td>8w; 0</td>
<td>I: progressive stage; NS; 4.0 (5.9)y</td>
<td>I: 35/33; 2</td>
<td>I: 34.1 (9.2); 16/19</td>
<td>Liang xue huo xue fu fang</td>
<td>Placebo decoction</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: progressive stage; NS; 3.7 (5.8)y</td>
<td>C: 27/25; 2</td>
<td>C: 31.0 (7.9); 11/16</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse event; BSA, body surface area; CHM, Chinese herbal medicine; C, control; D-B, double blind; F, female I, intervention; m, months; M, male; S-B, single blind, SD, standard deviation; NS, not stated; N/A, not applicable; RCT, randomised control trial; w, weeks; y, years


3.3.3 Interventions

Six studies investigated multi-ingredient formulations, while one utilised a single CHM, *Tripterygium wilfordii* (*Lei gong teng*) (Zhang et al., 1999). Four of the studies administered treatments in decoction form (liquid prepared from cooking herbs) (Su et al., 2010b, Dai et al., 2014b, Tan, 2008, Zhou et al., 2012a), while the remaining three administered treatment in capsule form (Ho et al., 2009) (Wang, 2003) (Zhang et al., 1999). All studies utilised different CHM formulations, with a total of 47 different CHM ingredients used; however, some formulation ingredients were common between multiple trials. *Rehmannia glutinosa* was used in all multi-ingredient studies (n=6), although it was processed in two different ways. Two studies used it in raw form, known as ‘*di huang*’ (Tan, 2008, Zhou et al., 2012a), and in three studies it was cooked with wine, referred to as ‘*shu di*’ (Ho et al., 2009, Su et al., 2010b, Tan, 2008). Although Dai (2014) also included *Rehmannia glutinosa*, they did not report whether the processed or non-processed form was administered.

*Salvia miltiorrhiza* was used in all multi-ingredient CHM studies except Dai (2014). *Angelica sinensis* was used in four studies (Su et al., 2010b, Dai et al., 2014b, Tan, 2008, Zhou et al., 2012a). Four studies did not detail the quantity of ingredients used (Dai et al., 2014b, Zhang et al., 1999) (Su et al., 2010b) (Wang, 2003), and three did not detail all ingredients in the formulations (Table 3.1)(Ho et al., 2009, Zhou et al., 2012a, Tan, 2008).

Chinese medicine syndrome was utilised by four studies (Dai et al., 2014b, Zhou et al., 2012a, Tan, 2008, Su et al., 2010b), while the remaining studies did not state whether syndrome was considered. After syndrome differentiation, intervention type remained the same for participants in each study except Tan (2008), in which one of
four different formulations was administered based on syndrome type (blood heat, blood dryness, blood deficiency or blood stasis).

All studies utilised placebo as a control arm, administered on its own in all studies except Dai (2014), which combined the placebo and CHM arms with cod liver oil. Placebo was administered in capsule form in three studies (Ho et al., 2009, Zhang et al., 1999, Wang, 2003), starch pills in one (Su et al., 2010b) and as decoction in two studies (Dai et al., 2014b, Zhou et al., 2012a). One study did not provide sufficient detail to identify the placebo form, nor did it detail dosage or administration (Tan, 2008). Su (2010) administered the placebo in a different form (pill) from its CHM (decoction). This study used the same frequency of administration for both arms, however the dosages differed. The remaining studies used the same dosage and administration procedures in both arms (Dai et al., 2014b, Ho et al., 2009, Wang, 2003, Zhang et al., 1999, Zhou et al., 2012a)(Table 3.2).
Table 3.2: Intervention/comparators of included RCTs (oral CHM vs. placebo)

<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Syndrome differentiation</th>
<th>CM principle of treatment</th>
<th>Chinese herbal medicine formula and ingredients</th>
<th>Preparations and dosage</th>
<th>Pharmacotherapy (specify)</th>
<th>Dosage and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dai, 2014</td>
<td>Wind heat; Blood stasis; Blood dryness</td>
<td>Remove heat to cool blood, promote blood circulation remove blood stasis, and nourish yin and blood.</td>
<td>Radix <em>rehmanniae recens</em> (<em>shu di</em>), <em>angelica sinensis</em> (<em>dang gui</em>), <em>radix paeoniae rubra</em> (<em>chi shao</em>), <em>ligusticum wallichii</em> (<em>chuan xiong</em>), <em>radices lithospermi</em> (<em>zi cao</em>), <em>curcuma zedoary</em> (<em>e zhu</em>), <em>chloranthus spicatus</em> (<em>zhong jie feng</em>), <em>rhizome smilacis glabrae</em> (<em>tu fu ling</em>), smoked plum (<em>wu mei</em>), <em>liquorice</em> (<em>gan cao</em>) etc.</td>
<td>Decoction 100mL po, bid</td>
<td>Placebo decoction (.5g caramel)</td>
<td>100mL po, bid</td>
</tr>
<tr>
<td>Ho, 2009</td>
<td>NS</td>
<td>NS</td>
<td>Wen tong hua yu fang: <em>ephedra sinica</em> (<em>ma huang</em>) 6g, <em>radix aconiti lateralis praeparata</em> (<em>fu zi</em>) 10g, <em>semen brassicae</em> (<em>bai jie zi</em>) 10g, <em>cortex cinnamomi</em> (<em>rou gui</em>) 5g, <em>rhizoma zingiberis</em> (<em>gan jiang</em>) 3g, <em>cornu cervi degelatinatum</em> (<em>lu jiao shuang</em>) 15g, <em>radix rehmanniae preparata</em> (<em>shu di</em>) 10g, <em>rhizoma smilacis glabrae</em> (<em>tu fu ling</em>) 60g, <em>cortex dictamn</em> (<em>bai xian pi</em>) 30g, <em>rhizoma imperatae</em> (<em>bai mao gen</em>) 30g, <em>salvia miltiorrhiza</em> (<em>dan shen</em>) 15g, <em>caulis spatholobi</em> (<em>ji xue teng</em>) 30g, <em>rhizoma lithospermi</em> (<em>zi zao</em>) 30g, <em>flos sophorae immuturus</em> (<em>huai hua mi</em>) 30g, <em>radix glycyrrhizae</em> (<em>gan cao</em>) 6g, <em>indigo naturalis</em> (<em>qing dai</em>) 6g</td>
<td>Capsule, NS</td>
<td>C1: Placebo capsule; C2: Methotrexate and folic acid</td>
<td>C1: Po, NS; C2: Methotrexate po, 2.5mg then increase, no more than 30mg per week; folic acid 5mg per day</td>
</tr>
<tr>
<td>Su, 2010</td>
<td>Blood stasis</td>
<td>Nourish Blood and clear dryness, invigorate Blood and remove stasis</td>
<td>Ke yin he ji: <em>angelica sinensis</em> (<em>dang gui</em>), <em>radix rehmanniae preparata</em> (<em>shu di</em>), <em>radix paeoniae rubra</em> (<em>chi shao</em>), <em>semen persicae</em> (<em>tao ren</em>), <em>radix sophorae flavescentis</em> (<em>ku shen</em>), <em>flos carthami</em> (<em>hong hua</em>), <em>herba taraxaci</em> (<em>pu gong ying</em>), <em>radix salviae miltiorrhizae</em> (<em>dan shen</em>), etc.</td>
<td>Decoction, 150mL po, bid</td>
<td>Placebo (Starch pill)</td>
<td>3.75g/(kg.d), po, bid</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Syndrome differentiation</td>
<td>CM principle of treatment</td>
<td>Chinese herbal medicine formula and ingredients</td>
<td>Preparations type and dosage</td>
<td>Pharmacotherapy (specify)</td>
<td>Dosage and administration</td>
</tr>
<tr>
<td>--------------------------------</td>
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<td>-----------------------------------------------</td>
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</tr>
<tr>
<td>Tan, 2008</td>
<td>4 types: Blood heat; Blood dryness; Blood deficiency; Blood stasis</td>
<td>Blood heat type: clear heat and cool Blood dryness Blood deficiency type: nourish Yin Blood stasis type: remove stasis</td>
<td>For blood heat type: flos sophorae immaturus (<em>huai hua mi</em>) 30g, radix lithospermi (<em>zi cao</em>) 15g, radix paeoniae rubra (<em>chi shao</em>) 15g, rhizoma imperatae (<em>bai mao gen</em>) 30g, radix rehmanniae (<em>di huang</em>) 30g, radix salviae miltiorrhizae (<em>dan shen</em>) 15g, radix scutellaria baicalensis (<em>huang qin</em>) 15g, gypsum fibrosum (<em>shi gao</em>) 30g; For blood dryness type: radix rehmanniae preparata (<em>shu di</em>) 30g, angelica sinensis (<em>dang gui</em>) 30g, radix astragali (<em>huang qi</em>) 30g, radix polygoni multiflori (<em>he shou wu</em>) 30g, radix salviae miltiorrhizae (<em>dan shen</em>) 30g, semen cannabis (huo ma ren) 15g, cortex <em>paeonia suffruticos</em> andr (<em>mu dan pi</em>) 15g, radix ophiopogonis (<em>mai dong</em>) 15g, radix asparagi (<em>tian men dong</em>) 15g, fructus tribuli (<em>bai ji li</em>) 15g, radix glycyrrhizae (<em>gan cao</em>) 10g; For blood deficiency type: rhizoma atractylodis macrocephalae (<em>bai zhu</em>) 30g, angelica sinensis (<em>gang gui</em>) 30g, radix paeoniae alba (<em>bai shao</em>) 30g, scierotium poriae cocos (<em>fu ling</em>) 30g, radix astragali (<em>huang qi</em>) 15g, caulis spatholobi (<em>ji xue teng</em>) 15g, fructus tribuli (<em>bai ji li</em>) 10g, radix glycyrrhizae (<em>gan cao</em>) 10g; blood stasis type: radix astragali (<em>huang qi</em>) 30g, angelica sinensis (<em>dang gui</em>) 30g, radix paeoniae rubra (<em>chi shao</em>) 30g, rhizoma chuanxiong (<em>chuan xiong</em>) 30g, semen persicae (<em>tao ren</em>) 15g, cortex dictamni (<em>bai xian pi</em>) 15g, pericarpium citri reticulatae (<em>chen pi</em>) 15g, flos carthami (<em>hong hua</em>) 10g, radix glycyrrhizae (<em>gan cao</em>) 10g</td>
<td>Decoction, one pack per day</td>
<td>Placebo</td>
<td>NS</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Syndrome differentiation</td>
<td>CM principle of treatment</td>
<td>Chinese herbal medicine formula and ingredients</td>
<td>Preparation type and dosage</td>
<td>Pharmacotherapy (specify)</td>
<td>Dosage and administration</td>
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<td>-------------------------------</td>
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</tr>
<tr>
<td>Wang, 2003</td>
<td>NS</td>
<td>NS</td>
<td>Fu fang qing dai jiao nang: indigo naturalis (<em>qing dai</em>), radix angelicae dahuricae (<em>bai zhi</em>), radix lithosperm (zi <em>cao</em>), radix salviae miltiorrhizae (<em>dan shen</em>), etc.</td>
<td>Capsule, 12 po, qd</td>
<td>Placebo</td>
<td>Capsule, 12 po, qd</td>
</tr>
<tr>
<td>Zhang, 1999</td>
<td>NS</td>
<td>NS</td>
<td>Lei gong teng jiao nang: tripterygium wilfordii (<em>lei gong teng</em>)</td>
<td>Capsule, 6 (18g)/d, po</td>
<td>Placebo capsule, 6 (18g)/d, po</td>
<td>6 capsules (18g)/d, po</td>
</tr>
<tr>
<td>Zhou, 2012</td>
<td>Wind heat and blood dryness</td>
<td>Cool Blood and invigorate Blood</td>
<td>Liang xue huo xue fu fang: folium isatis tinctoria (<em>da qing ye</em>) 15g, radix rehmanniae (<em>di huang</em>) 30g, radix scutellaria baicalensis (<em>huang qin</em>) 12g, radix lithosperm (zi <em>cao</em>) 9g, radix salviae miltiorrhizae (<em>dan shen</em>) 12g, radix paeoniae rubra (<em>chi shao</em>) 6g, cortex paeonia suffruticosanda (<em>mu dan pi</em>) 9g, angelica sinensis (<em>dang gui</em>) 12g, rhizoma smilacis glabrae (<em>tu fu ling</em>) 30g, cortex dictamni (<em>bai xian pi</em>) 9g, herba schizonepetae (<em>jing jie</em>) 6g, flos lonicerae (<em>jin yin hua</em>) 20g</td>
<td>Decoction, one pack a day</td>
<td>Placebo decoction</td>
<td>One pack a day</td>
</tr>
</tbody>
</table>

bid, twice per day; CM, Chinese medicine; g, grams; po, oral administration; NS, not stated
### 3.3.4 Treatment duration and follow-up

Treatment duration of studies ranged from four weeks (Wang, 2003, Zhang et al., 1999) to six months (Ho et al., 2009). Only one study did not state treatment duration (Tan, 2008). Treatment durations of four weeks (n=2) (Wang, 2003, Zhang et al., 1999) or eight weeks (n=2) (Dai et al., 2014b, Zhou et al., 2012a) were most common. None of the studies presented follow-up data after treatment (Table 3.1).

### 3.3.5 Outcome measures

Total effective rate (TER) was the primary outcome measure used for all included studies except Dai (2014), which only utilised PASI score. Rates were all based on percentage change to PASI score except Tan (2008), which based primary outcome on percentage of lesion reduction (95% and 50%). The endpoint for PASI score change varied for each study. Four studies indicated a PASI 90 endpoint as the greatest degree of improvement (Su et al., 2010b, Wang, 2003, Zhang et al., 1999, Zhou et al., 2012a), with PASI 70 considered mid-level improvement (Wang, 2003, Zhang et al., 1999) or PASI 60 (Su et al., 2010b). Zhou (2012) reported the greatest PASI reduction outcome of 95% and Ho (2009) had the lowest PASI reduction outcome with 75% (Table 3.3). Variation also existed in the lowest level improvement, with two studies reporting PASI 50 (Wang, 2003, Zhang et al., 1999), one PASI 25 (Su et al., 2010b) and one PASI 20 (Zhou et al., 2012a).
Table 3.3: Outcome measures of included RCTs (oral CHM vs. placebo)

<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Definition of effectiveness</th>
<th>Psoriasis lesions</th>
<th>Quality of life</th>
<th>Biological markers</th>
<th>Relapse rate</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dai, 2014</td>
<td>PASI change</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Ho, 2009</td>
<td>PASI 75, 50</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Su, 2010</td>
<td>PASI 90, 60, 25</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tan, 2008</td>
<td>Lesion reduction (%) 95, 50</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Wang, 2003</td>
<td>PASI 90, 70, 50</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Zhang, 1999</td>
<td>PASI 90, 70, 50</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Zhou, 2012</td>
<td>PASI 95, 60, 20</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>SF-36</td>
<td>Yes</td>
</tr>
</tbody>
</table>

DLQI, dermatology life quality index; QoL, quality of life; PASI, psoriasis area severity index; PDI, psoriasis disability index
Four of the studies specifically reported PASI assessment data (Dai et al., 2014b) (Ho et al., 2009) (Zhou et al., 2012a, Wang, 2003), while the remaining studies only reporting effective rates. Two studies presented QoL data, but only one utilised the most recognised QoL outcome for psoriasis, the dermatology life quality index (Finlay and Khan, 1994) as well as a non-dermatology specific QoL instrument, the SF-36 (Zhou et al., 2012a). Ho (2009) utilised the psoriasis disability index, a measure of QoL specific to psoriasis but not commonly used (Bhosle et al., 2006). Potential biological marker changes were reported in two studies (Dai et al., 2014b, Ho et al., 2009), with no data on relapse rates provided by any of the studies (Table 3.1).

3.3.6 Dropouts

Four of the seven studies reported dropouts, with Ho (2009) reporting the highest dropout rate (11/61) including seven from the intervention group (n=21). Zhang (1999) reported nine dropouts (n=61) with five from the control group (n=32). Wang (2003) reported seven dropouts (n=59), five from the control group (n=32). And Zhou (2012) reported two dropouts from the intervention group (n=35) and two from the control group (n=27) (Table 3.1).

3.3.7 Risk of bias assessment

Two studies were assessed as 'low risk' for sequence generation, as they reported techniques that were fully randomised with low potential risk in the method (Tan, 2008, Zhou et al., 2012a). The remaining studies were assessed as unclear because the method for sequence generation was not described in sufficient detail (Dai et al., 2014b, Ho et al., 2009, Su et al., 2010b, Wang, 2003, Zhang et al., 1999). Allocation concealment was reported satisfactorily in Wang (2003) and Zhou (2012), and so was assessed as low risk; however, for all other studies the reporting was insufficient to make clear
judgment on bias risk so were rated unclear (Dai et al., 2014b, Ho et al., 2009, Su et al., 2010b, Tan, 2008, Zhang et al., 1999).

Risk of bias assessments for blinding of participants and blinding of personnel were assessed as high risk for Ho (2009) and Su (2010) as they did not employ participant or personnel blinding to treatment allocation. Su (2010) administered the intervention in decoction form, yet the placebo was employed in pill form, indicating high risk of bias for inadequate blinding. Dai (2014) was assessed as unclear for personnel blinding and the remaining four studies were rated low risk for both categories (Tan, 2008, Wang, 2003, Zhang et al., 1999, Zhou et al., 2012a).

For blinding of outcome assessors all studies were rated unclear, as published details were insufficient to make a judgment. For incomplete outcome, only three studies were assessed as low risk (Su et al., 2010b, Tan, 2008, Dai et al., 2014b), considering none reported dropouts, final data were assumed to be complete. The other four studies were rated as high risk, as they did not include dropout data in their final analysis. There was no evidence to suggest bias so selective outcome reporting was considered low risk for all studies. Without available published protocols for each study, data could not be completely evaluated for selective outcome reporting, and as a result it could be argued this criterion should be assessed as unclear (Table 3.4)
Table 3.4: Risk of bias assessment of included trials (oral CHM vs. placebo)

<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants</th>
<th>Blinding of personnel</th>
<th>Blinding of outcome assessors</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dai, 2014</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Ho, 2009</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Su, 2010</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Tan, 2008</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Wang, 2003</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Zhang, 1999</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Zhou, 2012</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>
3.3.8 Efficacy

For outcome measure evaluation, Chinese guidelines recommend minimum PASI 60 for treatment to be considered successful. Internationally recognised clinical guidelines commonly consider treatment success as PASI 75 and below PASI 50 as treatment failure (Gordon and Ruderman, 2005). As reported in a similar systematic review, a PASI reduction of at least 60% was selected as the outcome criterion for meta-analysis and pooling of data (Zhang et al., 2014b).

Of those studies evaluating multi-ingredient CHM compared with placebo, four (n=215) used an outcome of PASI 60 or above (Ho et al., 2009, Zhang et al., 1999, Zhou et al., 2012a, Su et al., 2010b). These showed no significant effect for CHM intervention (RR: 2.74 [0.92, 8.21] I²=65%) (Figure 3.2).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Oral CHM Events</th>
<th>Placebo Events</th>
<th>Total Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho 2009</td>
<td>0</td>
<td>14</td>
<td>3</td>
<td>1.10%</td>
</tr>
<tr>
<td>Su 2010</td>
<td>20</td>
<td>25</td>
<td>7</td>
<td>35.0%</td>
</tr>
<tr>
<td>Zhang 1999</td>
<td>21</td>
<td>25</td>
<td>0</td>
<td>17.1%</td>
</tr>
<tr>
<td>Zhou 2012</td>
<td>19</td>
<td>35</td>
<td>6</td>
<td>27.3%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>106</td>
<td>106</td>
<td>100.0%</td>
<td>2.74 [0.92, 8.21]</td>
</tr>
<tr>
<td>Total events</td>
<td>60</td>
<td>16</td>
<td></td>
<td>0.67</td>
</tr>
</tbody>
</table>

Test for overall effect: 2 = 18.1 (p = 0.04); I² = 65%

Heterogeneity: Tau² = 0.67; Chi² = 8.53, df = 3 (p = 0.04); I² = 65%

Figure 3.2: Meta-analysis forest plot (PASI 60 and above)

For PASI score change, five studies (Dai et al., 2014b, Zhang et al., 1999, Zhou et al., 2012a, Ho et al., 2009, Wang, 2003) (n=141) showed effect in favour of CHM compared with placebo (MD –7.00 [-10.74, –3.27]); however, heterogeneity of the studies was quite high (I²=98%) (Figure 3.3).
Although not utilising PASI as an outcome, Tan (2008) study data (n=89) also showed superiority of CHM compared with placebo, where CHM reduced lesions by at least 50% (RR: 4.49 [2.40, 8.40]). For QoL via the dermatology life quality index only one study reported sufficient data (Zhou et al., 2012a), in which CHM showed improvement in health-related QoL of subjects (n=58) (MD: –4.08 [–7.56, –0.60]).

Known as a key inflammatory factor, tumour necrosis factor alpha (TNF-\(\alpha\)) is often targeted by conventional drugs for psoriasis (Tobin and Kirby, 2005). The TNF-\(\alpha\) biomarker was the only biomarker with results available in more than one study and able to be assessed using meta-analysis. Dai (2014) separated participants into four groups: three groups received different CHM (groups A, B and C) and one group placebo only (group D). As A, B and C all received oral CHM, subgroup classification was not important so subgroup data were combined. Sample size was added together for the CHM groups A, B and C (n=90), then mean was calculated using the formula:

\[
\frac{N_1M_1 + N_2M_2}{N_1 + N_2} = \text{E.g. M1, group one mean; N1, group one sample size}
\]

and standard deviation (SD) was calculated using the formula:

\[
\sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1M_2)}{N_1 + N_2 - 1}} = \text{(Higgins J, 2011).}
\]
Results were entered into a meta-analysis along with placebo data to be evaluated along with Ho’s (2009) data. Results showed CHM overall had an effect on TNF-α reduction (MD: –4.92 [-5.31, –4.53] I²=0%) (Figure 3.4).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Oral CHM Mean</th>
<th>SD</th>
<th>Total</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dai 2014</td>
<td>12.35</td>
<td>4.1</td>
<td>30</td>
<td>17.43</td>
<td>2.1</td>
<td>30</td>
<td>11.7%</td>
<td>–5.08 [-6.22, –3.95]</td>
<td></td>
</tr>
<tr>
<td>Su 2010</td>
<td>1.44</td>
<td>0.58</td>
<td>35</td>
<td>6.34</td>
<td>1.1</td>
<td>35</td>
<td>88.3%</td>
<td>–4.90 [-5.31, –4.49]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>125</td>
<td></td>
<td>65</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.0% –4.92 [-5.31, –4.53]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Ch² = 0.0%, df = 1 (P = 0.77), I² = 0%
Test for overall effect: Z = 24.91 (P < 0.00001)

Figure 3.4: Meta-analysis forest plot (TNF-α)

3.3.9 Safety

Adverse events data were presented in all but three studies (Su et al., 2010b, Dai et al., 2014b, Tan, 2008). Gastrointestinal symptoms were the most commonly reported adverse events, reported in three studies in the CHM arm (Ho et al., 2009) (Wang, 2003, Zhang et al., 1999). Wang (2003) reported seven gastrointestinal events, five mild and two moderate, while Zhang (1999) reported four events. Ho (2009) did not report the number of gastrointestinal events. Diarrhoea or loose stools were the next most commonly reported adverse events, four in the CHM group in Zhang (1999), and six in the CHM group and one in the placebo group of Zhou (2012), all considered mild. Other reported adverse events included menstrual disorder (Zhang et al., 1999), infection and abnormal liver function in the treatment group, and infection and increased liver enzymes in the placebo group (numbers of events not reported)(Ho et al., 2009).

Regardless of similarity of adverse events between the control and intervention arms of Ho (2009), the authors gauged the tolerability of CHM as moderate (Table 3.5)
<table>
<thead>
<tr>
<th>Study</th>
<th>Adverse events (number of events)</th>
<th>Author's conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dai, 2014</td>
<td>Not reported</td>
<td>N/A</td>
</tr>
<tr>
<td>Ho, 2009</td>
<td>I: infections and gastrointestinal symptoms, abnormal liver function</td>
<td>The tolerability of both methotrexate and CHM was moderate</td>
</tr>
<tr>
<td></td>
<td>C1 (placebo): infections and increased liver enzymes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C2 (methotrexate): nausea, vomiting, increased liver enzyme</td>
<td></td>
</tr>
<tr>
<td>Su, 2010</td>
<td>Not reported</td>
<td>N/A</td>
</tr>
<tr>
<td>Tan, 2008</td>
<td>Not reported</td>
<td>N/A</td>
</tr>
<tr>
<td>Wang, 2003</td>
<td>I: moderate gastrointestinal upset (2), mild gastrointestinal upset (5)</td>
<td>CHM is safe for psoriasis management</td>
</tr>
<tr>
<td></td>
<td>C (placebo): no AEs</td>
<td></td>
</tr>
<tr>
<td>Zhang, 1999</td>
<td>I: gastrointestinal upset (4), diarrhoea (4), menstrual disorder (1)</td>
<td>AEs caused by CHM are mild and were relieved by reducing dosage</td>
</tr>
<tr>
<td></td>
<td>C (placebo): no AEs</td>
<td></td>
</tr>
<tr>
<td>Zhou, 2012</td>
<td>I: loose stool (6)</td>
<td>All AEs were mild</td>
</tr>
<tr>
<td></td>
<td>C (placebo): loose stool (1)</td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse event; CHM, Chinese herbal medicine; C, control; I, intervention; N/A, not applicable
3.4 Discussion

3.4.1 Efficacy of oral CM vs. placebo

Although the systematic review found CHM significantly affects PASI change, CHM did not reduce PASI score by at least 60% compared with placebo. It is noted only four studies were eligible for PASI 60 assessment with a total of 215 participants so it is possible the sample size was not sufficient in power to detect significance as no studies reported a priori power. A post hoc power analysis was not performed in this review due to variation in the intervention types and unknown effect sizes. To ensure sufficient examination of future studies, a priori power analyses should be conducted using results from pilot studies on experimental CHM interventions providing effect size estimates for the population.

Oral CHM does not appear to have as potent effects as common oral systemic therapies that achieve PASI 75, such as infliximab (RR: 13.07, [8.60–19.87]), etanercept (8.39, [6.74–10.45]) and apremilast (5.83, [2.58–13.1]) (Nast et al., 2015b). Methotrexate has been reported to have less effect than the aforementioned systemic drugs (Schmitt et al., 2014). Ho’s (2009) comparison between oral CHM and methotrexate and placebo found both methotrexate and placebo to be superior to CHM. However, more sensitive analysis (after removal of Ho’s intervention data) may show that oral CHM effects approach that of systemic drugs for PASI 60 or above.

From previous systematic reviews, efficacy of topical therapies, vitamin D analogues (SMD: −0.58 [−0.71, −0.45]) and corticosteroid (SMD: −0.97 [−1.31, −0.62]), as well as their combined use (SMD: −1.24 [−1.53, −0.95]), are indicated to have less effect than oral CHM (MD: −7.00(−10.74, −3.27)(Mason et al., 2013).
With previous clinical and pre-clinical evidence suggesting its potential in immune disease, Zhang (1999) investigated use of a single ingredient oral CHM, *Tripterygium wilfordii*, for psoriasis (Lv et al., 2015) (Tao et al., 2001) (Ma et al., 2007). Despite achieving the greatest effect on PASI 60, no other reviewed studies included it in their formulations. The botanical has been indicated for use in rheumatoid arthritis, where it reduces immune response inflammation and T-cell proliferation, key aspects of psoriasis pathogenesis, which might explain its efficacy (Canter et al., 2006, Chan et al., 1999).

### 3.4.2 Safety

All studies that reported adverse events for oral CHM described them as relatively mild or at most moderate. Although *Tripterygium wilfordii* (from leaves, flowers and the skin of the roots (National Center for Complementary and Integrative Health (NCCIH) Clearinghouse, 2007)) is considered toxic, Zhang (1999) reported only mild gastrointestinal disturbances, which were relieved by reduction in dosage. Preparation and processing of *Tripterygium wilfordii* is important for reducing its toxicity (Tao et al., 2001). In addition, to further reduce toxic effects on the gastrointestinal tract, researchers and clinicians should consider the addition of *Glycyrrhiza radix*, which is often added to formulations to reduce toxic effects of other ingredients (Hempen and Fischer, 2009b). Of the included studies, only two reported inclusion of *Glycyrrhiza radix* in their intervention formulations (Ho et al., 2009, Tan, 2008). Tan (2008) used it in three out of the four formulations it administered to different groups and did not report any adverse events.

Ho (2009) utilised two CHM ingredients well known for their toxicity, *Ephedra sinica* and *Radix aconiti lateralis praeparata*; the latter’s toxicity can be reduced by
special processing (Flanagan et al., 2010) (Singhuber et al., 2009). It is unclear if *Glycyrrhiza radix* inclusion reduced the toxic effects of these herbs and further study would be needed to evaluate effects of the same formulations without its inclusion.

It is difficult to individually evaluate the safety of ingredients in each formulation, as numerous interactions are likely occurring between constituent compounds of ingredients. Such interaction would likely see synergism of some compound effects and neutralisation of others. However, the current review indicates that oral CHM forms of the utilised formulations are relatively safe with, at most, moderate side effects. This is similar to the risk profile of commonly utilised pharmaceutical therapy methotrexate. Other studies that reported adverse events evaluated CHM as safe overall (Wang, 2003), or with only mild risk (Zhang et al., 1999; Zhou et al., 2012a).

Further research is needed to investigate the safety of combined use of oral CHM and conventional therapy. Polypharmacy has proven to be an important issue for physicians with increasing numbers of products also increasing the risk of drug–drug interaction (Marengoni and Onder, 2015). As with any drug, CHM should be prescribed with caution, and where available toxicity evidence between herbal ingredients and conventional drugs should be considered to evaluate risk. For instance, common herbal supplement *Hypericum perforatum* (St John’s wort) should not be used with immunosuppressant cyclosporine A, which is sometimes prescribed for psoriasis (Mai et al., 2000). To reduce likelihood of severe adverse effects, patients with reduced liver or kidney function should be monitored while taking oral CHM. Similarly, for psoriasis sufferers with multiple co-morbidities, physicians should consider other co-morbidity medications along with psoriasis medications for potential herb–drug interactions (Scottish Government Model of Care Polypharmacy Working Group, 2015).
3.4.3 Methodological quality of included studies

Two of the four studies for PASI 60 outcome had no blinding of participants or personnel (Ho et al., 2009, Su et al., 2010b). Such insufficiency in design may have resulted in outcome bias and contributed to effect size. Similarly, blinding of participants was absent for one of five studies for PASI score outcomes (Ho et al., 2009).

Only one study (Ho et al., 2009) utilised the recommended treatment efficacy outcome PASI 75, making it difficult to pool or compare results with other international clinical trials. No included trials included all consolidated standards of reporting trials (CONSORT) items (Schulz et al., 2010). Such reporting would provide more detail on accuracy and specificity of each intervention for its target population. Furthermore, four studies had incomplete data reporting, raising concern over the quality and accuracy of reporting (Ho et al., 2009, Wang, 2003, Zhang et al., 1999, Zhou et al., 2012a). It was noted that the final assessment data for Wang (2003) and Zhang (2009) had identical outcomes despite differences in initial sample size and reported interventions. Age, duration of disease and gender descriptors was also identical for both studies, raising concern among reviewers of legitimacy. No other bias or conflict of interest was identified in the studies. Future trials need to improve the quality and content of their reporting. Publishing of study protocols would ensure consistency between investigated and reported outcomes.

3.4.4 Potential therapeutic actions of Chinese herbal medicine for psoriasis vulgaris

Despite formulation variation between studies, some CHM ingredients were common. The Chinese medicine actions and biological pathways of their constituents may help explain their repeated selection for clinical trials of psoriasis. Due to the large variety of CHM utilised in the studies it is not feasible to review the phytochemical activity of all
herbs. A brief review of the three most commonly used CHM in the reviewed studies was undertaken to present both theoretical anti-psoriatic Chinese medicine action and biological mechanisms.

Salvia miltiorrhiza (dan shen)

The Chinese medicine syndrome blood stagnation is commonly attributed to psoriasis and it is likely Salvia miltiorrhiza’s Chinese medicine functions of moving blood and breaking up blood stasis is why it was the most commonly utilised CHM in the reviewed studies (five studies) (Ho et al., 2009, Su et al., 2010b, Tan, 2008, Wang, 2003, Zhou et al., 2012a) (Hempen and Fischer, 2009b). Salvia miltiorrhiza is considered to possess anti-inflammatory, antioxidant and anti-proliferative effects, as well as protective effects on the liver and cardiovascular system (Wang et al., 2007). Biologically, Salvia miltiorrhiza constituents have been evidenced to suppress inflammatory mediators such as IFN-γ and IL-12, and it may also reduce mast cell degranulation and inhibit the aggregation of platelets (Bartosińska et al., 2011).

Proliferation of keratinocytes is a key feature of psoriatic skin and in vitro study of mouse keratinocytes indicated tanshinone IIA, a constituent of S. miltiorrhiza root, inhibited keratinocyte proliferation in a dose- and time-dependent manner by inducing apoptosis via the caspase pathway (Li et al., 2012a, Ma et al., 2013). Another possible mechanism of action for tanshinone IIA in keratinocytes is via inhibiting dimerization of the activator protein 1 transcription factor resulting in reduced interferon sensitivity, which in turn could lead to a reduced inflammatory response (Pedersen et al., 2012).

Angelica sinensis (dang gui)

Angelica sinensis (used in four studies) is thought to possess Chinese medicine functions of tonifying blood, moving blood and draining wind-dampness (Su et al., 2010b, Dai et al., 2014b, Tan, 2008, Zhou et al., 2012a), and so may reduce psoriasis by reducing the
dryness of skin (Hempen and Fischer, 2009b). Ferulic acid is one of its major constituents, which contains constituents evidenced to prolong prothrombin time and inhibit platelet aggregation (Chinese Pharmacopoeia Commission, 2005). Furthermore, it has both antimicrobial and hepato-protective effects. Other biological actions that may have some effect on psoriasis include its antioxidative actions and potential as a weak analgesic. There is also evidence it can reduce inflammation and inhibit cell proliferation of tumours (Hempen and Fischer, 2009b).

Rehmannia glutinosa (shu di/di huang)

In di huang (raw) form, the Chinese medicine functions of Rehmannia glutinosa (used in two studies) (Tan, 2008, Zhou et al., 2012a) are generally to cool heat, cool blood, stop bleeding and tonify yin, all functions that may reduce symptoms such as Auspitz sign (pinpoint bleeding from angiogenesis) (Hempen and Fischer, 2009b). When further processed by mixing with wine and steaming, the Chinese medicine functions of shu di (used in three studies) (Ho et al., 2009) (Su et al., 2010b, Tan, 2008) become less cooling and more tonifying.

Rehmannia glutinosa has been evidenced to be anti-inflammatory, inhibiting histamine release and production of TNF-α, both of which are known to be significant contributors to inflammation. An in vitro study reported that an aqueous extract of fresh R. glutinosa root inhibited the release of histamine and the production of TNF-α in mast cells (Kim et al., 1998). Study reports R. glutinosa aqueous extracts promote free radical scavenging activity due to suppression of pro-inflammatory gene expression, including TNF-α, monocyte chemotactic protein-1, interferon inducible protein-10, cyclooxygenase-2 and inducible nitric oxide synthase (Baek et al., 2012). There is further evidence that R. glutinosa may reduce production of cytokine IL-1, but how specific this is to psoriasis is unclear (Kim et al., 1999).
Catalpol, a compound of *R. glutinosa*, also shows anti-inflammatory action, reducing production of pro-inflammatory mediators such as inducible nitric oxide synthase, monocyte chemotactic protein-1, TNF-α and the receptor for advanced glycation end-products, as well as reducing the transcriptional activation of nuclear factor-jB (Wang et al., 1997, Astaf’eva et al., 2002, Chinese Pharmacopoeia Commission, 2005, Choi et al., 2013, Zhang et al., 2013b). Although not focused on psoriasis, several studies have indicated that extracts of *R. glutinosa* and its constituent catalpol have anti-inflammatory effects.

These are just the common CHM ingredients highlighted in this review that may have psoriasis-related mechanistic actions. More experimental research is needed to evaluate which are the most potent as anti-psoriatic therapies and to assess any toxicity. Those constituents with anti-inflammatory and/or anti-proliferative effects hold most promise for psoriasis treatment, as current conventional therapies target these pathways.

### 3.4.5 Limitations of the review

Due to variation in the primary outcomes for efficacy in the studies, only the outcomes PASI 60 or above and general PASI change had enough data to be pooled and evaluated using meta-analysis. Commonly, global treatment guidelines consider PASI 75 treatment effect to be effective; however, as the majority of studies did not state this outcome measure, oral CHM effectiveness for PASI 75 cannot be evaluated (The Australian Government, 2004). This makes it difficult to compare the effect size of CHM with results of other psoriasis therapies. Application of any significant weight to conclusions should first consider the relatively low sample sizes and risk of bias of each study. Three studies did not detail all the ingredients used in their interventions (Su et
al., 2010b, Dai et al., 2014b, Wang, 2003) so some CHM ingredients are missing from this review.

The review did not evaluate the potential phytochemical activity of all CHM ingredients, only the three most frequently used, and most likely to have anti-psoriatic activity, CHM ingredients. Further review is needed to evaluate the large number of phytochemicals of CHM utilised for psoriasis. Such research may provide data on common phytochemicals found in CHM that warrant further in vitro and in vivo study for development of potential new anti-psoriatic drugs.

The included studies provided little justification for how or why they selected their formulation and ingredients. This limits the conclusions that can be drawn from the frequency of herbs used as there may actually be herbs which are better indicated for psoriasis which were not utilised. As per CONSORT herbal extension recommendations for rationale (Gagnier et al., 2006a).

3.4.6 Clinical and future research implication of review findings

The sheer variety of CHM formulations and diverse ingredient selection makes it difficult to determine which are of greatest benefit for psoriasis. However, this review does indicate that various forms of administration type (decoction, capsule or pill) of CHM can benefit psoriasis, although the degree of effect for each is unclear. Dai (2014) used the decoction form and reported the greatest effect on PASI change (–13.09[–13.91, –12.27]); however, Zhou (2012) also used CHM in decoction form with less effect (–3.10[–4.23, –1.97]) than two studies utilising capsule form of CHM, Zhang (1999) and Wang (2003) (–7.52[–8.45, –6.59]).

Each study used different combinations of herbs, so future research should compare effects between different forms (i.e. capsules vs. decoction) of the same herbal
ingredients to investigate the impact on outcomes. In this review, the multiple-ingredient interventions administered by Dai (2014) had the greatest effect on PASI change (−13.09 [−13.91, −12.27]), and single-ingredient CHM *Tripterygium wilfordii* (*lei gong teng*) administered in Zhang (1999) had the greatest effect, achieving PASI 60 (46.31[2.95, 726.24]). As the CHM formulation of each study was unique, it was difficult to distinguish which ingredients had the greatest and least psoriatic therapeutic response. To better compare effects, future studies might consider additional arms consisting of different CHM formulations. More pre-clinical evidence such as *in vitro* and *in vivo* research may provide data for researchers to construct an optimised psoriasis-specific CHM formulation that could be further explored in clinical trials (May et al., 2012).

While reviewed studies reported psoriasis symptoms according to international treatment guideline recommendations, they did not consistently report on QoL effects. Future clinical trials should include reliable QoL instruments validated for psoriatic populations. Only one study (Zhou et al., 2012a) utilised the commonly recommended QoL outcome the dermatology life quality index, which found CHM had greater effect than placebo. To evaluate oral CHM for QoL, more data are clearly needed.

The common CHM ingredients highlighted in this review show potential anti-psoriatic activity such as anti-inflammation and anti-proliferation (Man et al., 2008, Tse et al, 2007); however, more research is needed to evaluate such effects. For Chinese medicine disease treatment, CHM selection varies according to syndrome classification based on physiological characteristics and symptoms of the sufferer along with inspection of the pulse and tongue. Chinese clinical guidelines identify three main Chinese medicine syndromes: blood heat, blood dryness and blood stasis (China Academy of Chinese Medicine, 2011). Clinicians and researchers should consider both
conventional biological activity potential of CHM and Chinese medicine theoretical basis when selecting formulation ingredients for prescription.

Formulations of CHM in this review appear safe for use in people with psoriasis, although populations were predominantly Asian; so safety is less clear for other ethnicity groups. Sample sizes were relatively low and so had insufficient power to detect statistical significance of outcomes. Future studies should conduct a priori power analysis to ensure sufficient sample sizes, minimise design bias and publish study details that follow the CONSORT and its extension for herbal interventions (Schulz et al., 2010, Gagnier et al., 2006b).

3.5 Conclusion

This systematic review compared seven RCT studies of oral CHM, identifying use of 47 different CHM. Following systematic review of oral CHM for psoriasis, data indicate CHM is relatively safe and has some efficacy for psoriasis. However, evaluation of oral CHM effect was only possible for PASI change and PASI 60. The effects of CHM compared with placebo were not significant for PASI 60 or above, however CHM was superior to placebo for overall PASI score change. The effect size of oral CHM was relatively modest compared with oral systemic treatments, and more likely reflects efficacy of conventional topical treatments. Limited data indicated CHM had greater improvement in QoL. Risk of adverse events from CHM was mild, however long-term safety is unknown.

The review process was limited by inconsistent reporting of intervention details and outcome measures, as well as low participant numbers. Chinese herbal medicine appeared to have some effect on psoriasis symptoms; however results are insufficient to draw sound conclusions on efficacy and safety. More high-quality studies are needed
that utilise targeted interventions, have psoriasis-specific outcome measures, utilise validated QoL instruments and report long-term follow-up periods. Given the growth of CAM therapy and increasing likelihood that CAM therapies may be utilised alongside conventional therapies, a second review of RCTs combining oral CHM with conventional therapy was proposed to evaluate efficacy and safety compared with conventional therapy alone.
Chapter 4 – The efficacy and safety of integrating oral Chinese herbal medicine and conventional medicine for psoriasis vulgaris: A systematic review

This chapter presents the methodology and results of a systematic review of RCTs of oral CHM combined with conventional medicine for psoriasis vulgaris. It evaluates published efficacy and safety evidence of their combined therapy and assesses the quality of published RCTs to date based on Cochrane risk of bias. Characteristics of the studies are compared and both CHM and conventional medicine interventions are presented. The most common CHM are also reviewed for phytochemicals, which have potential psoriatic biological activity.

4.1 Background, rationale and objectives

Having determined from review one (see Chapter 3), CHM has benefit for psoriasis and is relatively safe, which is also supported by previously conducted reviews, further investigation was needed to evaluate its use alongside conventional therapies (May et al., 2012, Wang and Liu, 2004). Conventional therapies are effective for psoriasis symptoms yet do not cure the disease and can cause unwanted side effects, particularly with long-term use (Nast et al., 2012, Menter et al., 2008). While integrated therapy using CHM and conventional therapy is common in China, such practice in westernised regions is relatively new (Xu and Chen, 2008). Individual limitations of conventional therapy and CHM have been discussed (see Chapter 2); however, the effects of their combined use for psoriasis are relatively unknown.

In order to advise clinicians, patients, policymakers and researchers on the safety and efficacy of such combined treatment further evaluation are needed. This review analyses data from published RCTs to investigate the efficacy and safety of oral CHM
combined with various forms of conventional pharmacotherapy for psoriasis vulgaris. This review also identifies the most common CHM ingredients administered in psoriasis RCTs and discusses their potential biological activity in psoriasis. The review aims to evaluate the feasibility of a clinical study on combined CHM and conventional therapy for psoriasis vulgaris. It also aims to determine the optimal population characteristics, intervention ingredients (both CHM and conventional), outcome measures, study duration and design for a subsequent clinical study. The systematic review evaluates data from RCTs involving CHM combined with conventional therapy, compared with conventional therapy alone and, where possible, meta-analyses of the data are presented. The results of this review have already been published (Zhang et al., 2014b), an updated search was conducted in May 2014 and new studies that were not included in the original search results are discussed in the supplementary search section 4.5.

4.2 Methods

4.2.1 Search strategy

The Cochrane Library, PubMed, Embase, CINAHL, CNKI and CQVIP were searched from their inception to November 2012. Three groups of search terms were used: condition (psoriasis vulgaris and synonyms); intervention type (oral CHM and synonyms); and study type (RCT and synonyms). These groups of terms were combined and the results downloaded to a dedicated file. The same search strategy was used as the previous review (Chinese medicine vs. Placebo See 3.2.1 for English database strategies and appendix 2 for Chinese database strategies); however, study selection differed as the current review focuses on RCTs of combined CHM and conventional therapy compared with conventional therapy alone, rather than compared with placebo.
4.2.2 Study selection and data extraction

Included studies were RCTs published in English or Chinese that compared oral CHM plus pharmacotherapy with pharmacotherapy alone. Participants were limited to people with psoriasis vulgaris, but no limits were placed on stage or severity of disease or participant age or gender. Journal articles, conference proceedings, and these were considered. If the RCT consisted of more than two arms, only the data for the CHM plus pharmacotherapy arm and the pharmacotherapy arm were included. Studies that used non-oral CHM or phototherapy, or treated other types of psoriasis were excluded. Studies with a third arm consisting of CHM alone were eligible for inclusion in the review; however, data from the CHM alone arm was excluded from analysis.

One reviewer screened the Chinese titles and abstracts, and another screened the English search results. Full-text articles were obtained for further assessment of eligibility. Any uncertainty was resolved through discussion with a third reviewer. Reasons for exclusion were recorded. Data were extracted from the remaining RCTs to an Excel spread sheet and crosschecked by two reviewers. When information was found to be unclear, attempts were made to contact the authors. In the event there was no reply, a judgment was made through discussion between all three reviewers.

4.2.3 Risk of bias assessment

Risk of bias was assessed by two reviewers using the Cochrane Collaboration tool (Higgins J, 2011) for the following items: sequence generation, allocation concealment, blinding of participants and practitioner, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other bias (defined as funding resource). As per the review in Chapter 3, two reviewers assessed each domain and disagreement was resolved through discussion with a third reviewer. Where published information
was not sufficient to make a judgment on a domain the authors were contacted to provide further information and if data were still insufficient the domain was judged as unclear.

4.2.4 Meta-analysis

Meta-analysis was carried out using Review Manager (the Cochrane Collaboration) 5.1. Studies were grouped according to the pharmacotherapy type used and the outcome measure. Dichotomous data were expressed as risk ratio (RR), and continuous data were presented as mean difference (MD), both with 95% confidence intervals (CI). A fixed-effect or random effect model was used according to heterogeneity. Any dropouts were included in the meta-analysis as ineffective following an intention-to-treat (ITT) approach.

4.3 Results

In total, 1883 records were obtained through database searches, and 198 potentially relevant articles were identified after screening titles and abstracts. Among them, 19 met the inclusion criteria for the review. Thirteen studies were included in meta-analyses for primary outcomes, of those six excluded from meta-analysis one study utilised different outcome measures to other studies (Yu and Pan, 2007), two studies did not define their outcome measure calculation (Kong, 2007a, Chen, 2010) one had outcome below required minimum improvement (Xie, 2006), one study reported incorrect data (Wan, 2012) and the last excluded study did not provide effect size data (Tan and Li, 2010) (Figure 4.1).

4.3.1 Description of studies

All included trials were conducted in hospitals in China and published in Chinese within the last 11 years. Three studies had a third arm for CHM alone (Huang, 2010, Wan, 2012,
Xie, 2006), but as indicated in the methods section this data was not included in the review.
Figure 4.1: Flow chart of study selection according to PRISMA guidelines

CHM, Chinese herbal medicine; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PT, pharmacotherapy; RCT, randomised controlled trial
Participants

The total number of participants included in the two arms of the 19 RCTs was 1691, with 915 in the CHM plus pharmacotherapy groups and 776 in the pharmacotherapy-only groups. There were inconsistencies in the number of participants reported in two studies, the text and results tables differing (Huang, 2010, Wan, 2012). Attempts were made to contact the authors but these were unsuccessful, so the numbers of participants in the results tables were used. Participants’ ages ranged from 13 to 70 years (Lin and Jin, 2012) and there were 571 males and 406 females. Two studies (Huang, 2010) (Luo, 2010) did not provide information on participant gender, and this information in Wan, although reported, was unclear (Wan, 2012).

All included RCTs recruited people with psoriasis vulgaris, with duration since initial onset varying from two weeks (Mao and Mao, 2007) to 11 years (Jin et al., 2009). Four studies reported a baseline psoriasis area severity index (PASI score) (all >10) (Jin et al., 2009, Tian, 2011, Wu et al., 2009a, Zheng, 2011). The other studies did not provide information on baseline disease severity, although baseline balance was reported in all studies. One study (Liu, 2005a) only included patients with stationary stage psoriasis vulgaris, while six other RCTs recruited patients known to be in progressive or stationary stages (Lin and Jin, 2012, Xie, 2006, Mao and Mao, 2007, Wu et al., 2009a, Yang et al., 2005, Zhang, 2012), and the remaining studies did not provide this information (Table 4.1) (Huang, 2010) (Jin, 2009 #2525, Kong, 2007a, Wan, 2012, Yu and Pan, 2007, Chen and Tan, 2004, Tan, 2008, Chen, 2010, Luo, 2010, Zheng, 2011, Tian, 2011, Shen and Zhao, 2005) (Jin et al., 2009) (Huang, 2010).
<table>
<thead>
<tr>
<th>Author, year, setting, country</th>
<th>Sample size (T/C); Average or range of age (T/C)</th>
<th>Treatment interventions</th>
<th>Control interventions</th>
<th>Treatment and follow-up duration</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Participants who reported AE (n=); SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mao 2007, Hospital, China</td>
<td>62 (31/31); Age: T: 45.48, C: 43.45</td>
<td>CHM decoction bid; Acitretin capsules, 10mg bid; compound Amino-polypeptide tablets, 5 tablets bid.</td>
<td>Acitretin capsules, 10mg bid; compound amino-polypeptide tablets, 5 tablets bid.</td>
<td>8 weeks; 3 months</td>
<td>TER based on 4 levels (PASI 90, 60, 30, 0); blood tests of liver and kidney function</td>
<td>Reported T&gt;C for TER; effect size of PASI 60: RR 1.09 [0.81, 1.46].</td>
<td>Mild AEs of skin dryness, pruritus, T/C: (1/3); No SAE</td>
</tr>
<tr>
<td>Jin 2009, Hospital, China</td>
<td>60 (30/30); Age: T: 37±16.1, C: 36±17.2</td>
<td>CHM decoction bid; Topically use Calcipotriol, bid.</td>
<td>Topically use Calcipotriol bid.</td>
<td>12 weeks; No follow-up</td>
<td>TER based on 4 levels (PASI 90, 60, 20, 0), PASI score.</td>
<td>Reported T&gt;C for TER and PASI score; effect size of PASI 60: RR 1.27 [1.01, 1.61]; effect size of PASI score: MD 1.63, [0.58, 2.68].</td>
<td>5 participants from two groups reported mild skin redness, caused by WM.</td>
</tr>
<tr>
<td>Kong 2007, Hospital, China</td>
<td>86 (45/41); Age: T: 32.7±8.21, C: 33.1±7.98</td>
<td>CHM decoction bid; Compound Amino-polypeptide tablets: 3-4 tablets bid, IV 10% gluconate calcium, 40ml qd.</td>
<td>Compound Amino-polypeptide tablets: 3-4 tablets bid, IV 10% gluconate calcium, 40ml qd.</td>
<td>6 weeks; No follow-up</td>
<td>TER based on 3 levels of lesion reduction, no scoring method.</td>
<td>Reported T&gt;C for TER, no definition for effectiveness, no effect size analysis.</td>
<td>No information for AE or SAE.</td>
</tr>
<tr>
<td>Wan 2012, Hospital, China</td>
<td>64 (32/32); Age: T: 13 to 66, C: 15 to 65.</td>
<td>CHM decoction bid; Compound Amino-polypeptide tablets: 5 tablets, bid.</td>
<td>Compound Amino-polypeptide tablets: 5 tablets, bid.</td>
<td>1 month; 6 months</td>
<td>TER based on 4 levels (lesion reduction 95, 75, 30, 0).</td>
<td>Reported T&gt;C for TER, significant errors in data reporting, no effect size analysis.</td>
<td>Reported no AE.</td>
</tr>
<tr>
<td>Yu 2007, Hospital, China</td>
<td>58 (30/28); Age: Total: 45.85</td>
<td>CHM powder: bid; topically use emollient; Compound Amino-polypeptide tablets: 5 tablets, bid.</td>
<td>Topically use emollient; Compound Amino-polypeptide tablets: 5 tablets, bid.</td>
<td>2 months; No follow-up</td>
<td>TER based on 4 levels of the combined score of PASI and DLQI</td>
<td>Reported T&gt;C for TER, no definition for effectiveness, no effect size analysis.</td>
<td>No information for AE or SAE.</td>
</tr>
<tr>
<td>Author, year, setting, country</td>
<td>Sample size (T/C); Average or range of age (T/C)</td>
<td>Treatment interventions</td>
<td>Control interventions</td>
<td>Treatment and follow-up duration</td>
<td>Outcome measures</td>
<td>Results</td>
<td>Participants who reported AE (n=); SAE</td>
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<tr>
<td>Liu 2005, Hospital, China</td>
<td>60 (40/20); Age: T: 33.63, C: 32.7</td>
<td>CHM decoction bid; Compound Aminopolypeptide tablets: 5 tablets, bid.</td>
<td>Compound Aminopolypeptide tablets: 5 tablets, bid.</td>
<td>No information</td>
<td>TER based on 4 levels of (PASI 95, 70, 30, 0)</td>
<td>Reported T&gt;C for TER; effect size of PASI 70: RR 1.93 [1.02, 3.64].</td>
<td>Mild AEs: dry mouth, dry skin, scaly skin, skin itchiness, p&lt;0.05 between T/C groups; No SAE</td>
</tr>
<tr>
<td>Yang 2005, Hospital, China</td>
<td>60 (30/30); Age: T: 38.42±10.78, C: 35.79±9.18</td>
<td>CHM pill: 18g, bid; Compound Aminopolypeptide tablets: 5 tablets, bid.</td>
<td>Compound Aminopolypeptide tablets: 5 tablets, bid.</td>
<td>1 month; No follow-up</td>
<td>TER based on 4 levels (PASI 90, 60, 30, 0)</td>
<td>Reported T&gt;C for TER and PASI score; effect size of PASI 60: RR 1.38 [0.92, 2.05]; effect size of PASI score: MD -0.44, [-2.54, 1.66].</td>
<td>Mild AEs of skin dryness, pruritus, T/C: (2/10); No SAE</td>
</tr>
<tr>
<td>Chen 2004, Hospital, China</td>
<td>56 (30/26); Age: T: 32.4 (16 to 65); C: 33.2 (17 to 63)</td>
<td>CHM decoction bid; Compound Aminopolypeptide tablets: 5 tablets, bid.</td>
<td>Compound Aminopolypeptide tablets: 5 tablets, bid.</td>
<td>6 weeks; No follow-up</td>
<td>TER based on 5 levels (lesions reduction 100, 90, 60, 30, 0); blood tests of liver and kidney function</td>
<td>Reported T&gt;C for TER; effect size of lesion measurement reduction 60%: RR 1.14 [0.86, 1.51].</td>
<td>Mild AEs: dry mouth, dry lips, dry skin, scaly skin, skin itchiness, p&lt;0.05 between T/C groups; No SAE</td>
</tr>
<tr>
<td>Tan 2010, Hospital, China</td>
<td>90 (50/40); Age: Total: 33.24±11.32</td>
<td>CHM decoction, bid; IV compound glycyrrhizin, 40ml qd; Topically use Tacalcitol, bid.</td>
<td>IV compound glycyrrhizin, 40ml qd; Topically used Tacalcitol, bid.</td>
<td>8 weeks; No follow-up</td>
<td>TER based on 4 levels (PASI 90, 60, 20, 0); blood tests of liver and kidney function</td>
<td>Reported T&gt;C, no data for effect size analysis.</td>
<td>3 mild AEs of skin irritation, caused by WM. No SAE</td>
</tr>
<tr>
<td>Author, year, setting, country</td>
<td>Sample size (T/C); Average or range of age (T/C)</td>
<td>Treatment interventions</td>
<td>Control interventions</td>
<td>Treatment and follow-up duration</td>
<td>Outcome measures</td>
<td>Results</td>
<td>Participants who reported AE (n=); SAE</td>
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<tr>
<td>Zhang 2012, Hospital, China</td>
<td>112 (56/56); Age: Total: 35.8±3.9</td>
<td>CHM decoction, tid; Acitretin capsules: 10mg tid.</td>
<td>Acitretin capsules: 10mg tid.</td>
<td>4 weeks; No follow-up</td>
<td>TER based on 4 levels (lesions reduction 95, 75, 30, 0).</td>
<td>Reported T&gt;C for TER; effect size of lesion measurement reduction 75%: RR 1.64, [1.23, 2.19].</td>
<td>No information for AE or SAE.</td>
</tr>
<tr>
<td>Huang 2010, Hospital, China</td>
<td>70 (40/30); Age: no information</td>
<td>Xiaoyin formula powder: 3.5g tid; Acitretin Capsules: 20mg/qd.</td>
<td>Acitretin Capsules: 20mg qd.</td>
<td>No information</td>
<td>TER based on 4 levels (lesions reduction 100, 60, 30, 0).</td>
<td>Reported T&gt;C for TER; effect size of lesion measurement reduction 60%: RR 1.31, [0.87, 1.96].</td>
<td>Mild AEs in both groups: dry mouth, dry lips, dry skin, scaly skin, caused by WM No SAE.</td>
</tr>
<tr>
<td>Chen 2010, Hospital, China</td>
<td>200 (150/50); Age: T: 42.3, C: 43</td>
<td>CHM decoction, bid; Acitretin capsules: 30mg tid, then 20mg tid.</td>
<td>Acitretin capsules: 30mg tid, then 20mg tid.</td>
<td>60 days, No follow-up</td>
<td>TER based on 3 levels of lesions reduction without scoring; change of blood IL-6, IL-8 level</td>
<td>Reported T&gt;C for TER, no definition for effectiveness, no effect size analysis.</td>
<td>No information for AE or SAE.</td>
</tr>
<tr>
<td>Luo 2010, Hospital, China</td>
<td>174 (74/100); Age: T: 38.0±3.1, C: 34.5±5.1</td>
<td>CHM decoction, bid; Acitretin capsules: 0.5mg/kg/d; IV compound glycyrrhizin, 30ml qd; topically use Calcipotriol, bid.</td>
<td>Acitretin capsules: 0.5mg/kg/d; IV compound glycyrrhizin, 30ml qd; topically use Calcipotriol, bid.</td>
<td>6 weeks, No follow-up</td>
<td>TER based on 4 levels (PASI 95, 60, 30, 0)</td>
<td>Reported T&gt;C for TER; effect size of PASI 60: RR 1.71 [1.30, 2.24].</td>
<td>Mild AEs in C group only, caused by WM; No SAE</td>
</tr>
<tr>
<td>Author, year, setting, country</td>
<td>Sample size (T/C); Average or range of age (T/C)</td>
<td>Treatment interventions</td>
<td>Control interventions</td>
<td>Treatment and follow-up duration</td>
<td>Outcome measures</td>
<td>Results</td>
<td>Participants who reported AE (n=); SAE</td>
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<tr>
<td>Wu 2009, Hospital, China</td>
<td>158 (79/79); Age: T: 37.5±13.2, C: 37.7±14.4</td>
<td>CHM decoction, qd; Acitretin capsules: 0.5mg/kg/d; boric acid ointment, bid.</td>
<td>Acitretin capsules: 0.5mg/kg/d; boric acid ointment, bid.</td>
<td>12 weeks, No follow-up</td>
<td>TER based on 4 levels (PASI 90, 60, 30, 0); PASI score; blood tests liver and kidney function.</td>
<td>Reported T&gt;C for TER and PASI score; effect size of PASI 60: RR 1.29 [1.10, 1.51]; effect size of PASI score: MD -4.03, [-4.97, -3.09].</td>
<td>Mild AEs in both groups, dry and scaly skin, caused by WM, p&lt;0.05 between T/C groups; No SAE</td>
</tr>
<tr>
<td>Xie 2006, Hospital, China</td>
<td>52 (32/20); Age: T: 32.5, C: 35</td>
<td>CHM decoction, bid; Acitretin capsules: 10mg tid for 30 days, then 10mg bid for 60 days.</td>
<td>Acitretin capsules: 10mg tid for 30 days, then10mg bid for 60 days.</td>
<td>3 months; No follow-up</td>
<td>TER based on 3 levels (lesions reduction 95, 50, 0).</td>
<td>Reported T&gt;C for TER, effect size of lesion measurement reduction 50%: RR:13.00 (0.63, 266.29)</td>
<td>Mild AEs: dry mouth, dry skin, scaly skin, skin itchiness, in C group only, no SAE</td>
</tr>
<tr>
<td>Zheng 2011, Hospital, China</td>
<td>120 (60/60); Age: T: 42.1±14.6, C: 42.3±15.4</td>
<td>CHM decoction, bid; Acitretin capsules: started from 20mg/day, then increase to 30-40mg/day, then decrease to 10-20mg/day.</td>
<td>Acitretin capsules: started from 20mg/day, then increase to 30-40mg/day, then decrease to 10-20mg/day.</td>
<td>8 weeks; No follow-up</td>
<td>TER based on 4 levels (PASI 95, 60, 30, 0); PASI score.</td>
<td>Reported T&gt;C for TER and PASI score; effect size of PASI 60: RR 2.00, [1.21, 3.32]; effect size of PASI score: MD -2.45, [-3.60, -1.30].</td>
<td>Mild AEs in both groups: gastrointestinal reaction in both groups; leukocyte decrease in C group only; No SAE</td>
</tr>
<tr>
<td>Tian 2011, Hospital, China</td>
<td>60 (30/30); Age: T: 36.2±9.8, C: 34.5±10.2</td>
<td>CHM decoction; Antihistamine, Vitamin C, B6, IV gluconate calcium.</td>
<td>Antihistamine, Vitamin C, B6, IV gluconate calcium.</td>
<td>60 days; No follow-up</td>
<td>TER based on 4 levels (PASI 90, 60, 20, 0); PASI score.</td>
<td>Reported T&gt;C for TER and PASI score; effect size of PASI 60: RR 2.27, [1.38, 3.74]; effect size of PASI score: MD -5.48, [-6.98, -3.98].</td>
<td>No information for AE or SAE</td>
</tr>
<tr>
<td>Author, year, setting, country</td>
<td>Sample size (T/C); Average or range of age (T/C)</td>
<td>Treatment interventions</td>
<td>Control interventions</td>
<td>Treatment and follow-up duration</td>
<td>Outcome measures</td>
<td>Results</td>
<td>Participants who reported AE (n=); SAE</td>
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<tr>
<td>Lin 2012, Hospital, China</td>
<td>89 (46/43); Age; T:13 to 76, C:14 to 73</td>
<td>Progressive stage: CHM decoction bid; stable stage and progressive stage: compound Danshen tablets, 2 tablets tid; Compound Amino-polypeptide tablets: 5 tablets tid; topically use Tazarotene and emollient</td>
<td>Compound Amino-polypeptide tablets: 5 tablets tid; topically use Tazarotene and emollient alternatively.</td>
<td>2-3 months; 1 year</td>
<td>TER based on 3 levels (lesions reduction 90, 70, ?); Reported T&gt;C for TER; effect size of lesion measurement reduction 70%: RR 2.12 [1.36, 3.30]</td>
<td>No information for AE or SAE.</td>
<td></td>
</tr>
<tr>
<td>Shen 2005, Hospital, China</td>
<td>60 (30/30); Age: total average 37</td>
<td>CHM decoction, bid; Compound Amino-polypeptide tablets: 5 tablets bid; topically use clobetasol propionate ointment.</td>
<td>Compound Amino-polypeptide tablets: 5 tablets bid; topically use clobetasol propionate ointment.</td>
<td>8 weeks; No follow-up</td>
<td>TER based on 4 levels (PASI 90, 60, 30, 0)</td>
<td>Reported T&gt;C for TER; effect size of PASI 60: RR 1.38 [0.92, 2.05].</td>
<td>Mild AEs in both groups: dry month, scaly skin, p&lt;0.05 between T/C groups; No SAE.</td>
</tr>
</tbody>
</table>

AE, adverse events; bid, twice a day; C, control; CHM, Chinese herbal medicine; DLQI, dermatology life quality index; ES, effect size; IV, intravenous drip; MD, mean difference; PASI, psoriasis area and severity index; qd, once a day; RR, risk ratio; SAE, severe adverse events; T>C, treatment group is significantly greater to control group; T, treatment; tid, three times a day; TER, total effective rate.
4.4.1 Supplementary search results

The previous review data has since been published (Zhang et al., 2014b) however an updated search was conducted in May 2013. These results are briefly presented here however were not included in systematic analyses as the studies were not considered prior to protocol development.

Supplementary search study characteristics

A further nine eligible studies were identified with treatment periods ranging from 4 weeks (Xie, 2012) to 12 weeks (Ma SY, 2012, Jiang et al., 2012a, Huang, 2012) with the most utilizing either 8 weeks (n=3) (Han and Yu, 2012, Liu et al., 2012a, Zhu XP, 2012) or 12 weeks (n=3) (Huang, 2012, Jiang et al., 2012a, Ma SY, 2012) treatment period. Only one study reported dropouts in both the intervention arm (n=3) and the control arm (n=5) (Ma SY, 2012). Of the intervention arms the most utilized conventional therapy was acitretin (n=5) (Zhai XF, 2012, Xie, 2012, Ma SY, 2012, Liu et al., 2012a, Jiang et al., 2012a). The most common utilized topical conventional therapy was calcipotriol (n=2) (Zhai XF, 2012, Liu et al., 2012a) (Table 4.4)
**Table 4.2 Characteristics of supplementary RCTs (oral CHM plus pharmacotherapy vs. pharmacotherapy for psoriasis vulgaris)**

<table>
<thead>
<tr>
<th>First author; publication year; country; setting</th>
<th>Study design; blinding; number of arms</th>
<th>Treatment duration; follow-up duration</th>
<th>Stage; severity and duration of psoriasis</th>
<th>No. of participants randomised/assessed; dropouts</th>
<th>Age: mean (SD) (or range); gender M/F</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han, 2012 (Han and Yu 2012), China; hospital outpatients</td>
<td>RCT; NS; 2</td>
<td>8w; 0</td>
<td>I: progressive stage and stationary stage; psoriasis lesion area &gt; 20% BSA; 25 (6.7)m</td>
<td>I: 66/66; 0</td>
<td>I: 32.2 (7.3); 35/31</td>
<td>Liang xue jie du yang yin tang, acitretin, compound flumetasone ointment</td>
<td>Acitretin, Compound flumetasone ointment</td>
</tr>
<tr>
<td>Huang, 2012 (Huang 2012), China; hospital outpatients</td>
<td>RCT; NS; 2</td>
<td>12w; 0</td>
<td>I: NS; NS; 4.5 (0.3)y</td>
<td>I: 58/58; 0</td>
<td>I: 38.8 (0.6); 32/26</td>
<td>Tripterygium glycosides single herb, tacalcitol ointment, tazarotene gel</td>
<td>Tacalcitol ointment tazarotene gel</td>
</tr>
<tr>
<td>Jiang, 2012 (Jiang, Chen et al. 2012), China; hospital out/inpatient</td>
<td>RCT; S-B; 2</td>
<td>3m; 3m</td>
<td>I: NS; NS; 4.2 (2.8)y</td>
<td>I: 30/30; 0</td>
<td>I: 33.4 (4.3); 16/14</td>
<td>Shen di ke li, acitretin</td>
<td>Acitretin</td>
</tr>
<tr>
<td>Liu, 2012 (Liu, Liu et al. 2012), China; hospital outpatients</td>
<td>RCT; NS; 2</td>
<td>8w; 0</td>
<td>Total: progressive stage; psoriasis lesion area &lt; 30% BSA; NS</td>
<td>I: 42/42; 0</td>
<td>I: 40 (10.3); 24/18</td>
<td>Run zao zhi yang jiao nang, acitretin, calcipotriol ointment</td>
<td>Acitretin, calcipotriol ointment</td>
</tr>
<tr>
<td>First author; publication year; country; setting</td>
<td>Study design; blinding; number of arms</td>
<td>Treatment duration; follow-up duration</td>
<td>Stage; severity and duration of psoriasis</td>
<td>No. of participants randomised/assessed; dropouts</td>
<td>Age: mean (SD) (or range); gender M/F</td>
<td>Intervention</td>
<td>Control</td>
</tr>
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</tr>
<tr>
<td>Ma, 2012, China; hospital outpatients</td>
<td>RCT; S-B; 2</td>
<td>12w; 12m</td>
<td>I: stationary stage; NS; 7.3 (0.9)</td>
<td>I: 79/76; 3</td>
<td>I: 37.5 (13.2); 48/31</td>
<td>Da huang zhe chong wan, acitretin</td>
<td>Acitretin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: stationary stage; NS; 7.5 (1.2)</td>
<td>C: 79/74; 5</td>
<td>C: 37.7 (14.4); 50/29</td>
<td></td>
<td></td>
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<tr>
<td>Xie, 2012 (Xie 2012), China; hospital outpatients</td>
<td>RCT; NS; 2</td>
<td>4w; 0</td>
<td>Total: NS; NS; 8.5y</td>
<td>I: 50/50; 0</td>
<td>Total: 35.5 (3.2); 49/45</td>
<td>Run zao zhi yang jiao nang, acitretin, clobetasol propionate ointment</td>
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<td></td>
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<td></td>
<td>C: 44/44; 0</td>
<td></td>
<td></td>
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<tr>
<td>Zhai, 2012, China; hospital outpatients</td>
<td>RCT; NS; 2</td>
<td>7w; 0</td>
<td>I: NS; psoriasis lesion area&gt;30% BSA; 12.1 (3.2)y</td>
<td>I: 85/85; 0</td>
<td>I: 30.7 (4.1); NS</td>
<td>Unnamed formula, aritretin, calcipotriol</td>
<td>Aritretin, calcipotriol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: NS; psoriasis lesion area&gt;30% BSA; 10.2 (2.5)y</td>
<td>C: 100/100; 0</td>
<td>C: 33.4 (4.3); NS</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>C: 56/56; 0</td>
<td></td>
<td></td>
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<tr>
<td>Zhu, 2012 (Zhu, Deng et al. 2012), China; hospital outpatients</td>
<td>RCT; NS; 2</td>
<td>6w; 0</td>
<td>I: NS; NS; 37.9m</td>
<td>I: 50/50; 0</td>
<td>I: 41.2; 34/16</td>
<td>Er dong huo xue tang, Methotrexate</td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: NS; NS; 39.2m</td>
<td>C: 26/26; 0</td>
<td>C: 40.7; 11/15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhu XP 2012, China; hospital</td>
<td>RCT; NS; 2</td>
<td>8w; 0</td>
<td>I: NS; NS; NS</td>
<td>I: 90/90, 0</td>
<td>I: 34.6, 7/83</td>
<td>CHM formula (no name), routine care</td>
<td>Routine care</td>
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<tr>
<td></td>
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<td></td>
<td>C: NS; NS; NS</td>
<td>C: 196/196, 0</td>
<td>C: 35.7, 25/171</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C, control; D-B, double blind; F, female I, intervention; m, months; M, male; S-B, single blind; SD, standard deviation; ST, subtotal; T, total; NS, not stated; N/A, not applicable; RCT, randomised control trial; w, weeks; y, years
Interventions

### Table 4.3: Chinese herbal medicine formulas and ingredients used in included RCTs

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>CHM formula</th>
<th>CHM form</th>
<th>CHM ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mao 2007</td>
<td>No name</td>
<td>Granule powder</td>
<td>For progressing stage: Radix rehmanniae (<em>di huang</em>) 30g, rhizoma smilacis glabrae (<em>tu fu ling</em>) 30g, sophorae immaturus (<em>sheng huai hua</em>) 15g, rhizoma imperatae (<em>bai bao gen</em>) 30g, radix lithospermi (<em>zi cao gen</em>) 15g, radix paoniae rubra (<em>chi shao</em>) 15g, radix salviae miltiorrhizae (<em>dan shen</em>) 15g, gentiana scabra (<em>long dan cao</em>) 10g, radix scutellaria baicalensis (<em>huang qin</em>) 10g, radix glycyrrhizae (<em>gan cao</em>) 10g.</td>
</tr>
<tr>
<td>Wang 2012</td>
<td>Er Dong Huo Xue Tang</td>
<td>Decoction</td>
<td>Radix ophiopogonis (<em>mai dong</em>) 15g, radix asparagi (<em>tian dong</em>) 15g, <em>xue shen</em> 15g, <em>angelica sinensis</em> (<em>dang gui</em>) 15g, <em>radix chuanxiong</em> (<em>chuan xiong</em>) 10g, <em>radix sparganii</em> (<em>san leng</em>) 10g, <em>zedoary rhizome</em> (<em>e zhu</em>) 10g, <em>semen persicae</em> (<em>tao ren</em>) 10g, <em>fructus aurantii</em> (<em>zhi ke</em>) 10g, <em>herba artemisiae scopariae</em> (<em>yin chen</em>) 20g, <em>radix glycyrrhizae</em> (<em>gan cao</em>) 10g.</td>
</tr>
<tr>
<td>Liu 2005</td>
<td>Jian Pi yi Shen Tang</td>
<td>Decoction</td>
<td><em>Sciortium poriae cocos</em> (<em>fu ling</em>) 10-20g, <em>radix codonopsis</em> (<em>dang shen</em>) 10g, <em>atactylodes macrocephala</em> (<em>chao bai zhu</em>) 10-30g, <em>semen dolichoris lablab</em> (<em>bai bian dou</em>) 10g, <em>rhizoma Dioscoreae</em> (<em>shan yao</em>) 10-20g, <em>herba epimedii</em> (<em>xian ling pi</em>) 10-30g, <em>radix astragali</em> (<em>zhi huang qi</em>) 15-30g, <em>rhizoma smilacis glabrae</em> (<em>tu fu ling</em>) 30g, <em>semen persicae</em> (<em>tao ren</em>) 30g, <em>cortex dictamni</em> (<em>bai xian pi</em>) 30g, <em>indigo naturalis</em> (<em>qing dai</em>) 30g.</td>
</tr>
<tr>
<td>Yang 2005</td>
<td>Pi Fu Bing Xue Du Wan</td>
<td>Patent pill</td>
<td><em>Angelica sinensis</em> (<em>dang gui</em>), <em>Radix Paeoniae Rubra</em> (<em>chis shao</em>), <em>fructus forsythiae</em> (<em>lian qiao</em>), <em>flos lonicerae</em> (<em>jin yin hua</em>), <em>periostracum cicadaceae</em> (<em>chan tui</em>), <em>lithospermum erythrorhizon root</em> (<em>zi cao</em>), etc., in total 39 herbs.</td>
</tr>
<tr>
<td>Chen 2004</td>
<td>No name</td>
<td>Decoction</td>
<td><em>Lithospermum erythrorhizon root</em> (<em>zi cao</em>) 15g, <em>polygongum cuspidatum</em> (<em>hu zhang</em>) 15g, <em>flos lonicerae</em> (<em>jin yin hua</em>) 15g, <em>salvia miltiorrhiza</em> (<em>dan shen</em>) 15g, <em>rehmannia glutinosa</em> (<em>di huang</em>) 12g, <em>platycodon grandiflorum</em> (<em>jie geng</em>) 12g, <em>folium isatis tinctoria</em> (<em>da qing ye</em>) 12g, <em>cortex Paeoniae suffruticosa</em> andr (<em>dan pi</em>) 12g, <em>radix paoniae rubra</em> (<em>chi shao</em>) 12g, <em>sophorae immaturus</em> (<em>huai hua</em>) 12g, <em>angelica sinensis</em> (<em>dang gui</em>) 12g, <em>caulis spatholobi</em> (<em>ji xue teng</em>) 25g.</td>
</tr>
<tr>
<td>Zhang 2012</td>
<td>Qing Ying Tang</td>
<td>Decoction</td>
<td><em>Cornu bubali</em> (<em>shui niu jiao</em>) 30g, <em>rehmannia glutinosa</em> (<em>di huang</em>) 15g, <em>radix scrophulariae</em> (<em>xuan shen</em>) 9g, <em>lophatherum</em> (<em>zhu ye xin</em>) 3g, <em>radix ophiopogonis</em> (<em>mai dong</em>) 9g, <em>salvia miltiorrhiza</em> <em>radix</em> (<em>dan shen</em>) 6g, <em>coptis rhizome</em> (<em>huang lian</em>) 5g, <em>flos lonicerae</em> (<em>jin yin hua</em>) 9g, <em>fructus forsythiae</em> (<em>lian qiao</em>) 6g.</td>
</tr>
<tr>
<td>Huang 2010</td>
<td>Xiao Yi ke Li</td>
<td>Granule powder</td>
<td><em>Rehmannia glutinosa</em> (<em>di huang</em>) 3.5g, <em>cortex paeoniae suffruticosa</em> andr (<em>mu dan pi</em>) 3.5g, <em>angelica sinensis</em> (<em>dang gui</em>) 3.5g, <em>sophorae flavescentis</em> (<em>ku shen</em>) 3.5g, <em>flos lonicerae</em> (<em>jin yin hua</em>) 3.5g, <em>radix scrophulariae</em> (<em>xuan shen</em>) 3.5g, <em>flos carthami</em> (<em>hong hua</em>) 3.5g, <em>cortex dictamn</em> (<em>bai xian pi</em>) 3.5g, etc.</td>
</tr>
<tr>
<td>Author, Year</td>
<td>CHM formula</td>
<td>CHM form</td>
<td>CHM ingredients</td>
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<tr>
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</tr>
<tr>
<td>Chen 2010</td>
<td>Ke Yin Yi Hao</td>
<td>Decoction</td>
<td>Radix lithospermi (<em>zi cao</em>) 5g, cornu bubali (<em>shui niu jiao</em>) 20g, rehmannia glutinosa (<em>di huang</em>) 15g, mu cortex paonia suffruticosa andr (<em>dan pi</em>) 15g, radix paoniae rubra (<em>chi shao</em>) 17g, sargentodoxa cuneata (<em>hong teng</em>) 20g, scolopendra (<em>wu gong</em>) 2, buthus martensi (<em>quan xie</em>) 9g, flos carthami (<em>hong hua</em>) 15g, angelica sinensis (<em>dang gui</em>) 20g, radix scutellaria baicalensis (<em>huang qin</em>) 15g, fructus forsythiae (<em>lian qiao</em>) 20g.</td>
</tr>
</tbody>
</table>
| Xie 2006     | Tui Yin Tang  | Decoction | Rehmannia glutinosa (*di huang*) 30g, rhizoma smilacis glabrae (*tu fu ling*) 30g, angelica sinensis (*dang gui*) 15g, radix polygoni multiflori (*he shou wu*) 15g, ligustrum lucidum (*nu zhen zi*) 15g, rhizoma polygonati (*huang jing*) 15g, fructus tribuli (*bai jii*) 15g, radix ophiopogonis (*mai dong*) 10g, zaocys (*wu shao she*) 2, flos lonicerae (*jin yin hua*) 10g, cortex paonia suffruticosa andr (*mu dan pi*) 10g, radix glycyrrhizae (*gan cao*) 6g.  
*For blood stasis*, add semen persicae (*tao ren*) 10g, flos carthami (*hong hua*) 10g;  
*For red skin* gypsum fibrosum (*sheng shi gao*) 30g. |
| Jin 2009     | No name      | Decoction | Rhizoma sparganii (*san leng*), zedoary rhizome (*er zhu*), semen persicae (*tao ren*), flos carthami (*hong hua*), caulis spatholobi (*ji xue teng*), lignum euonymi suberalati (*gui jian yu*), semen coicis (*sheng yi yi ren*), spica prunellae (*xia ku cao*), pericarpium citri reticulatae (*chen pi*), no dosage information.  
**Blood heat type:** rehmannia glutinosa (*di huang*) 30g, radix paoniae rubra (*chi shao*) 9g, radix lithospermi (*zi cao*) 9g, cornu bubali (*shui niu jiao*) 30g, folium isatis tinctoria (*da qing ye*) 30g, herba hedyotidis diffusae (*bai hua she she cao*) 30g, salvia miltiorrhizae radix (*dan shen*) 30g, semen persicae (*tao ren*) 29g, radix glycyrrhizae (*gan cao*) 3g;  
**Blood deficiency type:** rehmannia glutinosa (*di huang*) 30g, radix rehmanniae recen (*shu di*) 30g, angelica sinensis (*dang gui*) 15g, caulis spatholobi (*ji xue teng*) 30g, salvia miltiorrhizae radix (*dan shen*) 15g, radix scrophulariae (*xuan shen*) 15g, semen cannabis (*huo ma ren*) 10g, folium isatis tinctoria (*da qing ye*) 15g, radix sophorae tonkinensis (*shan dou gen*) 10g, cortex dictamn (*bai xian pi*) 15g, polygonum bistorta rhizome (*cao he che*) 15g, fructus forsythiae (*lian qiao*) 15g;  
**Blood dryness type:** caulis spatholobi (*ji xue teng*) 30g, rhizoma smilacis glabrae (*tu fu ling*) 30g, angelica sinensis (*dang gui*) 15g, rehmannia glutinosa (*di huang*) 15g, radix clematidis (*wei ling xian*) 15g, rhizoma dioscoreae (*shan yao*) 15g, lu feng gang (*honeycomb*) 15g;  
**Blood stasis type:** semen persicae (*tao ren*) 10g, flos carthami (*hong hua*) 10g, rhizoma sparganii (*san leng*) 10g, zedoary rhizome (*e zhu*) 10g, angelica sinensis (*dang gui*) 10g, zaocys (*wu shao she*) 10g, jia xue teng 30g, rhizoma smilacis glabrae (*tu fu ling*) 30g, herba hedyotidis diffusae (*bai hua she she cao*) 30g, cortex dictamn (*bai xian pi*) 15g, radix paoniae rubra (*chi shao*) 15g, salvia miltiorrhizae radix (*dan shen*) 20g, radix glycyrrhizae (*gan cao*) 6g. |
| Kong 2008    | No name      | No information | **Blood heat type:** rehmannia glutinosa (*di huang*) 30g, radix paoniae rubra (*chi shao*) 9g, radix lithospermi (*zi cao*) 9g, cornu bubali (*shui niu jiao*) 30g, folium isatis tinctoria (*da qing ye*) 30g, herba hedyotidis diffusae (*bai hua she she cao*) 30g, salvia miltiorrhizae radix (*dan shen*) 30g, semen persicae (*tao ren*) 29g, radix glycyrrhizae (*gan cao*) 3g;  
**Blood deficiency type:** rehmannia glutinosa (*di huang*) 30g, radix rehmanniae recen (*shu di*) 30g, angelica sinensis (*dang gui*) 15g, caulis spatholobi (*ji xue teng*) 30g, salvia miltiorrhizae radix (*dan shen*) 15g, radix scrophulariae (*xuan shen*) 15g, semen cannabis (*huo ma ren*) 10g, folium isatis tinctoria (*da qing ye*) 15g, radix sophorae tonkinensis (*shan dou gen*) 10g, cortex dictamn (*bai xian pi*) 15g, polygonum bistorta rhizome (*cao he che*) 15g, fructus forsythiae (*lian qiao*) 15g;  
**Blood dryness type:** caulis spatholobi (*ji xue teng*) 30g, rhizoma smilacis glabrae (*tu fu ling*) 30g, angelica sinensis (*dang gui*) 15g, rehmannia glutinosa (*di huang*) 15g, radix clematidis (*wei ling xian*) 15g, rhizoma dioscoreae (*shan yao*) 15g, lu feng gang (*honeycomb*) 15g;  
**Blood stasis type:** semen persicae (*tao ren*) 10g, flos carthami (*hong hua*) 10g, rhizoma sparganii (*san leng*) 10g, zedoary rhizome (*e zhu*) 10g, angelica sinensis (*dang gui*) 10g, zaocys (*wu shao she*) 10g, jia xue teng 30g, rhizoma smilacis glabrae (*tu fu ling*) 30g, herba hedyotidis diffusae (*bai hua she she cao*) 30g, cortex dictamn (*bai xian pi*) 15g, radix paoniae rubra (*chi shao*) 15g, salvia miltiorrhizae radix (*dan shen*) 20g, radix glycyrrhizae (*gan cao*) 6g. |
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>CHM formula</th>
<th>CHM form</th>
<th>CHM ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan 2010</td>
<td>Liang Xue Xiao Yin Tang</td>
<td>Decoction</td>
<td>Rehmannia glutinosa (<em>di huang</em>) 30g, sheng huai hua 30g, rhizoma smilacis glabrae (<em>tu fu ling</em>) 20g, rhizoma imperatae (<em>bai mao gen</em>) 15g, ban lan gen 15g, radix lithospermi (<em>zi cao</em>) 15g, radix paeoniae rubra (<em>chi shao</em>) 10g, cortex paeonia suffruticosa andr (<em>mu dan pi</em>) 10g, radix scrophulariae (<em>xuan shen</em>) 10g, flos lonicerae (<em>jin yin hua</em>) 10g, fructus forsythiae (<em>lian qiao</em>) 10g, cao he che 10g, radix glycyrrhizae (<em>sheng gan cao</em>) 10g. <strong>For lesions on upper body:</strong> rhizoma chuanxiong (<em>chuan xiong</em>); <strong>For lesions on lower body:</strong> fructus chaenomelis (<em>mu gua</em>), radix achyranthis bidentatae (<em>chuan niu xi</em>); <strong>For sore throat:</strong> fructus arctii (<em>niu bang zi</em>), radix sophorae tonkinensis (<em>shan dou gen</em>); <strong>For stomach discomfort:</strong> atractylodes macrocephala (<em>sheng bai zhu</em>), pericarpium citri reticulatae (<em>chen pi</em>), semen coicis (<em>yi yi ren</em>); <strong>For itchiness:</strong> sophorae flavescentis (<em>ku shen</em>), cortex dictamn (<em>bai xian pi</em>).</td>
</tr>
<tr>
<td>Wu 2009</td>
<td>Yin Xie Kang</td>
<td>Decoction</td>
<td>Radix astragali (<em>huang qi</em>), rehmannia glutinosa (<em>di huang</em>), radix lithospermi (<em>zi cao</em>), salvia miltiorrhizae radix (<em>dan shen</em>), angelica sinensis (<em>dang gui</em>), radix asparagi (<em>tian dong</em>), radix ophiopogonis (<em>mai dong</em>), rhizoma smilacis glabrae (<em>tu fu ling</em>), herba hedyotidis diffusae (<em>bai hua she she cao</em>), no dosage information</td>
</tr>
<tr>
<td>Luo 2010</td>
<td>No name</td>
<td>Decoction</td>
<td>Angelica sinensis (<em>dang gui</em>) 12g, rehmannia glutinosa (<em>di huang</em>) 30g, radix scrophulariae (<em>xuan shen</em>) 15g, radix lithospermi (<em>zi cao</em>) 9g, (<em>chi shao</em>) 6g, cortex paeonia suffruticosa andr (<em>mu dan pi</em>) 9g, semen persicae (<em>tao ren</em>) 10g, salvia miltiorrhizae radix (<em>huan qin</em>) 12g, radix saposhnikoviae (<em>fang feng</em>) 10g, sororae flavescentsis (<em>ku shen</em>) 10g, radix glycyrrhizae (<em>gan cao</em>) 10g</td>
</tr>
<tr>
<td>Zheng 2011</td>
<td>Xiao Yin Ke Bi Tang</td>
<td>Decoction</td>
<td>Cornu bubali (<em>shui niu jiao</em>) 20g, rehmannia glutinosa (<em>di huang</em>) 10g, cortex paeonia suffruticosa andr (<em>mu dan pi</em>) 10g, radix paeoniae rubra (<em>chi shao</em>) 15g, rhizoma smilacis glabrae (<em>tu fu ling</em>) 30g, sororae flavescentsis (<em>ku shen</em>) 12g, cortex dictamn (<em>bai xian pi</em>) 12g, fructus kochiae (<em>di fu zi</em>) 12g, radix lithospermi (<em>zi cao</em>) 15g, periostracum cicadae (<em>chan tui</em>) 10g, radix saposhnikoviae (<em>fang feng</em>) 10g, rhizoma imperatae (<em>bai mao gen</em>) 30g, rhizoma atractylidis (<em>cang zhu</em>) 10g</td>
</tr>
<tr>
<td>Tian 2011</td>
<td>Qing Fei Liang Xue Tang</td>
<td>Decoction</td>
<td>Cornu bubali (<em>shui niu jiao</em>) 30g, rehmannia glutinosa (<em>di huang</em>) 15g, radix paeoniae rubra (<em>chi shao</em>) 15g, cortex paeonia suffruticosa andr (<em>dan pi</em>) 10g, angelica sinensis (<em>dang gui</em>) 10g, cortex dictamn (<em>bai xian pi</em>) 10g, caulis spatholobi (<em>ji xue teng</em>) 20g, rhizoma smilacis glabrae (<em>tu fu ling</em>) 25g, radix lithospermi (<em>zi cao</em>) 20g, flos lonicerae (<em>jin yin hua</em>) 15g, radix scutellariae barbatae (<em>ban zhi lian</em>) 10g, herba hedyotidis diffusae (<em>bai hua she she cao</em>) 20g, zaocys (<em>wu shao she</em>) 10g, salvia miltiorrhizae radix (<em>dan shen</em>) 20g, radix glycyrrhizae (<em>gan cao</em>) 10g</td>
</tr>
<tr>
<td>Yu 2007</td>
<td>Qing Re Huo Xue</td>
<td>Decoction</td>
<td>Sheng huai hua, flos carthami (<em>hong hua</em>), rehmannia glutinosa (<em>di huang</em>), radix scrophulariae (<em>xuan shen</em>), caulis spatholobi (<em>ji xue teng</em>), angelica sinensis (<em>dang gui</em>), rhizoma chuanxiong (<em>chuan xiong</em>), rhizoma sparganii (<em>san leng</em>), zedoary rhizome (<em>er zhu</em>), rhizoma smilacis glabrae (<em>tu fu ling</em>), herba solani lyrati (<em>shu yang quan</em>), no dosage detail</td>
</tr>
<tr>
<td>Author, Year</td>
<td>CHM formula</td>
<td>CHM form</td>
<td>CHM ingredients</td>
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<td>--------------</td>
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</tr>
<tr>
<td>Lin 2012</td>
<td>No name</td>
<td>Decoction</td>
<td>Sophorae flavescentis (<em>ku shen</em>) 15g, angelica sinensis (<em>dang gui</em>) 15g, rhizoma menispermi (<em>bei dou gen</em>) 10g, anemarrhena rhizome (<em>zhi mu</em>) 10g, radix scutellariae barbatae (<em>ban zhi lian</em>) 20g, rhizoma smilacis glabrae (<em>tu fu ling</em>) 30g, bai mao gen 30g, rehmannia glutinosa (<em>di huang</em>) 30g</td>
</tr>
<tr>
<td>Shen 2005</td>
<td>Xiao Yin Fang</td>
<td>Decoction</td>
<td>Radix astragali (<em>huang qi</em>) 30g, angelica sinensis (<em>dang gui</em>) 15g, rehmannia glutinosa (<em>di huang</em>) 15g, rhizoma chuanxiong (<em>chuan xiong</em>) 12g, radix paeoniae rubra (<em>chi shao</em>) 12g, radix scrophulariae (<em>xuan shen</em>) 12g, cortex paeonia suffruticosa andr (<em>mu dan pi</em>) 12g, salvia miltiorrhizae radix (<em>dan shen</em>) 12g, semen persicae (<em>tao ren</em>) 9g, flos carthami (<em>hong hua</em>) 9g, radix curcumae (<em>yu jin</em>) 9g, cortex dictamn (<em>bai xian pi</em>) 15g, rhizoma dioscoreae hypoglaucae (<em>bi xie</em>) 15g, rhizoma smilacis glabrae (<em>tu fu ling</em>) 15g, fructus gardeniae (<em>zhi zi</em>) 9g, flos lonicerae (<em>jin yin hua</em>) 9g</td>
</tr>
</tbody>
</table>
In total, 70 different herbs were included in the studies. The most frequently used herbs were *Rehmannia glutinosa* root (*di huang*) (n=15 studies), *Angelica sinensis* root (*dang gui*) (n=12), *Smilax glabra* root (*tu fu ling*) (n=11), *Paeonia veitchii* root (*chi shao*) (n=9), *Salvia miltiorrhiza* root (*dan shen*) (n=9) and *Lithospermum erythrorhizon* root (*zi cao*) (n=9). Eleven studies used a single conventional pharmacotherapy drug as a comparator (Huang, 2010, Wan, 2012, Xie, 2006, Chen and Tan, 2004, Jin et al., 2009) (Zheng, 2011, Liu, 2005a, Zhang, 2012, Chen, 2010, Yu and Pan, 2007, Shen and Zhao, 2005), six studies used two (Wu et al., 2009a, Kong, 2007b, Yu and Pan, 2007, Tan, 2008, Lin and Jin, 2012, Shen and Zhao, 2005) and two studies combined three drugs (Luo, 2010, Tian, 2011). In total, 10 different drugs were used, including topical vitamin D3 analogues, calcipotriol (Luo, 2010, Jin et al., 2009) and tacalcitol (Tan and Li, 2010) as ointments (n=3), corticosteroid clobetasol propionate ointment (n=1)(Shen and Zhao, 2005) and a combination of retinoid tazarotene with emollient (n=1)(Lin and Jin, 2012). The oral retinoid acitretin was used in eight studies (Huang, 2010, Xie, 2006, Luo, 2010, Mao and Mao, 2007, Wu et al., 2009a, Zheng, 2011, Zhang, 2012, Chen, 2010).

In addition, pharmacotherapies that are used in China for psoriasis management were employed, such as oral Diyin tablets (n=9)(Wan, 2012, Mao and Mao, 2007, Chen and Tan, 2004, Liu, 2005a, Kong, 2007a, Shen and Zhao, 2005, Yu and Pan, 2007, Yang et al., 2005, Lin and Jin, 2012), which contain multiple amino acids and peptides, aminophylline and chlorpheniramine maleate, and aim to regulate immune response, improve microcirculation, benefit metabolism, provide microelements, and reduce the keratinocyte proliferation present in psoriasis (Song et al., 2013, Yang, 2011). Compound glycyrrhizin solution via IV drip was also used (n=2)(Luo, 2010, Tan and Li, 2010), which contains glycyrrhizin, cysteine hydrochloride and glycine, and is said to produce an effect similar to a glucocorticoid, including reduced inflammation (Zhu and
Hu, 2011). Intravenous drip containing 10% calcium gluconate solution was also used (n=2), which aims to reduce itching in various dermatological conditions (Zhao, 2009, Tian, 2011, Kong, 2007a). It should be noted that these pharmacotherapies are not recommended by international psoriasis treatment guidelines.

**Supplementary search interventions of studies**

As found in RCTs of the main review, no study utilized same CHM, with a variety of different herbal formulation ingredients administered. Only one study used a single herb (Huang, 2012) as treatment the rest of the studies used multiple ingredients as their CHM intervention. Three studies administered the CHM intervention in decoction form (Han and Yu, 2012), two in granule form (Jiang et al., 2012a, Zhai XF, 2012), two in capsule form and one each in tablet (Huang, 2012) and pill form (Ma SY, 2012). Only two of the nine studies stated using syndrome differentiation to determine treatment (Zhai XF, 2012, Zhu XP, 2012) (Table 4.5).
Table 4.4: Supplementary search intervention/comparators of included RCTs (oral CHM plus pharmacotherapy vs. pharmacotherapy for psoriasis vulgaris)

<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Syndrome differentiation</th>
<th>CM principle of treatment</th>
<th>Chinese herbal medicine formula and ingredients</th>
<th>Preparation type and dosage</th>
<th>Pharmacotherapy</th>
<th>Dosage and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han, 2012</td>
<td>NS</td>
<td>Cool blood, remove toxin, nourish Yin</td>
<td><strong>Liang xue jie du yang yin tang:</strong> rehmannia glutinosa (di huang) 30g, paeonia suffruticosa (mu dan pi) 15g, paeoniae radix Rubra (chi shao) 15g, arnebia euchroma (zi cao) 15g, rubiae radix et rhizoma (qian cao) 15g, smilacis glabrae rhizoma (tu fu ling) 30g, isatidis radix (ban lan gen) 30g, hedyotis diffusae herba (bai hua she she cao) 30g, sophorae tonkinensis radix et rhizoma (shan dou gen) 10g, lehniae radix (bei sha shen) 10g, ophiopogonis radix (mai dong) 10g. Individual modification according to symptoms</td>
<td>Decoction, one pack a day</td>
<td>Acitretin and Compound flumetasone ointment</td>
<td>Acitretin, 20-60mg, qd-bid, po; topical Compound flumetasone ointment, qd</td>
</tr>
<tr>
<td>Huang, 2012</td>
<td>NS</td>
<td>NS</td>
<td>Tripterygium glycosides single herb</td>
<td>Tablet, 30mg tid</td>
<td>Tacalcitol ointment and Tazarotene gel</td>
<td>Topical apply tacalcitol ointment bid, tazarotene gel qn</td>
</tr>
<tr>
<td>Jiang, 2012</td>
<td>NS</td>
<td>Clear heat, cool blood, remove toxin, clear lesions, nourish Yin and produce body fluid</td>
<td><strong>Shen di ke li:</strong> scrophulariae radix (xuan shen), rehmannia glutinosa (di huang), paeonia suffruticosa (mu dan pi), paeoniae radix rubra (chi shao), chrysanthemi indici flos (ye ju hua), taraxaci herba (pu gong ying), isatidis radix (ban lan gen), violae herba (zi hua di ding), gardeniae fructus (zhi zi), smilacis glabrae rhizoma (tu fu ling), fritillariae cirrhosae bulbus (bei mu), trichosanthis radix (tian hua fen), platycodonis radix (jie geng), glycyrhizae radix et rhizoma (gan cao)</td>
<td>Granule, one pack a day</td>
<td>Acitretin</td>
<td>Initial dosage 10mg qd, then 20mg qd, then 10mg qd, po</td>
</tr>
</tbody>
</table>

bid, twice per day; CM, Chinese medicine; po, oral administration; qn, nightly; NS, not stated; tid, three times a day
<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Syndrome differentiation</th>
<th>CM principle of treatment</th>
<th>Chinese herbal medicine formula and ingredients</th>
<th>Preparation type and dosage</th>
<th>Pharmacotherapy</th>
<th>Dosage and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu, 2012</td>
<td>NS</td>
<td>Nourish blood and Yin, clear wind, stop itching, nourish intestines, promote bowel motion</td>
<td><strong>Run zao zhi yang jiao nang</strong>: polygoni multiflori radix (he shou wu), polygoni multiflori radix Praeparata (zhi he shou wu), rehmannia glutinosa (di huang), mori folium (sang ye), sophorae flavescentis radix (ku shen), cannabis sativa (hong huo ma)</td>
<td>Capsule, 4 tid</td>
<td>Acitretin and calcipotriol ointment</td>
<td>Acitretin, 30mg qd po, topical calcipotriol ointment bid</td>
</tr>
<tr>
<td>Ma, 2012</td>
<td>NS</td>
<td>Nourish blood and Yin, clear dryness, invigorate blood, remove stasis</td>
<td><strong>Da huang zhe chong wan</strong>: rhei radix et rhizoma (da huang), eupolyphaga steleophaga (tu bie chong), hirudo (shuí zhī), tabanidae (mang chong), holotrichia (qí cáo), armeniacae semen amarum (xing ren), persicæ Semen (tao hua), scutellariae radix (huāng qín), rehmannia glutinosa (di huang), paeonieæ radix alba (bái shào)</td>
<td>Pill, 3g tid po</td>
<td>Acitretin</td>
<td>20mg qd po</td>
</tr>
<tr>
<td>Xie, 2012</td>
<td>NS</td>
<td>Nourish blood and Yin, clear wind, stop itching, nourish intestines, promote bowel motion</td>
<td><strong>Run zao zhi yang jiao nang</strong>: polygoni multiflori radix (he shou wu), polygoni multiflori radix praeparata (zhi he shou wu), rehmannia glutinosa (di huang), mori folium (sang ye), sophoræ flavescentis Radix (ku shen), cannabis sativa (hong huo ma)</td>
<td>Capsule 2.0g tid po</td>
<td>Acitretin and Clobetasol propionate ointment</td>
<td>Acitretin 20mg qd po, topical clobetasol propionate ointment bid</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Syndrome differentiation</td>
<td>CM principle of treatment</td>
<td>Chinese herbal medicine formula and ingredients</td>
<td>Preparation type and dosage</td>
<td>Pharmacotherapy</td>
<td>Dosage and administration</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>--------------------------</td>
<td>-------------------------------------------------</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Zhai, 2012</td>
<td>Yes (Blood heat type)</td>
<td>Clear heat, cool blood, clear toxin and wind</td>
<td><strong>Unnamed formula:</strong> rehmannia glutinosa (di huang) 30g, scrophulariae radix (xuan shen) 15g, paeoniae radix alba (bai shao) 12g, gypsum fibrosum (sheng shi gao) 30g, anemarrhenae rhizoma (zhi mu) 9g, imperatae rhizoma (bai mao gen) 30g, arctii fructus (niu bang zi) 9g, schizonepetae Herba (jing jie) 9g, glycyrrhizae radix et rhizoma (gan cao) 6g, lonicerae Japonicae Flos (jin yin hua) 15g, cimicifugae rhizoma (sheng ma) 3g, ophiopogonis radix (mai dong) 9g, mou tan cortex (mu dan pi) 9g, scutellariae radix (huang qin) 15g, smilacis glabrae rhizoma (tu fu ling) 30g</td>
<td>Granule, no information of dosage</td>
<td>Acitretin and calcipotriol ointment</td>
<td>Acitretin: 10mg tid, po Calcipotriol: topical bid</td>
</tr>
<tr>
<td>Zhu, 2012</td>
<td>NS</td>
<td>Clear heat, remove toxin, clear dryness and dampness, invigorate blood and remove stasis</td>
<td><strong>Er dong huo xue tang:</strong> asparagi radix (tian men dong) 15g, ophiopogonis radix (mai dong) 15g, angelicae sinensis radix (dang gui) 15g, scrophulariae radix (xuan shen) 15g, salviae miltiorrhizae radix et rhizoma (dan shen) 30g, rehmannia glutinosa (di huang) 30g, salviae miltiorrhizae radix et rhizoma (dan shen) 30g, spatholobi caulis (ji xue teng) 30g, indigo naturalis (qing dai) 10g, dictamni cortex (bai xian pi) 10g, persicae semen (tao ren) 10g</td>
<td>Decoction, one pack a day</td>
<td>Methotrexate</td>
<td>Methotrexate 2.5-5mg tid po</td>
</tr>
<tr>
<td>Zhu XP 2012</td>
<td>Yes (Blood heat type and blood stasis type)</td>
<td>CM principle of treatment</td>
<td>Chinese herbal medicine formula and ingredients</td>
<td>Preparation type and dosage</td>
<td>Pharmacotherapy</td>
<td>Dosage and administration</td>
</tr>
<tr>
<td>-------------</td>
<td>---------------------------------------------</td>
<td>---------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------</td>
<td>----------------</td>
<td>-------------------------</td>
</tr>
</tbody>
</table>
|             | For blood heat type: clear heat, cool blood, remove toxin; For blood stasis type: nourish blood and remove blood stasis | For blood heat type: bubali cornu (shui niu jiao) 30g, rehmannia glutinosa (di huang) 30g, paeoniae radix rubra (chi shao) 15g, moutan cortex (mu dan pi) 15g, lonicerae japonicae flos (jin yin hua) 15g, dictamni cortex (bai xian pi) 30g, sophorae flavescentis radix (ku shen) 10g, smilacis glabrae rhizoma (tu fu ling) 20g, coptidis rhizoma (huang lian) 10g, forsythiae fructus (lian qiao) 10g  
For blood stasis type: rehmannia glutinosa (di huang) 15g, rehmanniae radix praeparata (shu di huang)15g, asparagi radix (tian men dong)10g, ophiopogonis radix (mai dong)10g, scrophulariae radix (xuan shen) 15g, angelicae sinensis radix (dang gui) 12g, paeoniae radix rubra (chi shao)15g, salviae miltiorrhizae radix et rhizoma (dan shen) 30g, curcumae rhizoma (e zhu)10g, bombyx batryticatus (jiang can) 10g, sophorae flavescentis radix (ku shen) 10g, dictamni cortex (bai xian pi) 20g | Decoction, one pack a day | Routine care | NS |
Treatment duration and follow-up

The shortest treatment duration was one month (Wan, 2012, Zhang, 2012) (Yang et al., 2005), while the longest was three months (Xie, 2006, Lin and Jin, 2012). The most common treatment duration was eight weeks (Mao and Mao, 2007, Zheng, 2011, Shen and Zhao, 2005, Tan and Li, 2010). All studies applied CHM and pharmacotherapy for equal durations. One study had a follow-up examination at three months (Mao and Mao, 2007), one at six months (Wan, 2012) and another at one year (Lin and Jin, 2012).

Outcome measures

All studies employed total effective rate (TER) as the primary outcome measure. This was calculated based on PASI score reduction in ten studies (Luo, 2010), (Mao and Mao, 2007, Jin et al., 2009, Tian, 2011, Wu et al., 2009a, Zheng, 2011, Liu, 2005a, Shen and Zhao, 2005, Tan and Li, 2010, Yang et al., 2005), lesion score reduction in five studies (Huang, 2010, Wan, 2012, Xie, 2006, Chen and Tan, 2004, Zhang, 2012, Lin and Jin, 2012) and a combination of PASI and the dermatological life quality index scores in one study (Yu and Pan, 2007), although the latter did not provide information on the method of score calculation. Two studies did not specify the scoring method used (Chen, 2010, Kong, 2007a).

The TERs were categorised as ‘cured’, ‘remarkably effective’, ‘effective’ and ‘ineffective’; however, the definition of these categories varied among the studies. For example, in four studies PASI score reductions of 90, 60 and 30% (PASI 90, 60, 30) were used (Mao and Mao, 2007, Wu et al., 2009a, Shen and Zhao, 2005, Yang et al., 2005), another study used 95, 70 and 30% (PASI 95, 70, 30) as the criteria (Liu, 2005a), and another employed lesion score reductions of 95, 75 and 30% (Zhang, 2012). Furthermore, the symptom scoring methods used in seven studies had not been validated (Huang, 2010, Wan, 2012, Xie, 2006, Chen and Tan, 2004, Zhang, 2012, Yu and
Pan, 2007, Lin and Jin, 2012). PASI 60 or a lesion score reduction of 60% was the most common criterion for ‘remarkably effective’. The actual PASI score was reported in five studies (Jin et al., 2009, Tan and Li, 2010, Wu et al., 2009a, Zheng, 2011, Yang et al., 2005) and one study reported serum IL-6 and IL-8 levels (Chen, 2010).

Adverse events (AEs) were monitored by all studies, with 10 studies examining full blood count, urine tests and blood tests for renal and liver function (Huang, 2010, Xie, 2006, Luo, 2010, Mao and Mao, 2007, Chen and Tan, 2004, Jin et al., 2009, Tian, 2011, Kong, 2007a, Shen and Zhao, 2005, Tan and Li, 2010).

Supplementary search outcome measures

Psoriasis severity was most commonly reported using PASI reduction (n=5) (Jiang et al., 2012a, Liu et al., 2012a, Ma SY, 2012) with the other four studies reporting lesion reduction (Han and Yu, 2012, Huang, 2012, Xie, 2012, Zhu et al., 2012) (%). Four of the studies reporting PASI score reduction also reported overall PASI score also (Jiang et al., 2012a, Liu et al., 2012a, Ma SY, 2012, Zhu XP, 2012). Greatest PASI reduction was reported as PASI95 (n=1) (Zhai XF, 2012) with the majority of studies using PASI90 as the upper most improvement (n=4) (Jiang et al., 2012a, Liu et al., 2012a, Ma SY, 2012, Zhu XP, 2012). Lowest PASI outcome was PASI 20 (n=1) (Liu et al., 2012a) with most reporting lowest improvement as PASI 30 (n=3) (Jiang et al., 2012a, Ma SY, 2012, Zhai XF, 2012). No studies reported outcomes for QoL nor did any studies report data for psoriasis related biological markers. Only two studies presented data on relapse rates (Jiang et al., 2012a, Ma SY, 2012) (Table 4.7).
Table 4.5: Outcome measures of included RCTs (oral CHM plus pharmacotherapy vs. pharmacotherapy for psoriasis vulgaris)

<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Definition of effectiveness</th>
<th>Psoriasis lesions</th>
<th>Quality of life</th>
<th>Biological markers</th>
<th>Relapse rate</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han 2012</td>
<td>Lesion reduction (%) 95, 50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Huang 2012</td>
<td>Lesion reduction (%) 90, 70, 30</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Jiang 2012</td>
<td>PASI 90, 60, 30</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Liu 2012</td>
<td>PASI 90, 60, 20</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Ma 2012</td>
<td>PASI 90, 60, 30</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Xie 2012</td>
<td>Lesion reduction (%) 90, 60, 25</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Zhai 2012</td>
<td>PASI 95, 60, 30</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Zhu 2012</td>
<td>Lesion reduction (%) 90, 60, 30</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Zhu XP 2012</td>
<td>PASI 90, 60, 25</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
**Dropouts**

Of the total 19 studies, 17 reported no dropouts or were judged as having no dropouts, as they reported equal numbers of participants’ randomised and completed. One study did not provide information on dropouts or number completed (Tan and Li, 2010). One study reported eight dropouts (three from the treatment group and five from the control group) due to minor AEs or loss of contact during follow-up (Wu et al., 2009a). Although this study mentioned treating dropouts as ineffective in the data analysis, the dropouts were not included in the data table, so the numbers were adjusted for meta-analysis.

**Use of Chinese medicine syndrome differentiation for psoriasis vulgaris**

According to Evidence-based Guidelines for Clinical Practice in Chinese Medicine (China Academy of Chinese Medicine, 2011) the most common syndrome in the progressive stage of psoriasis vulgaris is blood heat syndrome, while blood stasis syndrome is common in the stationary stage. The guidelines indicate that the CHM prescription should be modified according to the syndrome to maximise the efficacy of treatment. Among the 19 studies, one study (Mao and Mao, 2007) employed two different CHM formulas for the two stages of psoriasis vulgaris, one study used four formulas to treat four syndromes (Kong, 2007a), six studies used individual modification according to patients’ symptoms (Xie, 2006, Tian, 2011),(Wu et al., 2009a, Liu, 2005a, Kong, 2007a, Tan and Li, 2010) and all other studies used one standardised formula (Table 4.1).

**4.3.2 Risk of bias assessment**

One study was assessed as low risk for sequence generation as it used a randomisation number table (Tian, 2011); the other 18 studies were assessed as unclear due to lack of information. Allocation concealment was not reported by any study so all were assessed
as unclear; all studies received high-risk assessments for blinding of participants and practitioner as none reported a blinding method or used a placebo for the CHM; all studies were judged as unclear for blinding of outcome assessors as no details were reported. For incomplete outcome data, 13 studies were assessed as low risk because there were no dropouts while Wu (2009) was judged as low risk because the dropout numbers were low and balanced across the two groups (X²=0.476, d.f.=1, P=0.49). Tan and Li (Tan and Li, 2010) did not report dropouts and was assessed as unclear, while two studies were assessed as high risk as the numbers of participants reported in the post-treatment section did not match the number of participants being randomised and no explanations provided for the differences (Huang, 2010, Wan, 2012) (Table 4.3).

All studies were assessed as low risk for selective reporting, except Tan (2010), which was assessed as unclear; however, none of the studies rated low risk had published trial protocols so it could be argued they should be all assessed as unclear. For other bias, no conflict of interest from funding sources was detected in any of the studies. Wan (2012) was excluded from efficacy meta-analyses due to inconsistency in the results tables and consequent high risk of bias in the results. Following sensitivity analysis it was decided data would still be included for the subgroup analysis of studies for effect with CHM modification, where its impact was minor due to the large number of included studies (Figure 4.7).
Table 4.6: Risk of bias assessment of included RCTs (oral CHM plus pharmacotherapy vs. pharmacotherapy for psoriasis vulgaris)

<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessors</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
<th>Other Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen, 2004</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Chen, 2010</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Huang, 2010</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Jin, 2009</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Kong, 2007</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Lin, 2012</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Liu, 2005</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Luo, 2010</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Mao, 2007</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Shen, 2005</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Tan, 2010</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Tian, 2011</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Wan, 2012</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Wu, 2009</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Xie, 2006</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Yang, 2005</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Yu, 2007</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Zhang, 2012</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Zheng, 2011</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
4.3.3 Supplementary search risk of bias

All studies were rated high risk for blinding of participants and personnel with a further three studies assessed as high risk for allocation concealment (Huang, 2012, Xie, 2012, Zhu XP, 2012). Ma 2012 was rated high risk for incomplete data reporting (Table 4.6).
Table 4.7: Risk of bias assessment of supplementary search RCTs (oral CHM plus pharmacotherapy vs. pharmacotherapy for psoriasis vulgaris)

<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants</th>
<th>Blinding of personnel</th>
<th>Blinding of outcome assessors</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han 2012</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Huang 2012</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Jiang 2012</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Liu 2012</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Ma 2012</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Xie 2012</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Zhai 2012</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Zhu 2012</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Zhu XP 2012</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
4.3.4 Efficacy

All studies reported superior efficacy for the combination of CHM and pharmacotherapy in terms of the TER at the end of treatment, and five studies reported that the combination was more effective for PASI score reduction (Jin et al., 2009, Tian, 2011, Wu et al., 2009a, Zheng, 2011, Yang et al., 2005).

Grouping studies for analysis

Some studies used the PASI score as a basis for TER calculation, while other studies used lesion score based on Chinese guidelines. The definition of effectiveness also differed between studies. Clinical guidelines suggest the criterion for treatment success should be a PASI score reduction of 75% (PASI 75) or greater, and treatment failure considered PASI score reduction of 50% (PASI 50) or less (Nast et al., 2012). For measuring effectiveness of treatment in China, PASI 60 is considered by Consensus of Diagnosis and Treatment of Psoriasis Vulgaris in Integrative Medicine (Chinese Medical Association, 2009) as the cut-off level. Ten studies reported the number of participants achieving a 60% reduction in PASI or symptom scores, and three studies reported 70 or 75% reductions, so 60% reduction or more in PASI or symptom score was selected as the criterion for meta-analysis of TER. Analysis was based on conventional treatment type with the initial meta-analysis including all treatment types, and then subgroup analysis was performed including only those recommended by international treatment guidelines.

First analysis: Efficacy of oral CHM and conventional therapies (all types)

TER based on PASI 60 and above

For the first meta-analysis, four studies were excluded as they did not report effect size (Kong, 2007a, Yu and Pan, 2007, Tan and Li, 2010, Chen, 2010), another was excluded
due to significant data errors (Wan, 2012) and one study reported an effect size of only 50% lesion reduction, which was below the predetermined 60% cut-off (Xie, 2006).

This left nine studies suitable for pooling for TER based on PASI 60 and above (Jin et al., 2009, Liu, 2005b, Luo, 2010, Mao and Mao, 2007, Shen and Zhao, 2005, Tian, 2011, Wu et al., 2009a, Yang et al., 2005, Zheng, 2011). The overall effect favoured CHM combined with conventional medicine compared with conventional therapy alone (RR: 1.44 [1.24, 1.68]) (Figure 4.2).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CHM and VM</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jin, L 2009</td>
<td>20</td>
<td>30</td>
<td></td>
<td>15.9%</td>
<td>1.27 [1.01, 1.61]</td>
</tr>
<tr>
<td>Liu, Z 2005</td>
<td>27</td>
<td>40</td>
<td></td>
<td>4.8%</td>
<td>1.03 [1.02, 3.04]</td>
</tr>
<tr>
<td>Luo, X.F. 2010</td>
<td>53</td>
<td>74</td>
<td></td>
<td>34.1%</td>
<td>1.71 [1.30, 2.24]</td>
</tr>
<tr>
<td>Mao, H 2007</td>
<td>24</td>
<td>31</td>
<td></td>
<td>13.1%</td>
<td>1.05 [0.81, 1.36]</td>
</tr>
<tr>
<td>Shen, W.G. 2005</td>
<td>22</td>
<td>30</td>
<td></td>
<td>9.2%</td>
<td>1.38 [0.92, 2.09]</td>
</tr>
<tr>
<td>Tian, Y 2011</td>
<td>25</td>
<td>30</td>
<td></td>
<td>6.8%</td>
<td>2.27 [1.38, 3.74]</td>
</tr>
<tr>
<td>Wu, S.M. 2009</td>
<td>70</td>
<td>76</td>
<td></td>
<td>20.3%</td>
<td>1.28 [1.10, 1.51]</td>
</tr>
<tr>
<td>Yang, D 2005</td>
<td>22</td>
<td>30</td>
<td></td>
<td>9.2%</td>
<td>1.38 [0.92, 2.09]</td>
</tr>
<tr>
<td>Zheng, X.T. 2011</td>
<td>30</td>
<td>60</td>
<td></td>
<td>6.8%</td>
<td>2.06 [1.21, 3.52]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>401</strong></td>
<td><strong>405</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.44 [1.24, 1.68]</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Ratio M.H. Random, 95% CI</th>
<th>Total events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>301</strong></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.02; Chi² = 16.30, df = 8 (P = 0.05), P = 48%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.70 (P &lt; 0.00001)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4.2**: Total effective rate (TER) based on PASI 60 and above

**TER based on 60% lesion elimination or more**

Four studies were suitable for meta-analysis as they used outcome TER lesion elimination of 60% or greater. Pooled effects showed combined therapy to be superior to conventional therapy alone (RR: 1.48 [1.13, 1.93]) (Chen and Tan, 2004, Huang, 2010, Lin and Jin, 2012, Zhang, 2012) (Figure 4.3).
Figure 4.3: Total effective rate (TER) based on lesion elimination of 60% and above

PASI score change

Five studies were included based on general PASI score change (Jin et al., 2009, Tian, 2011, Wu et al., 2009a, Yang et al., 2005, Zheng, 2011), where pooled mean differences of studies again showed significantly greater effect in combined treatment than conventional therapy alone (MD: −2.17 [−4.76, 0.43]); however, heterogeneity (I²) for this meta-analysis was very high at 95% (Jin et al., 2009, Tian, 2011, Wu et al., 2009a, Yang et al., 2005, Zheng, 2011). This heterogeneity was likely due to the variation between the interventions used in the studies (Figure 4.4).

Figure 4.4: Psoriasis area severity index (PASI) score
Second analysis: Efficacy of oral CHM and conventional therapy recommended by international guidelines

For the second analysis, six studies were excluded as the pharmacotherapies used were not recommended by international guidelines for psoriasis treatment (Wan, 2012, Chen and Tan, 2004, Tian, 2011, Liu, 2005a, Kong, 2007a). As these drugs could not be considered reliable comparators, only studies that employed well-recognised pharmacotherapies were included in the second meta-analysis, such as oral acitretin, which was used in eight studies (Huang, 2010, Xie, 2006, Luo, 2010, Mao and Mao, 2007, Wu et al., 2009a, Zheng, 2011, Zhang, 2012) (Chen, 2010); four studies used other well-recognised topical drugs (Luo, 2010) (Jin et al., 2009, Shen and Zhao, 2005, Tan and Li, 2010). Of the eight studies that used acitretin as a comparator, Huang (Huang, 2010) had errors in the results, Chen (Chen, 2010) did not provide information on the criteria for effectiveness and Xie (Xie, 2006) used 50% rather than 60% lesion score reduction as a criterion, so these three studies were excluded from the meta-analysis pool.

Efficacy of oral CHM and guideline-recommended conventional therapy for TER 60 and above

Five studies of acitretin provided TER data suitable for pooling in three groups (Luo, 2010, Mao and Mao, 2007, Wu et al., 2009a, Zhang, 2012, Zheng, 2011). Group 1.1 used acitretin alone as the pharmacotherapy with PASI 60 as the criterion and found CHM plus acitretin to be superior to acitretin alone (RR: 2.00 [1.21, 3.32])(Zheng, 2011). Group 1.2 used acitretin alone as the pharmacotherapy with a 75% symptom reduction as the criterion, and found CHM plus acitretin to be superior to acitretin alone (RR: 1.64 [1.23, 2.19])(Zhang, 2012). The pooled effect for these two studies was RR: 1.77 (1.36, 2.29), I^2=0%. Group 1.3 included three studies that used acitretin plus other drugs as pharmacotherapy (Luo, 2010, Mao and Mao, 2007) (Wu et al.). The pool showed a
superior effect of the combination of CHM plus pharmacotherapy (RR: 1.40 [1.22, 1.60] I²=62%). Of these three studies, two found that adding CHM was more effective than the pharmacotherapy alone (Luo, 2010, Mao and Mao, 2007), but one study showed no benefit (Wu et al., 2009a). However, sensitivity analysis found the heterogeneity in this group was due to Luo (Luo, 2010). After Luo (2010) was removed the heterogeneity was reduced to 17% (RR: 1.25 [1.08, 1.46]). The overall effect for these five studies showed superiority for the combined groups (RR: 1.50 [1.33, 1.70]) with moderate heterogeneity (I²=56%) (Figure 4.5). Sensitivity analysis showed that the removal of Mao (2007) and Wu (2009) reduced the heterogeneity to zero (RR: 1.74 [1.44, 2.10]). These studies used different co-interventions in addition to acitretin: Mao (2007) used Diyin tablets, and Wu (2009) used topical boric acid ointment, which may have contributed to the heterogeneity.
### Figure 4.5: Forest plot total effective rate (TER) on the psoriasis area and severity index (PASI) 60 and above

**Efficacy of oral CHM and guideline-recommended conventional therapy for PASI score**

The actual PASI score was reported in two of the five included acitretin studies and these were combined in meta-analysis (Wu et al., 2009a, Zheng, 2011). Group 2.1 used only acitretin as pharmacotherapy and showed superiority to the CHM plus acitretin group (MD: −2.45 [−3.85, −1.05]) (Zheng, 2011). Group 2.2 used acitretin combined with boric acid ointment as pharmacotherapy and found the combined therapy to be more effective in terms of PASI score (MD: −4.03 [−4.97, −3.09]) (Wu et al., 2009a). The pooled effect for these two studies showed CHM plus acitretin was more effective than acitretin alone (MD: −3.54 [−4.32, −2.76]), but the heterogeneity was high ($I^2=70\%$) (Figure 4.6).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM + acitretin vs acitretin alone (PASI 60)</th>
<th>Acitretin alone</th>
<th>Risk ratio</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>Weight M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td></td>
<td>30 60 15</td>
<td>60 60 9.8%</td>
<td>2.00 [1.21, 3.32]</td>
<td>2.00 [1.21, 3.32]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60 15</td>
<td>60 9.8%</td>
<td>2.00 [1.21, 3.32]</td>
<td>2.00 [1.21, 3.32]</td>
</tr>
<tr>
<td>Total events</td>
<td>30 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test for overall effect:** $Z = 2.68 (P = 0.007)$

**1.1.2 CHM + acitretin vs acitretin alone (lesion score reduction 75%)**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM + acitretin vs acitretin alone (lesion score reduction 75%)</th>
<th>Acitretin alone</th>
<th>Risk ratio</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>Weight M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td></td>
<td>46 56 28</td>
<td>56 56 18.2%</td>
<td>1.64 [1.23, 2.19]</td>
<td>1.64 [1.23, 2.19]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>56 28</td>
<td>56 18.2%</td>
<td>1.64 [1.23, 2.19]</td>
<td>1.64 [1.23, 2.19]</td>
</tr>
<tr>
<td>Total events</td>
<td>46 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test for overall effect:** $Z = 3.37 (P = 0.0008)$

**1.1.3 CHM + acitretin + co-interventions vs acitretin + co-interventions (PASI 60)**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>CHM + acitretin + co-interventions vs acitretin + co-interventions (PASI 60)</th>
<th>Acitretin alone</th>
<th>Risk ratio</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>Weight M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td></td>
<td>147 147</td>
<td>117 117</td>
<td>1.40 [1.22, 1.60]</td>
<td>1.40 [1.22, 1.60]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>300 326</td>
<td>100%</td>
<td>1.50 [1.33, 1.70]</td>
<td>1.50 [1.33, 1.70]</td>
</tr>
<tr>
<td>Total events</td>
<td>223 180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>$x^2 = 5.21$, df = 2 ($P = 0.07$), $I^2 = 62%$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test for overall effect:** $Z = 4.84 (P = 0.00001)$

**Test for subgroup differences:** $x^2 = 2.59$, df = 2 ($P = 0.29$), $I^2 = 99.9\%$
Only single studies were available for other standard pharmacotherapies. Jin et al. (2009) used topical calcipotriol and showed a benefit for the combined therapy group based on PASI 60 (RR: 1.27 [1.01, 1.61]), but an opposite effect for PASI score (MD: 1.63 [0.58, 2.68]) (Jin et al., 2009). Shen and Zhao (2005) used topical clobetasol propionate combined with oral Diyin tablets and showed benefits for the combined therapy group for PASI 60 (RR: 2.27 [1.38, 3.74]) and for PASI score (MD: –5.48 [–6.98, –3.98]) (Shen and Zhao, 2005). Recurrence of psoriasis vulgaris was reported at the three-month follow-up of one study as 0% in the combined therapy group versus 12.9% in the acitretin control (Mao and Mao, 2007), but it was not explained how the recurrence rate was determined.

**Third analysis: Efficacy of CHM formulation modification for psoriasis**

The third analysis consisted of all studies except Tan 2010, as it reported no data for participants reaching treatment goals. For analysis, studies were grouped according to use of modified or standardised CHM for treatment of participants. The pooled studies not utilising modified CHM (1.52 [1.32, 1.75] I²=51%) had slightly greater effect than studies pooled which did utilise modified CHM (1.46 [1.30, 1.46] I²=12%) (Figure 4.7).
Figure 4.7: Subgroup analysis of Chinese herbal medicine (CHM) with or without syndrome modification

4.3.4 Safety

either that AEs only occurred in the pharmacotherapy group (Xie, 2006, Luo, 2010, Zheng, 2011) or the occurrence in the pharmacotherapy group was significantly higher than that in the CHM plus pharmacotherapy group (Chen and Tan, 2004, Wu et al., 2009a, Liu, 2005a, Shen and Zhao, 2005, Yang et al., 2005). Five studies (Huang, 2010, Luo, 2010, Jin et al., 2009, Wu et al., 2009a, Tan and Li, 2010) concluded that all the AEs were caused by the pharmacotherapies used in the trials. No serious AE was reported in any study.

4.3.5 Supplementary search safety

Two studies did not report on adverse events (Zhu XP, 2012, Zhu et al., 2012) yet Zhu 2012 still concluded that adding CHM to MTX treatment reduces the adverse events of MTX. Only Jiang 2012 reported no adverse events were experienced in either the intervention or control arms. Zhai 2012 reported no AEs in the intervention group however dry skin (n=34) and increased in cholesterol (n=4) were reported in the control arm. Xie 2012 reported the same symptoms in their control and intervention groups however described all events as mild. Dry skin and itch was reported in both control and intervention arms of the remaining studies (Han and Yu, 2012, Huang, 2012, Liu et al., 2012a). Two studies concluded adverse events were caused by the conventional therapy (Huang, 2012, Ma SY, 2012) whilst four studies concluded CHM reduced the adverse events of conventional therapy (Han and Yu, 2012, Liu et al., 2012a, Zhai XF, 2012, Zhu XP, 2012). Two studies concluded safety of both CHM and conventional therapy for psoriasis vulgaris (Jiang et al., 2012a, Xie, 2012) (Table 4.8).
Table 4.8: Adverse events of included RCTs (oral CHM plus pharmacotherapy vs. pharmacotherapy for psoriasis vulgaris)

<table>
<thead>
<tr>
<th>Study</th>
<th>Adverse Events</th>
<th>Authors’ conclusion</th>
</tr>
</thead>
</table>
| Han, 2012 | I: dry skin (47), skin itch (5), high ALT (10), high cholesterol (10)  
C: dry skin (60), dry mouth and lips (42), red skin and itch (9), high GPT (11), high cholesterol (12) | Adding CHM could reduce the AEs caused by acitretin      |
| Huang, 2012 | I: dry skin (2), itch (2), red skin (1), burning sensation (1)  
C: dry skin (2), itch (1), red skin (1), burning sensation (1) | Mild AEs were caused by the pharmacotherapy drugs         |
| Jiang, 2012 | None reported                                                                | Both treatments safe for psoriasis vulgaris               |
| Liu, 2012  | I: dry skin (18), dry mouth (5), skin itch (7)  
C: dry skin (32), dry mouth (34), skin itch (32), high cholesterol (2) | Adding CHM could reduce the AEs caused by acitretin      |
| Ma 2012    | Both groups reported AEs including dry mouth and lips, dry eyes, dry skin, scaly skin, | The AEs were caused by acitretin                          |
| Xie, 2012  | I: dry skin and lips, high cholesterol, all AEs are mild  
C: dry skin and lips, high cholesterol, all AEs are mild | Both treatments are safe for psoriasis vulgaris          |
| Zhai 2012  | I: no AEs                                                                     | Adding CHM could reduce the AEs caused by acitretin      |
| Zhu, 2012  | Not reported                                                                  | Adding CHM could reduce the AEs caused by Methotrexate   |
| Zhu XP, 2012 | Not reported                                                                  | NS                                                       |
AE, adverse event; ALT, Alanine aminotransferase; CHM, Chinese herbal medicine; GPT, glutamate pyruvate transaminase; NS, Not stated
4.4 Discussion

4.4.1 Methodological quality of included studies

The risk of bias assessments identified deficiencies in sequence generation and allocation concealment, and there was no blinding in any of the studies, which may have impacted on the results. In one study of oral CHM plus calcipotriol, there was contradiction between the result for TER and that for PASI score. The TER showed a benefit for the combination group at weeks 8 and 12 of treatment, while the mean PASI score showed the opposite result at the same time points, but no explanation was provided (Jin et al., 2009). Of the five studies that provided PASI scores, four showed a benefit for the combination therapy group (Tian, 2011, Wu et al., 2009a, Zhang, 2012, Yang et al., 2005) while one showed a benefit for the control (Jin et al., 2009). One reason for the difference between the reported results and those found in this meta-analysis is likely the adoption of an ITT approach, and another is the statistical analysis approach. Using risk ratio, a criterion of 60% improvement or higher removed any small improvement events. Considering the diversity of pharmacotherapies used in the studies and the differences in outcome measures, results from the first meta-analysis (Figures 4.2, 4.3 and 4.4), as well as the pooled data for modification of CHM (Figure 4.7), should be considered with caution.

Although some studies used the PASI as an outcome (Jin et al., 2009, Tian, 2011, Wu et al., 2009a, Yang et al., 2005, Zheng, 2011), none reported PASI 75, making it difficult to directly compare results with international studies of conventional treatments, where guidelines recommend PASI 75 a primary outcome measure (Castela et al., 2012, The Australian Government, 2004).
Only one study mentioned a QoL assessment, but no group data were provided (Yu and Pan, 2007). Participant flow diagrams were not provided by any study, none of the studies covered all items listed in the CONSORT statement (Moher D, 2001) and ITT was not employed in data analysis. These aspects compromise the reliability of the results and future trials need to address these issues. Further, a number of studies failed to report effect sizes or supplied effect sizes on outcomes that are not typically recommended, hence were unable to be pooled. Future studies should employ and report common outcome measures as recommended by international guidelines.

4.4.2 Safety of oral CHM combined with pharmacotherapy

All of the mild AEs were reported as probably due to the pharmacotherapies, but there were no clear justifications for these judgments. Five studies concluded that there were significantly fewer AEs in the CHM plus pharmacotherapy groups than in the pharmacotherapy groups (Chen and Tan, 2004, Wu et al., 2009a, Liu, 2005a, Shen and Zhao, 2005, Yang et al., 2005), suggesting that adding oral CHM may have reduced the occurrence of AEs from the pharmacotherapy, such as skin dryness, skin itchiness, and dry mouth and lips with Diyin tablets (Chen and Tan, 2004, Liu, 2005a, Shen and Zhao, 2005, Zhang, 2012) and dry or scaly skin with acitretin (Wu et al., 2009a). It is unclear, though, why Diyin tablets had such effects and further study is needed to evaluate possible biological mechanisms.

The approaches used for collecting AE data were not clearly described, and the lack of blinding increased the risk of bias in AE data reporting and collection. No serious AE was reported, but only 13 studies reported on AEs, and only four studies monitored liver and kidney function. Among the five studies included in the meta-analysis of acitretin, Zhang did not report on AEs (Zhang, 2012) while the other four reported only
mild AEs, as did Xie (Xie, 2006). Two of these studies monitored liver and kidney function. Therefore, combination of CHM with acitretin did not appear to result in additional AEs, at least with short-term use.

4.4.3 Efficacy of oral CHM combined with pharmacotherapy for psoriasis vulgaris

Although all studies in this review concluded that combinations of oral CHM and pharmacotherapy were superior to pharmacotherapy alone, at end of the treatment phase this was not necessarily confirmed by the effect size analyses. Six studies did not provide data suitable for the calculation of the effect size (Huang, 2010, Wan, 2012, Chen, 2010, Kong, 2007a, Tan and Li, 2010, Yu and Pan, 2007). Of the remaining 13 studies, nine showed significant differences in TER in favour of the combined therapy groups (Luo, 2010) (Jin et al., 2009, Tan and Li, 2010, Wu et al., 2009a, Zheng, 2011, Liu, 2005a, Zhang, 2012) (Lin and Jin, 2012) (Yang et al., 2005) and four showed no difference (Xie, 2006, Mao and Mao, 2007, Chen and Tan, 2004, Shen and Zhao, 2005). The present systematic review indicates greater effect of combined therapy, although the true effect size is difficult to predict considering the variation in design between the studies.

For the second meta-analysis, results are likely to be more reliable due to pooling of similar studies, where only five of the studies that used oral acitretin as a comparator were included. Four of these studies found combination of CHM and acitretin was more effective than acitretin alone, but this was only at the end of the treatment period. Only three studies provided recurrence rates, one at 3 months (Mao and Mao, 2007), one at 6 months (Wan, 2012) and the other at 12 months (Lin and Jin, 2012). These favoured combined treatment, but there was no definition of how recurrence was determined. Consequently, although results indicate that combined therapy provides longer-term
benefit than conventional therapy alone, the review cannot provide recommendation on how long positive effects may last nor the size of such effects. More studies need to report follow-up and use a recognised method to evaluate relapse rate (Pathirana et al., 2009).

For previous studies of conventional topical therapy, between 7% and 85% of people in the studies achieve PASI 75 (Castela et al., 2012). From results of the current review it seems such treatment effect is enhanced when combined with oral CHM. Use of oral CHM would likely see a greater percentage of people achieve PASI 60 and PASI 70 than with conventional therapy alone. More research is needed to evaluate the specific effect of oral CHM when it is combined with conventional therapy.

4.4.4 Potential therapeutic actions of CHM for psoriasis vulgaris

Although different herbal formulas were used in the studies, certain plants appeared in multiple formulas. The herbs used in the nineteen studies included in this review are listed in Table 4.2. In these studies, three constituents appear repeatedly: R. glutinosa root (di huang) (n=16), S. miltiorrhiza root (dan shen) (n=10) and L. erythrorhizon root (zi cao) (n=10). Each of these plants has received recent research attention for activities of relevance to psoriasis therapy.

Rehmannia glutinosa root

See 3.4.4 Rehmannia glutinosa.

Salvia miltiorrhiza root

See 3.4.4 Salvia miltiorrhiza.

Lithospermum erythrorhizon root

Shikonin, a bioactive in L. erythrorhizon root, has shown an inhibitory effect on angiogenesis (Hisa et al., 1998) and has been investigated for its anti-proliferative
effects on a number of cell lines, including liver cancer HepG2 cells (Yingkun et al., 2010) and lung cancer A549 cells (Wang et al., 2013). An in vitro study reported inhibitory effects of L. erythrorhizon extracts on lipopolysaccharide-stimulated production of inflammatory cytokines (Han et al., 2008). In rats, L. erythrorhizon extract inhibited release of histamine induced by compound 48/80 and inhibited activation of nuclear factor-kappa B and I kappa B-alpha degradation (Kim et al., 2007). In an atopic dermatitis model in mice, oral L. erythrorhizon extract reduced scratching behaviour, serum IgE, and epidermal hyperproliferation (Kim et al., 2009a). These experiments on cell lines or animal models suggest these plants could have anti-inflammatory and/or anti-proliferative effects in humans.

4.6 Conclusion

This systematic review evaluated administration of oral CHM combined with conventional therapy, 19 eligible RCTs had meta-analyses conducted and a further nine identified in a follow up search are reported on. There is considerable diversity in both the herbal medicines and conventional therapies used. Generally, meta-analysis showed combined therapy had a greater effect on psoriasis. When meta-analysis was restricted to studies using well-known pharmacotherapy as control interventions with 60% or greater clinical improvement in psoriasis as the outcome seven studies remained: five that used oral acitretin, one that used topical calcipotriol, and one used topical clobetasol propionate.

At end of treatment, for the pooled result of the five studies the combination of CHM plus acitretin provided more benefit than acitretin alone and there were no serious AEs reported. Adequate blinding was not implemented in any of the studies so results of the meta-analysis must be evaluated with caution. While published data
indicate combined treatment may reduce long-term risk of relapse, the number of studies reporting follow-up was inadequate and methods for calculating relapse were unclear. Thus, no sound conclusions can be made on the long-term benefits or safety of combined therapy.

**Research and clinical implications**

In westernised countries, treatment guidelines may recommend combination therapy for psoriasis; however, typically this only encompasses conventional therapies such as topical corticosteroids or systemic treatments combined with UVB therapy (Armstrong et al., 2014). In China, physicians prescribe therapy from CHM and conventional medicine, where decisions aim to optimise benefits and reduce drawbacks of both treatment types to enhance outcomes for patients (Xu and Chen, 2008). Potential advantages of such combined treatment include enhanced efficacy and minimising side effects from treatment, which may lead to quicker and safer outcomes for patients. It could also see reduction in the cost of conventional treatments, if cheaper conventional therapies can be enhanced by addition of CHM.

From review it appears integrating conventional treatment with CHM treatment does in fact enhance treatment effect, with reductions in PASI severity and increased elimination of lesions. Given this is yet to be recommended in treatment guidelines and is thus likely underutilised, some psoriasis patients may be missing out on an optimised approach to treatment.

It has been suggested that a two-phase combined therapy aimed at suppressing both innate and adaptive immune responses would be helpful for treatment of inhomogeneous psoriatic plaques, and integrative therapy such as addition of CHM may provide such a biological action (Albanesi, 2014). More research, though, is needed into
the biological aspects of combined CHM and conventional therapy to ensure it is indeed safe for long-term use and to evaluate biologically how the increased effect may occur.

Both first and second line conventional therapies were utilised alongside CHM, with acitretin most common. While there was clearly benefit of combining CHM with acitretin, cost to government can be high for long term treatment (Australian Government - Department of Health, 2014). Calcipotriol is another first line conventional therapy however it is considerably cheaper than acitretin. Combining it with CHM may have increased efficacy in moderate to severe case than first line therapies on their own, warranting further research.

The most common outcome measure provided in the included studies was TER based on PASI, and in order to continue to pool future clinical study results with previous results clinical trials should also utilise PASI as the primary outcome measure.

Only a few of the reviewed RCTs included follow-up data, so in order to evaluate long-term benefits of combined therapy, such as any reduction on relapse rate, clinical studies should include sufficient follow-up data collection periods. Follow-up data may also identify any long-term cost benefits of combined therapy, such as reduced health resource utilisation, when compared with conventional therapy alone. Clinical study should include health resource utilisation to assist health bodies assess the cost benefit of combined therapy.

This systematic review does indicate merit in further investigation of CHM combined with conventional therapy for psoriasis. Due to the large variation of CHM utilised in the studies, it is unclear which CHM ingredients deserve further investigation. Although some ingredients were more frequently used than others, perhaps indicating which should be further explored for psoriasis, review results were not sufficient to evaluate which CHM were most effective. As such, the systematic review could not
clearly establish which CHM should be utilised for the proposed psoriasis vulgaris clinical study and further investigation was needed.
Chapter 5 – Determining a Chinese herbal formula for further psoriasis investigation

This chapter explains how the clinical trial oral CHM formulation was determined. An overview of Chinese medicine syndrome differentiation is presented along with details of how therapeutic guidelines; literature review, phytochemical activity and expert opinion were incorporated into early development of a concept formulation and guided selection of the final formulation. The ingredients of subsequent formulations are investigated for relevant Chinese medicine and potential psoriatic biological actions.

5.1 Background

Following comprehensive reviews of the relevant literature (see chapters 2, 3 and 4) it was concluded that psoriasis vulgaris is the most prevalent phenotype and current available conventional therapies may inadequately treat cases that are mild to moderate in severity. Typically, conventional treatment guidelines recommend topical creams such as corticosteroids for mild to moderate psoriasis (Menter et al., 2009). Previous systematic reviews have demonstrated positive therapeutic effects of some topical botanicals for psoriasis when compared with placebo, although the quality of the evidence supporting it is low (Deng et al., 2013). Review evidence suggests that combining therapies, such as topical and oral, may improve treatment outcomes while minimising risk of side effects. While various topicals therapies such as creams, ointments or gels have been evidenced to be efficacious and their side effects tolerable, it has been identified that adherence is often low (Bewley and Page, 2011). Given mild efficacy and adherence issues of topical interventions it was determined that development of a topical CHM intervention was not ideal.
As discussed previously (see 2.7.1 Background of therapeutic guideline treatment recommendations), oral systemics and stronger therapies such as biologics are recommended only in severe or unresponsive mild–moderate cases of psoriasis due to potential side effect and high costs. This identifies a gap in treatment options for people with mild–moderate cases, in which, alone, conventional topical therapy is not effective. It was recognised that development of an effective oral CHM therapy with low risk of side effects may fill such a treatment gap and enhance outcomes for people using conventional topicals. From review, oral CHM was shown to be effective for psoriasis compared with placebo, and when combined with conventional therapy might further enhance effects (see Chapter 4).

It was concluded that further rigorous clinical controlled study of oral CHM combined with topical conventional therapy should be undertaken. The two systematic reviews (see Chapter 3 and Chapter 4) identified numerous CHM formulations that have been investigated clinically for psoriasis, yet no optimum CHM formulation has been recognised. In order to develop an evidence-based CHM oral formulation to be further investigated through clinical trial, both Chinese medicine theory such as syndrome differentiation and scientific evidence such as biological activity were considered. The subsequently developed formulation was then further refined following discussion with Chinese medicine dermatology experts. This chapter discusses how the oral CHM investigative intervention (PSORI-CM01) was formulated and developed, its ingredients and the manufacturing processes required for its production.

5.2 Overview of Chinese herbal formula development for psoriasis vulgaris

To assist in the development of an oral CHM formulation a comprehensive review was undertaken of published clinical evidence, treatment guidelines and major Chinese
medicine textbooks. Treatment guidelines, where available, were first reviewed to follow best practice approach to formula development. From these guidelines Chinese medicine syndrome types were reviewed as well as the symptomology used to differentiate each syndrome type and the recommended formulations. This became the starting point for the developed formulation. From available published literature reviews and the literature reviews conducted in previous chapters, oral CHM use was recorded and their frequency of use analysed to identify potential further key CHM that should be considered in the final formulation. To reduce the number of herbs in the formulation and ensure the CHM also had biological significance for their inclusion, key phytochemical mechanistic pathways for psoriasis were also reviewed for short-listed ingredients.

Following these steps, the initial formulation was reviewed by CHM and psoriasis experts to further refine the formulation ingredients. Following expert review, a second formulation (PSORI-CM01) was proposed as the intervention to be used in the clinical trial. PSORI-CM01 was then further investigated to explore the scientific evidence of the constituents based on their possible biological anti-psoriatic activity. The resulting formulation, PSORI-CM01, was intended to target mild–moderate psoriasis vulgaris, yet be safe and efficacious for people of all Chinese medicine psoriatic ‘syndrome’ types. This section describes the process of determining the oral CHM ingredients utilised in the clinical trial.

5.3 Methods

Development of an optimised CHM formulation for further investigation requires understanding the Chinese medicine principals for selection of herbs and the potential biological activity of constituents in the herbs. This section details the methods
employed to determine ingredients of the investigative CHM formulation. First Chinese medicine syndromes of psoriasis were reviewed, and then available treatment guidelines for Chinese medicine were investigated. These guidelines further assisted determine the major psoriasis syndrome types and their accompanying symptoms. Chinese herbal medicine data from literature reviews of oral CHM for psoriasis (Chapter 3 and 4) was then considered to identify the most suitable CHM candidates for the formulation. Psoriatic like phytochemical activities of chief CHM constituents were then reviewed. Lastly the resulting CHM formulation was presented to dermatological and CHM experts for further optimization.

5.3.1 What is Chinese medicine syndrome differentiation?

While conventional medicine prescribes treatments according to disease (e.g. antibiotics for a bacterial infection) or its symptoms (e.g. paracetamol for pain), Chinese medicine goes further and differentiates a disease according to its specific Chinese medicine pattern or ‘syndrome’ (Mei, 2011). Syndrome differentiation is fundamental to Chinese medicine philosophy, ensuring each patient is diagnosed and treated according to their syndrome type irrespective of the conventional medical or disease diagnosis. Subsequently, conventionally diagnosed diseases are typically identically treated according to relevant condition treatment guidelines; however, in Chinese medicine two people with identical conventional diagnoses may receive very different treatment prescriptions. Syndrome differentiation is determined by the patient's medical history, symptomology, physical appearance, left and right radial pulses and tongue appearance (Lu and Chen, 2011). These observations are evaluated using Chinese medicine theory, and then treatment is tailored and prescribed for each individual based on the syndrome findings.
Using such an individualised method to discern treatment ensures prescribed treatment targets the most current disease presentation and ensures specificity to the patient’s condition with appropriate and safe dosage. Such methods enhance treatment effect and reduce risk of side effects. When Chinese medicine syndrome is not considered and Chinese medicine prescription is administered solely based on disease type, effects may be reduced and risk of adverse events increased.

Syndrome differentiation by clinicians is largely subjective and although efforts have been made to standardise Chinese medicine theory surrounding its use, variation remains (Schnyer et al., 2005). In 2007, the WHO standardised some of the terminology used in Chinese medicine, which has assisted development of Chinese medicine clinical guidelines for many conditions (World Health Organisation (WHO) Regional Office for the Western Pacific, 2007) In fact, clinical practice guidelines now exist for common diseases accompanied by standardised Chinese medicine syndrome and appropriate treatment recommendations (China Academy of Chinese Medicine, 2011) (Shin et al., 2013).

Based on objective symptoms as well as a person’s specific responses to set questions and/or evaluation of key pulse and tongue features, research tools have been developed to clinically assist determination of patient syndrome type (Chen et al., 2012) (Schnyer et al., 2005). Such tools provide a more systematic approach to syndrome differentiation, by reducing inter-rater variation in research studies and enhancing the validity of Chinese medicine clinical trial results (O’Brien et al., 2009). Such standardisation has seen further development of guidelines for Chinese medicine and related syndromes by the State Administration of Traditional Chinese Medicine, with further work underway by the International Organization for Standardization Technical Committee (ISO TC/249) to further standardise aspects of Chinese medicine.
Despite the development of some standardised research tools, there is currently no guide for how researchers should incorporate syndrome differentiation into clinical trials; however, the use of syndrome differentiation in clinical trials of Chinese medicine is still advocated by the Medical Research Council, the National Institute of Health and the WHO (O’Brien et al., 2009) (Yan et al., 2009).

It has been recognised that syndrome differentiation can be utilised at numerous time points and potentially on multiple occasions throughout a study (Li et al., 2013). For instance, as an inclusion criterion, syndrome differentiation may ensure an intervention is appropriate for the sample (Jiang et al., 2012a). When used for diagnostic or treatment purposes, the intervention may be tailored for the individual according to their syndrome type (Smith et al., 2012). In other instances, syndrome type may be ascertained to add further context to results and further statistical analysis may be performed on the data, such as evaluating treatment response between syndrome types (Hsu et al., 2003). Lu et al (Lu et al., 2009, Lu and Chen, 2011) suggest that Chinese medicine syndrome may also have relevance to conventional drug treatment response, where it may help determine whether a person is likely to respond to drug treatment or not. It has been evidenced that people with similar psoriasis symptoms but different Chinese medicine syndrome type may have different concentrations and activation of key inflammatory cell components, which impact on their condition (Li et al., 1997).

Despite being an important factor for Chinese medicine disease treatment, syndrome differentiation is often overlooked in clinical trial design. In a study examining characteristics of Chinese medicine RCTs from 15 international trial databases...
registries, Liu et al report for CHM that only 22.4% (65 of 290 studies) included syndrome differentiation in trial design, with syndrome differentiation more commonly used for recruitment than for treatment (54 trials (18.6%) compared with 11 trials (3.8%)) (Liu et al., 2013).

Fortunately, syndrome reporting in research is improving, which will help future researchers improve their study design and develop interventions. Increased syndrome reporting would also give experts the opportunity to better evaluate clinical significance and implications of trial results. When syndrome differentiation is not stated in trials, the validity and conclusions that can be drawn from results are limited. A targeted formulation based on syndrome differentiation, for instance, may provide greater efficacy than a formulation specific for the disease but not considering syndrome type (Bensoussan et al., 1998). Indeed, meta-analysis of RCTs has found syndrome differentiation can improve the effect of treatments, although the true effects of utilising syndrome differentiation are still unclear (Kou and Chen, 2012) (Yan et al., 2009).

Despite support for inclusion of syndrome differentiation in CHM clinical studies, a systematic review of acupuncture RCTs concluded that syndrome differentiation does not influence efficacy (Cao et al., 2012). To date, no such systematic review has investigated the influence of syndrome differentiation on the efficacy of CHM in RCTs. As part of this thesis I attempted to determine whether the utilisation of syndrome differentiation could increase the efficacy of CHM by systematically reviewing CHM RCTs similar to the approach by Cao et al (Cao et al., 2012). Unfortunately, due to inconsistent and unclear reporting of syndrome differentiation use in publications, the screening and data extraction process required significant inferences to be made by the reviewers. For instance, commonly studies did not stipulate whether syndrome was differentiated, thus it was decided to include such studies if modification of the
formulation was made based on the symptoms of subjects. Such reviewer assumptions significantly reduce the accuracy of the data and the review was discontinued. For such a review to be conducted in the future, studies need to report clearly on: whether or not they utilised syndrome differentiation; the theory or evidence that supports their syndrome classifications; what relationship syndrome had with the intervention (e.g. syndrome type resulted in, increasing or reducing dosage or frequency, adding or subtracting ingredients); how syndrome classification was determined (e.g. symptoms, severity); and at what stages of the study syndrome was differentiated (e.g. recruitment of subjects, allocation to intervention, grouping of data for analysis).

The addition of such syndrome or pattern differentiation parameters to the CONSORT extension for reporting herbal medicines and journal publication requirements would ensure more research studies reported it (Gagnier et al., 2006b). Such reporting would allow future meta-analysis of CHM studies based on syndrome type and assist evaluation of any benefits of syndrome utilisation in clinical studies. The development of pre-defined diagnostic tools such as the TEAMSI-TCM would reduce inter-rater variation and increase reliability of results (Grant et al., 2013). Research is also needed on the effects of syndrome utilisation on the severity and frequency of adverse events in clinical trials.

5.3.2 What are the known Chinese medicine syndromes for psoriasis?

Given specifying treatment based on syndrome type may enhance outcomes, it was considered important to identify the syndrome types associated with psoriasis. As discussed in Chapter 1, there are many phenotypes of psoriasis, each with different appearance and symptoms. First described over 1600 years ago, Chinese medicine
classification of syndrome types for psoriasis varies, which has resulted in some conjecture as to how many syndrome types exist (Iliev and Broshtilova, 2003).

As the intervention being developed for the present study was being investigated in vulgaris type psoriasis only, only syndrome types relevant for this phenotype were considered. Chinese medicine guidelines for psoriasis (Lu et al., 2012b) recommend treatment based on three primary syndrome types, blood stagnation, blood heat and blood dryness, of which blood stagnation is reported as the most prevalent type in China (52.8%) (Zhang et al., 2009a, Zhang and Qu, 2002, China Academy of Chinese Medicine, 2011, He et al., 2011).

5.3.3 Reviewing treatment guidelines for psoriasis

Health care physicians rely on published treatment guidelines to inform them of best practice and guide their prescriptions. In Australia, conventional psoriasis treatment recommendations are published in the dermatology therapeutic guidelines (Dermatology Expert Group, 2004). These guidelines are supported by the Australian Therapeutic Goods Administration, which regulates pharmaceutical dose prescriptions and Medicare, which further guide dosage and authorise pharmaceuticals to be subsidised and administered under the Pharmaceutical Benefits Scheme (Australian Government - Department of Health and Ageing, 2012). Such guidelines do not inform Chinese medicine practitioners on CHM treatment nor are Australian Chinese medicine therapeutic guidelines available; instead, Chinese guidelines were reviewed for psoriasis treatment for the current study (China Academy of Chinese Medicine, 2011).

The Chinese guidelines were reviewed and summarised according to the following classifications: Chinese medicine syndrome type, the syndromes clinical manifestations, accompanying symptoms, the person’s tongue appearance and their pulse
characteristics associated with each syndrome type (China Academy of Chinese Medicine, 2011). From these data (Table 5.1), a universal herbal formula was developed suitable for all relevant syndrome types (1. wind heat and blood dryness, 2. Blood deficiency and wind dryness, 3. Blood stasis). As the prevalence of each syndrome type in the Australian population is unknown the formulation needed to be suitable for all types. Future epidemiological studies of the Australian population might consider exploring the prevalence of syndrome types and evaluating any difference from the Chinese population. Such investigation was outside the scope of this project so, instead, the assumption was made that syndrome types of Australians are similar to the Chinese population. To enhance the likelihood of reaching recruitment targets it was decided that syndrome type would not be utilised as an inclusion criteria. Therefore, the formulation was developed to be applicable to all syndrome types.
### Table 5.1: Guidelines on syndrome differentiation for psoriasis (China Academy of Chinese Medicine, 2011)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical manifestation</th>
<th>Accompanying symptoms</th>
<th>Tongue appearance</th>
<th>Pulse on palpation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wind heat and blood dryness</td>
<td>New bright red papules or maculopapules of varying sizes develop continuously, auspitz's sign when the scale is removed, Koebner's phenomenon happens occasionally.</td>
<td>Itching, anxiety, dry mouth, constipation, yellow urine</td>
<td>Red tongue with yellow or greasy coating</td>
<td>Slippery, string taut or rapid</td>
</tr>
<tr>
<td>Blood deficiency and wind dryness</td>
<td>Long-term disease, lesions manifest as light red and patchy, covered with plenty of dry silvery white scales. Parts of lesions have disappeared. Dry and chapped skin with itch or pain.</td>
<td>Dry mouth, constipation</td>
<td>Red tongue body with thin white coating</td>
<td>Wiry and slow</td>
</tr>
<tr>
<td>Blood stasis</td>
<td>The disease duration is long and at stable stage. Dull red, hard and thick plaques are covered by thick, dry, silvery-white scales, with itch.</td>
<td>No obvious general symptoms</td>
<td>Dark purple or red tongue body with petechial spots.</td>
<td>Pulse is uneven, or wiry and slow</td>
</tr>
</tbody>
</table>

#### 5.3.4 Reviewing published literature of oral CHM for psoriasis

For the current study, evidence of oral CHM for psoriasis from published studies (English only) was also considered for development of the formulation. Oral CHM formulations were recorded from publications found during the previous systematic reviews (see chapters 3 and 4), including controlled studies, reviews, clinical case studies, expert commentaries and in vitro or in vivo experiments. The variety and frequency of CHM utilised were then explored as well as any supporting evidence for their use by the authors. While not being an exhaustive collection of CHM psoriasis-related publications, 116 different psoriasis-related CHM ingredients were identified (Appendix 3). Chinese herbal medicine ingredients most frequently used for psoriasis
and those indicated to most strongly influence psoriasis were then considered for inclusion in the formulation for the present investigation.

5.3.5 Reviewing phytochemical activity of oral CHM for psoriasis

Although meta-analysis and systematic review have previously identified CHM efficacy in clinical trials and identified those CHM most commonly used in research, there is as yet no comprehensive evaluation of their individual or combined efficacy (Tse, 2003). The short-listed CHM ingredients were further evaluated for key phytochemicals with potential anti-psoriatic activity to ensure they had biological significance for psoriasis, not just a Chinese medicine basis for their use. PubMed was searched for articles detailing the constituent compounds of each CHM and PubChem was further searched to evaluate the biological activity of these phytochemicals (Table 5.2).

5.3.6 Expert opinion and consultation for formulation of oral CHM for psoriasis

Candidate CHM ingredients for psoriasis were then reviewed by a team of Chinese medicine and psoriasis specialists. The specialists evaluated the collected data, giving consideration to currently available evidence and recommendations of Chinese psoriasis treatment guidelines. Following discussion with specialists, CHM ingredients found to be less suitable for the target population (mild–moderate psoriasis vulgaris and all three syndrome types) were eliminated. The remaining ingredients constituted the final proposed formulation (Table 5.3), and the specialists made recommendations on the dosage for each.
5.4 Results

5.4.1 First oral CHM formulation: Primarily developed from Chinese guidelines

A previously published review identified 174 different herbs that had been used in research for psoriasis (Tse, 2003, Tan et al., 2011). As blood stagnation is recognised as the most prevalent syndrome type, the first proposed formulation was developed based on the formula Xue Fu Zhu Yu Tang (China Academy of Chinese Medicine, 2011). Consisting of dang gui (angelica sinensis), di huang (rehmannia glutinosa), tao ren (prunus persica), hong hua (carthamus tinctorius), chi shao (paonia veitchii), chai hu (radix bupleuri), gan cao (radix glycyrrhizae), niu xi (achyranthis bidentatae radix), jie geng (platycodon grandiflorum), zhi ke (fructus aurantii) and chuan xiong (ligusticum chuanxiong). Each of the formulations ingredients has Chinese medicine functions, which improve the syndrome of blood stagnation, as well as some evidence of anti-psoriatic biological activity (Table 5.2). Each herb’s Chinese medicine functions and relevant anti-psoriatic biological activity is briefly discussed:

*Angelica sinensis (dang gui)*

Chinese medicine actions and potential psoriasis biological mechanisms are discussed in 3.4.4

*Rehmannia glutinosa (di huang)*

Chinese medicine actions and potential psoriasis biological mechanisms are discussed in 3.4.4

*Prunus persica (tao ren)*

Prunus persica (tao ren) has Chinese medicine function of moving and breaking up blood stasis. Biological mechanism shows it to prolong thrombin time and inhibits
platelet aggregation, which is important for clotting of blood (Yang et al., 2011). Such action may reduce Auspitz’s sign (pinpoint bleeding) a key feature of psoriasis plaques.

*Carthamus tinctorius (hong hua)*

Carthamus tinctorius (*hong hua*) has Chinese medicine functions of moving and breaking up blood stasis as well as relieving pain. It’s ability to inhibit a number of different cytokines, including anti-psoriasis key inflammatory target TNF-α, as well as reduce growth and proliferation of epidermal cells support its biological pathway activity in psoriasis (Zhang and Qu, 2002, Tse, 2003).

*Paeonia veitchii (chi shao)*

Chinese medicine actions and potential psoriasis biological mechanisms are discussed in Chapter 6

*Radix bupleuri (chai hu)*

Radix bupleuri (chai hu) has Chinese medicine functions to move and regulate qi stagnation whilst also raising qi. Biological activity as shown it to have anti-inflammatory action as well as effects on the immunological lymphocyte response in mice, which both have applicability to psoriasis development and progression (Ushio et al., 1991, Jiang et al., 2012b).

*Radix glycyrrhizae (gan cao)*

Radix glycyrrhizae (gan cao) is primarily added to Chinese herbal formulations to harmonize other herbal ingredients. This reduces the experience of adverse events from other herbal ingredients. It also has function to clear fire and tonify spleen and stomach. Biological evidence has shown it to suppress some immune activity whilst enhancing other activity (Bartosińska et al., 2011). Histamine release inhibition has been reported in rats where its action has been likened to that of a corticosteroid (World Health Organization, 2010).
Achyranthis bidentatae radix (niu xi)

Achyranthis bidentatae radix (niu xi) is another herb with Chinese medicine function of moving and breaking up blood stagnation. Scientific study has shown it enhances chondrocyte proliferation through promotion of cell division during cell replication (Yu et al., 2013a). Interestingly this evidence of cartilage support is reflected in another Chinese medicine function it has, to strengthen sinews and bones. However how this might relate to psoriasis is not known.

Platycodon grandiflorum (jie geng)

Platycodon grandiflorum (jie geng) has Chinese medicine functions of moving, regulating and raising qi. It is another herb which has shown evidence it has anti-inflammatory activity which may indicate its potential benefit for psoriasis (World Health Organization, 1999).

Fructus aurantii (zhi ke)

Fructus aurantii (zhi ke) is indicated for Chinese medicine conditions requiring movement and raising of qi. Biologically it has been indicated to have both antibacterial and anti-inflammatory activity, which may indicate it for both preventing flare-ups of psoriasis and controlling its symptoms (Zhou et al., 2011).

Ligusticum chuanxiong (chuan xiong)

Ligusticum chuanxiong (chuan xiong) has unique Chinese medicine functions to move both blood and qi whilst also expelling wind. The wind component is commonly experienced as itch in Chinese medicine, a symptom which can often aggravate psoriasis sufferers (Zhang and Qu, 2002). Scientific research has shown ligusticum chuanxiong inhibits the growth and proliferation of epidermal cells, which is one of the most characteristic histological features of psoriasis contributing to its macroscopic appearance see chapter 2.2.
Expert opinion further theorised the other two syndrome types (blood heat and blood dryness) have underlying blood stagnation as their 'root', thus these syndrome types were likely to be treated effectively with a modified version of the same formula. Chinese guidelines acknowledge people may have a more complex condition consisting of multiple syndrome types (e.g. blood heat and blood stagnation, or blood dryness and blood stagnation), thus they recommend formulation modification (inclusion or exclusion of ingredients) based on the symptoms of the sufferer. Following review of the literature, it was determined the addition of *dan shen*, *ku shen* and *huang qi* were the optimum additions to the Xue Fu Zhu Yu Tang formula.

*Salvia miltiorrhizae Radix (dan shen)*

*Salvia miltiorrhizae* Radix (*dan shen*) is indicated in the guidelines as treatment for blood heat type psoriasis through inclusion in the Ke Yin formula 2. Its primary Chinese medicine theory related functions for psoriasis are to activate blood circulation (enhancing the actions of the other herbs in the formulation), cool blood and reduce swelling of sores (e.g. psoriasis lesions) (Chen and Chen, 2004). It has also shown anti-hypertensive, antimicrobial, antipyretic, anti-inflammatory and hepatoprotective effects. In addition, it may play a role in the treatment of psoriasis through its suppression of IFN-c and IL-12 as well as mast cell degranulation (Yuqi, 2005, Tse, 2003).

*Sophora angustifolia (ku shen)*

Although not recommended for blood stagnation, *Sophora angustifolia (ku shen)* is recommended for both blood heat and blood dryness in the formulation Xiao Yin Ke Li (China Academy of Chinese Medicine, 2011). Its primary psoriasis-related Chinese medicine functions are to clear damp heat. It is also understood to be an antibiotic, anti-parasitic, antimycotic (to treat fungal infections of the skin), as well as suppress the
growth of keratogenetic cells by way of stimulating TNF-α, with evidence it can suppress pathogenic CD4+ T-cell differentiation and the overall immune response (Gao et al., 2009b, Tan et al., 2011, Kim and Kim, 2012, Zhang and Qu, 2002).

*Astragalus membranaceus (huang qi)*

*Astragalus membranaceus (huang qi)* is not mentioned in the Chinese guidelines for psoriasis; however, Chinese medicine theory indicates ‘qi deficiency’ can be a possible cause of blood stagnation as sufficient qi is required for blood to move (Jingyi Zhao, 2011, Chen, 2004). While moving blood is an important Chinese medicine treatment approach for psoriasis, blood movement is enhanced by strengthening and supplementing qi. This may see longer-term relief of psoriasis symptoms than just moving blood alone. The primary Chinese medicine function of huang qi is to tonify qi (Chinese Pharmacopoeia Commission, 2005). Laboratory research has identified huang qi to be a potential 5-lipoxygenase inhibitor in intact leukocytes and platelets, which may be valuable for managing skin conditions such as psoriasis (Prieto et al., 2003). Published articles also state huang qi enhances T-cells and natural killer cell function promoting humeral immunity and potentially reducing psoriasis symptoms (Yuqi, 2005). Furthermore, *in vitro* studies in rats have found huang qi can significantly inhibit vaginal epithelium mitosis and the expression of proliferating cell nuclear antigen. Furthermore, huang qi promotes development of the granular layer and reduces the serum level of endothelin (ET)-1 in rats, possibly by blocking multiple pathogenic psoriasis linkages (Zhang and Gu, 2007).

For each ingredient, based on recommendations from the Pharmacopoeia of the people’s republic of China and evidenced from available PubChem data, one chief constituent (referred to as a marker) was chosen as a primary active constituent for each ingredient, and possible mechanisms for therapeutic efficacy in psoriasis were
evaluated by reviewing the activity of the constituent compounds (Chinese Pharmacopoeia Commission, 2005).
Table 5.2 First developed oral CHM formulation ingredients and constituent compound functions

<table>
<thead>
<tr>
<th>Chinese herb name</th>
<th>Botanical herb name</th>
<th>Adult dosage raw form (g)</th>
<th>CM function 1</th>
<th>CM function 2</th>
<th>CM function 3</th>
<th>Potential psoriatic biological mechanisms</th>
<th>Chosen biological marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dang gui</td>
<td><em>Angelica sinensis</em> (Apiaceae)</td>
<td>9</td>
<td>Tonifies blood</td>
<td>Moves blood</td>
<td>Drains wind dampness</td>
<td>Prolongs prothrombin time, inhibits platelet aggregation, has antimicrobial, hepato-protective and weak analgesic, antiphlogistic, tumour-inhibiting and antioxidative actions (Hempen and Fischer, 2009a)</td>
<td>Ferulic acid (Chinese Pharmacopoeia Commission, 2005)</td>
</tr>
<tr>
<td>Di huang</td>
<td><em>Rehmannia glutinosa</em></td>
<td>9</td>
<td>Cools heat</td>
<td>Cools blood</td>
<td>Cools fire</td>
<td>Inhibits the release of histamine and production of TNF-α and IL-1 (Kim et al., 1999)</td>
<td>Catalpol (Wang et al., 1997, Astaf'eva et al., 2002, Chinese Pharmacopoeia Commission, 2005)</td>
</tr>
<tr>
<td>Tao ren</td>
<td><em>Prunus persica</em> (Rosaceae)</td>
<td>12</td>
<td>Moves blood</td>
<td>Breaks up blood stasis</td>
<td>Unblocks the bowels</td>
<td>Prolongs thrombin time and inhibits platelet aggregation (Yang et al., 2011)</td>
<td>Amygdalin (Liu et al., 2012b)</td>
</tr>
<tr>
<td>Hong hua</td>
<td><em>Carthamus tinctorius</em> (Asteraceae)</td>
<td>9</td>
<td>Moves blood</td>
<td>Breaks up blood stasis</td>
<td>Relieves pain</td>
<td>Inhibit the production of TNF-α, IL-1 a, IL-1 b and IL-6 and the growth and proliferation of epidermal cells (Zhang and Qu, 2002, Tse, 2003) Extracts methanol and ethanol; anti-inflammatory and antimicrobial (World Health Organization, 2007)</td>
<td>Kaempferol (Chinese Pharmacopoeia Commission, 2005)</td>
</tr>
<tr>
<td>Chinese herb name</td>
<td>Botanical herb name</td>
<td>Adult dosage raw form (g)</td>
<td>CM function 1</td>
<td>CM function 2</td>
<td>CM function 3</td>
<td>Potential psoriatic biological mechanisms</td>
<td>Chosen biological marker</td>
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<tr>
<td>Gan cao</td>
<td><em>Radix glycyrrhizae</em> (Fabaceae)</td>
<td>3</td>
<td>Harmonises and tonifies the qi</td>
<td>Harmonises and tonifies the spleen and stomach</td>
<td>Clears fire</td>
<td>Immunosuppressive and immuno-enhancing activities, prevents side effects of herbal therapy (Bartosińska et al., 2011) Inhibits histamine release from rat mast cells; corticosteroid-like activity (World Health Organization, 2010)</td>
<td>Glycyrrhizin (glycyrrhizic acid, glycyrrhizinic acid) (World Health Organization, 2010, Chinese Pharmacopoeia Commission, 2005)</td>
</tr>
<tr>
<td>Chuan xiong</td>
<td><em>Ligusticum chuangxiong Hort.</em> (Apiaceae)</td>
<td>4.5</td>
<td>Moves blood</td>
<td>Moves and regulates qi</td>
<td>Dispels wind</td>
<td>Inhibits growth and proliferation of epidermal cells (Zhang and Qu, 2002)</td>
<td>—</td>
</tr>
<tr>
<td>Chinese herb name</td>
<td>Botanical herb name</td>
<td>Adult dosage raw form (g)</td>
<td>CM function 1</td>
<td>CM function 2</td>
<td>CM function 3</td>
<td>Potential psoriatic biological mechanisms</td>
<td>Chosen biological marker</td>
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<tr>
<td>Ku shen</td>
<td>Sophora flavescens (Fabaceae)</td>
<td>3-15</td>
<td>Clears damp heat</td>
<td>Dispels wind</td>
<td>Stops itching</td>
<td>Suppresses growth of keratogenetic cells, stimulates TNF-α and suppresses pathogenic CD4+ T-cell differentiation (Tan et al., 2011, Kim and Kim, 2012) Strong antimicrobial activity against mutans streptococci (Kim et al., 2013a) Anticancer (Sun et al., 2012)</td>
<td>Oxymatrine (Sun et al., 2012, Chinese Pharmacopoeia Commission, 2005)</td>
</tr>
<tr>
<td>Dan shen</td>
<td>Salvia miltiorrhiza (Lamiaceae)</td>
<td>6-15</td>
<td>Moves blood</td>
<td>Breaks up blood stasis</td>
<td>Cools heat</td>
<td>Suppresses IFN-γ and IL-12; degranulates mast cell (Bartosińska et al., 2011) Inhibits platelet aggregation</td>
<td>Tanshinone IIA (Ma et al., 2013)</td>
</tr>
<tr>
<td>Huang qi</td>
<td>Astragalus membranaceus (Fabaceae)</td>
<td>9-30</td>
<td>Harmonises and tonifies the qi</td>
<td>Raises collapsed yang</td>
<td>Stabilises the exterior</td>
<td>Inhibits epithelium mitosis and expression of PCNA; promotes development of granular layer; reduces serum level of ET-1 (Zhang and Gu, 2007)</td>
<td>Astragaloside IV (Chinese Pharmacopoeia Commission, 2005, Zhou et al., 2011)</td>
</tr>
<tr>
<td>Niu xi</td>
<td>Achyranthis bidentatae radix</td>
<td>9</td>
<td>Moves blood</td>
<td>Breaks up blood stasis</td>
<td>Strengthens sinews and bones</td>
<td>Enhances chondrocyte proliferation (Yu et al., 2013a)</td>
<td>Oleanolic acid (Chinese Pharmacopoeia Commission, 2005)</td>
</tr>
<tr>
<td>Chinese herb name</td>
<td>Botanical herb name</td>
<td>Adult dosage raw form (g)</td>
<td>CM function 1</td>
<td>CM function 2</td>
<td>CM function 3</td>
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<td>Chosen biological marker</td>
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</tr>
<tr>
<td>Zhi ke</td>
<td><em>Fructus aurantii</em></td>
<td>6</td>
<td>Moves and regulates qi</td>
<td>Raises the yang qi</td>
<td>Breaks up lumps</td>
<td>Antibacterial and anti-inflammatory(Zhou et al., 2011)</td>
<td>Naringin (Park et al., 2005, Zhang et al., 2012, Chinese Pharmacopoeia Commission, 2005)</td>
</tr>
</tbody>
</table>

Note: Adult dosage and Chinese medicine function were adapted from (Bensky et al., 1993) and (Zhou et al., 2011) with further expert advice.

Abbreviations: CD, cluster of differentiation; CM, Chinese medicine; ET, endothelin; IFN-γ, interferon gamma; IL, interleukin; T-cell, thymus lymphocyte; TNF-α, tumour necrosis factor alpha; PCNA, proliferating cell nuclear antigen
5.4.2 Second CHM formulation (PSORI-CM01): The origin and evidence for its utilisation in psoriasis vulgaris

Following the development of the first formulation, details of the ingredients and supporting evidence for their use was sent to dermatologist specialists in China for feedback and comment on its suitability for clinical trial investigation. After discussion it was determined that the initial formulation, while being theoretically suitable, may not be optimal and should be further considered. Instead of further modifying the developed formulation, a pre-existing formulation with extensive clinical use was chosen for a pilot clinical controlled study in an Australian population with mild to moderate psoriasis vulgaris.

Of the formulations identified through literature review there was one in particular (PSORI-CM01), developed and tested by dermatologists in China, which had extensive evidence suggesting its efficacy for psoriasis. Originally known as Yinxieling, the formulation was developed by well-known CM dermatologist Professor Xuan Guowei (Zhong et al., 2004, Wang and Huang, 2009). It was also originally formulated to target the most prevalent psoriatic Chinese medicine syndrome type, blood stagnation (Lu et al., 2014a) and had been previously investigated by a member of the research team (Prof. Chunjian Lu).

Early human study evaluated Yinxieling fumigation effects on psoriasis related protein expression in subjects with psoriasis vulgaris (n=30). For twelve subjects they were assessed as cured following treatment with an effective rate of 96.7%. Further blood showed T-bet and GATA3 restored to normal levels following fumigation, both correlating with PASI score change(Wei et al., 2008). Early oral administration human single blind study (n=84) of Yinxieling decoction with or without auricular acupuncture
(8 weeks), in subjects with psoriasis vulgaris found both groups had significant reduction in PASI score. This significance was greater in subjects with initial PASI > 10, although this group also had greater room for improvement (Lu et al., 2012a). More recent oral human study (n=120) of *Yinxieling* in decoction form found it significantly decreased TNF-α and IL-8 as well as reduced PASI significantly for all syndrome types. It was noted the control group did not have significant reduction in PASI (Dai et al., 2014b).

Following *in vitro, in vivo*, high-performance liquid chromatography, electrospray ionisation hybrid linear trap quadrupole Orbitrap mass spectrometry (UHPLC-(-) ESI-MS) techniques and clinical studies, it has since been optimised to its current form (PSORI-CM01) (Gu et al., 2009) (Han Ling, 2011), and was suitable for further clinical evaluation under controlled conditions (Lu et al., 2014a, Chen et al., 2015) (Figure 5.1). Researchers were already in the early stages of investigating PSORI-CM01 in a Chinese population with severe psoriasis, although a protocol of how it would be implemented had not yet been developed (Wen et al., 2014).

![Figure 5.1: UHPLC-(-) ESI-MS of (A) standards and (B) PSORI-CM01(Chen et al., 2015)](image-url)
The optimised formula of PSORI-CM01 comprises seven ingredients: *Paeonia lactiflora* root (*chi shao*), *Curcuma wenyujin* rhizome (*e zhu*), *Sarcandra glabra* (*zhong jie feng*), *Glycyrrhiza uralensis* root and rhizome (*gan cao*), *Prunus mume* fruit (*wu mei*), *Arnebiae radix* (*hong tiao zi cao*) and *Smilax glabra* rhizome (*tu fu ling*) (Table 5.3). The constituent compounds of each ingredient of PSORI-CM01 were reviewed and those most likely to have potential therapeutic mechanistic action for psoriasis were identified. For each ingredient (principlc herb listed first), the most likely biologically psoriasis active constituent was considered the main therapeutic marker for that ingredient (Table 5.3). These were then later explored using mass spectrometry techniques, using various samples to determine the final optimised preparation (Lu et al., 2014a). It was found that granulated extract was phytochemically content superior to pill and decoction forms of PSORI-CM01 (Chen et al., 2015) (Figure 5.2).

<table>
<thead>
<tr>
<th>Analyte *</th>
<th>KLJ-1</th>
<th>KLJ-2</th>
<th>PJ-3</th>
<th>PJ-4</th>
<th>PJ-5</th>
<th>TJ-6</th>
<th>TJ-7</th>
<th>TJ-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-O-Caffeoylquinic acid (16)</td>
<td>520.94</td>
<td>531.48</td>
<td>391.56</td>
<td>132.01</td>
<td>429.07</td>
<td>122.89</td>
<td>30.68</td>
<td>121.18</td>
</tr>
<tr>
<td>5-O-Caffeoylquinic acid (22)</td>
<td>514.55</td>
<td>503.94</td>
<td>391.56</td>
<td>146.51</td>
<td>488.10</td>
<td>123.45</td>
<td>27.30</td>
<td>183.64</td>
</tr>
<tr>
<td>4-O-Caffeoylquinic acid (24)</td>
<td>601.74</td>
<td>545.00</td>
<td>558.82</td>
<td>211.85</td>
<td>683.57</td>
<td>129.75</td>
<td>40.53</td>
<td>160.64</td>
</tr>
<tr>
<td>5-O-Caffeoylquinic acid (39)</td>
<td>540.55</td>
<td>520.10</td>
<td>789.39</td>
<td>324.27</td>
<td>397.06</td>
<td>133.60</td>
<td>153.44</td>
<td>429.46</td>
</tr>
<tr>
<td>Paoniflorin (40)</td>
<td>5855.02</td>
<td>6030.52</td>
<td>7218.12</td>
<td>5177.23</td>
<td>5368.14</td>
<td>2326.21</td>
<td>445.51</td>
<td>3511.46</td>
</tr>
<tr>
<td>Liquiritin (51)</td>
<td>1654.18</td>
<td>1650.73</td>
<td>892.15</td>
<td>360.64</td>
<td>1115.65</td>
<td>145.56</td>
<td>71.55</td>
<td>248.20</td>
</tr>
<tr>
<td>Neoastilbin (56)</td>
<td>2545.86</td>
<td>2767.29</td>
<td>2442.62</td>
<td>423.15</td>
<td>1680.52</td>
<td>369.88</td>
<td>124.14</td>
<td>588.89</td>
</tr>
<tr>
<td>Astitilin (60)</td>
<td>3819.23</td>
<td>4061.92</td>
<td>3743.95</td>
<td>844.53</td>
<td>2575.83</td>
<td>661.96</td>
<td>174.14</td>
<td>879.05</td>
</tr>
<tr>
<td>Neoisoastilbin (64)</td>
<td>2459.06</td>
<td>2359.70</td>
<td>1872.94</td>
<td>736.75</td>
<td>2211.36</td>
<td>605.51</td>
<td>154.36</td>
<td>802.79</td>
</tr>
<tr>
<td>Isoastilbin (67)</td>
<td>879.60</td>
<td>916.61</td>
<td>650.53</td>
<td>260.87</td>
<td>902.06</td>
<td>244.03</td>
<td>74.96</td>
<td>418.97</td>
</tr>
<tr>
<td>Engeletin (79)</td>
<td>678.32</td>
<td>740.00</td>
<td>503.10</td>
<td>196.27</td>
<td>621.69</td>
<td>165.13</td>
<td>84.25</td>
<td>274.81</td>
</tr>
<tr>
<td>Isoengeletin (82)</td>
<td>543.19</td>
<td>1089.55</td>
<td>348.12</td>
<td>132.29</td>
<td>331.67</td>
<td>119.27</td>
<td>16.30</td>
<td>116.39</td>
</tr>
<tr>
<td>Liquiritigenin (87)</td>
<td>224.07</td>
<td>246.07</td>
<td>477.28</td>
<td>62.14</td>
<td>202.73</td>
<td>75.50</td>
<td>24.55</td>
<td>130.18</td>
</tr>
<tr>
<td>glycyrrhizic acid (107)</td>
<td>2225.13</td>
<td>2359.89</td>
<td>2610.50</td>
<td>933.51</td>
<td>2770.51</td>
<td>306.01</td>
<td>68.44</td>
<td>257.72</td>
</tr>
</tbody>
</table>

KLJ (1&2), granulated extract method 1 & 2; PJ, Pill formulation 1 & 2; TJ (6,7 & 8), decoction form method 1, 2 & 3

Figure 5.2: Contents of 14 key phytochemicals of PSORI-CM01 (µg/g or ug/mL)(Chen et al., 2015)
**Table 5.3: Second developed oral CHM formulation (PSORI-CM01) ingredients and constituent compound functions**

<table>
<thead>
<tr>
<th>Chinese herb name</th>
<th>Botanical herb name</th>
<th>CM function 1</th>
<th>CM function 2</th>
<th>CM function 3</th>
<th>Potential psoriatic biological mechanisms</th>
<th>Likely psoriatic active contained compounds</th>
<th>Chosen biological marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi shao</td>
<td><em>Paeonia lactiflora</em> root</td>
<td>Clears heat and cools blood</td>
<td>Dispels blood stasis and relieves pain</td>
<td>Reduces swelling and sores</td>
<td>Platelet aggregation inhibitor (daucosterol, paeoniflorin (Koo et al., 2010)), Inhibits lipolysis; antioxidant (eugeniin, paeoniflorin), Anti-inflammatory (paeoniflorin, paeonol) Antipyretic (paeoniflorin, paeonol) (Chen et al., 2011).</td>
<td>Daucosterol eugeniin paeoniflorin paeonol</td>
<td>Paeoniflorin</td>
</tr>
<tr>
<td>Tu fu ling</td>
<td><em>Smilax glabra</em> rhizome</td>
<td>Eliminates toxic heat</td>
<td>Dispels toxic heat from the skin</td>
<td>Promotes normal urination</td>
<td>Antineoplastic (Astilbin) Anti-inflammatory (astilbin, dihydroquercetin) (dihydroquercetin modulates cytokine network: IFN-γ) ICAM-1 protein, as well as miRNA expression in human keratinocytes Cytotoxic (caffeoylshikimic acid) Antibacterial (syringic acid) (Zhou et al., 2011)</td>
<td>Astilbin caffeoylshikimic acid dihydroquercetin isoengelitin syringic acid</td>
<td>Syringic acid</td>
</tr>
<tr>
<td>E zhu</td>
<td><em>Curcuma wenyujin</em> rhizome</td>
<td>IBC and breaks up blood stasis</td>
<td>Activates qi circulation and relieves pain</td>
<td>Antineoplastic (furanodiene, curdione, curcumol)(Gao et al., 2009a, Sun et al., 2009)</td>
<td>Curcumol curdione furanodiene</td>
<td>Furanodiene</td>
<td></td>
</tr>
<tr>
<td>Chinese herb name</td>
<td>Botanical herb name</td>
<td>CM function 1</td>
<td>CM function 2</td>
<td>CM function 3</td>
<td>Potential psoriatic biological mechanisms</td>
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</tr>
<tr>
<td>Zhong jie feng</td>
<td>Sarcandra glabra (Chloranthus glaber)</td>
<td>Reduces heat in the blood</td>
<td>Activates blood to remove ecchymosis</td>
<td>Dispels wind and eliminates damp</td>
<td>Increase platelet production (Zhong 2005) Antineoplastic; choleretic; cytotoxic (isofraxidin) (Zhou et al., 2011) Antibacterial; antineoplastic (fumaric acid) (Zhou et al., 2011) Antibacterial (Staphylococcus aureus, Coccus catarrhal, Bacillus pyocyaneus, Bacillus proteus, B. typhosus and Bacillus dysenteriae) (Succinic acid) (Zhou et al., 2011)</td>
<td>Coumarone fumaric acid isofraxidin succinic acid</td>
<td>Isofraxidin Fumaric acid</td>
</tr>
<tr>
<td>Gan cao</td>
<td>Glycyrrhiza uralensis root and rhizome</td>
<td>Harmonises and tonifies the qi</td>
<td>Harmonises and tonifies the spleen and stomach</td>
<td>Clears fire</td>
<td>Immunosuppressive and immuno-enhancing activities (Bartosińska et al., 2011) Anti-inflammation (glycyrrhetinic acid, glycyrrhizinic acid, isoliquiritin, isoquercitrin) Antibacterial (formononetin, glabrene, glabridin, labrol, glycyrrhetinic acid, hispaglabridin A and B, hydroxyglabrol, isoquercitrin, licochalcone B, pinocembrin, wighteone) Antiallergic (glycyrrhetinic acid, glycyrrhizinic acid, licochalcone B antineoplastic (glycyrrhetinic acid, isoliquiritigenin Cytotoxic (isoliquiritigenin, pinocembrin Inhibits cell proliferation (isoliquiritigenin)</td>
<td>Formononetin glabrene glabridin labrol glycyrrhetinic acid glycyrrhizinic acid hispaglabridin A and B hydroxyglabrol isoliquiritigenin isoliquiritin isoquercitrin licochalcone B pinocembrin wighteone</td>
<td>Glycyrrhizin (glycyrrhi-zic acid)</td>
</tr>
<tr>
<td>Chinese herb name</td>
<td>Botanical herb name</td>
<td>CM function 1</td>
<td>CM function 2</td>
<td>CM function 3</td>
<td>Potential psoriatic biological mechanisms</td>
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</tr>
<tr>
<td>Wu mei</td>
<td><em>Prunus mume</em> fruit</td>
<td>Stops sweating due to lung qi deficiency</td>
<td>Binds the intestines</td>
<td>Generates body fluids</td>
<td>Antibacterial (<em>Staphylococcus aureus</em>, <em>Bacillus coli</em>, <em>Bacillus dysenteriae</em> and <em>B. typhosus</em>); Antineoplastic and cytotoxic (Hou et al., 2001) (naringenin) Anti-inflammatory (macrophages, COX-2 inhibitor, inhibits COX-2 expression) (Calixto et al., 2003); (naringenin); Amygdalin citric acid hydrocyanic acid malic acid naringenin picric acid</td>
<td>Ursolic acid Naringenin</td>
<td></td>
</tr>
<tr>
<td>Hong tiao zi cao</td>
<td><em>Arnebiae</em> Radix (or <em>Arnebia euchroma</em> or Radix <em>Lithosperm i seu</em> <em>Arnebiae</em>)</td>
<td>Remove heat from blood</td>
<td>Promote blood circulation</td>
<td>Reduce toxicity and facilitate eruptions</td>
<td>Anti-inflammatory (acetyllakannin, shikonin) Antineoplastic (alkannin angelate) Antibacterial (<em>Staphylococcus aureus</em>, <em>Staphylococcus epidermidis</em>) (deoxyshikonin, dimethylacrylshikonin, dimethylacrylalkannin, shikonin, teracrylshikonin) Treatment of allergic purpure (dimethylacrylalkannin) (Zhou et al., 2011)</td>
<td>Alkannin (β-dimethylacrylalkanin) isolated compounds: acetyllakannin alkannin angelate caffeic acid deoxyshikonin dimethylacrylalkannin (Alkannin) dimethylacrylshikonin nahikonin, teracrylshikonin</td>
<td>Alkannin</td>
</tr>
</tbody>
</table>

Note: Adult dosage and Chinese medicine function are adapted from Bensky 1993 (Bensky et al., 1993) and (Zhou et al., 2011). COX, cyclooxygenase ICAM, intercellular adhesion molecule; IFN-γ, interferon gamma.
5.5 Discussion

Although the first formulation (Table 5.2) may have premise for efficacy in psoriasis, it has no pre-existing clinical evidence reports. There is clinical evidence to support each of its ingredients individually; however, the synergistic and/or antagonistic consequences of combining them are unknown. The cost and time requirements of an RCT necessitate optimal interventions, so the PSORI-CM01 formulation (Table 5.3), which has significant prior clinical evidence of its potential efficacy, was chosen for the proposed trial.

Although originally formulated for the syndrome of blood stagnation, PSORI-CM01 has since been optimised and research results indicate it also has benefit for blood dryness and blood heat syndromes (Wang and Huang, 2009, Dai et al., 2014b). Despite this evidence, its effect in an Australian mild–moderate severity psoriatic population is unknown. As the prevalence of syndrome types is also unknown for the Australian population, the RCT was designed to assess syndrome type of participants at several time points during the trial.

As technology for identifying constituents of substances, such as high-performance liquid chromatography, improves there is likely to be new compounds discovered (Bai et al., 2013). In the current study, we endeavoured to outline all known compounds in each ingredient in the formulation. Although a primary constituent was chosen as a marker for each ingredient, this marker is not necessarily the most biologically active for psoriasis. Markers were chosen using the Chinese pharmacopeia, and in vitro and in vivo evidence of all the known constituents. Those with the most evidence of psoriatic-like bioactivity were shortlisted, and those with the greatest concentration in the ingredient were identified. Using this method, the constituent
identified was often the same as that recommended by pharmacopeia, however this was not always the case.

It should be noted that selection of a suitable marker should not be based solely on its concentration. Consideration needs to be given to the processing the substance will undergo to prepare it for therapeutic use, and the disease it is being administered for. Some processing methods such as boiling at high temperatures may denature the constituent to such a degree it becomes undetectable and subsequently may lose its therapeutic activity. For other constituents, although still detectable in large quantities, following processing they may be inert. Identification of the constituents and understanding their chemical structures can assist in development of manufacturing and processing methods to ensure they remain in significant concentrations in the end product. Processing and manufacturing methods should provide the optimum yield of constituents known to be biologically relevant for the investigated condition.

5.6 Conclusion

The first developed formulation was primarily based on review of published oral CHM for psoriasis as well as recommendations from available Chinese medicine guidelines. While it was developed in a rigorous manner, the clinical efficacy of the formulation is yet unknown. Although the first formulation does merit further in vitro, in vivo and clinical research investigation, due to the costs and time involved in the conduct of an RCT it was decided a formulation with significant previous efficacy would be best utilised.

Of those identified in the reviews, a formulation based on Yinxieling was deemed the most suitable (PSORI-CM01). One member of the research team had previous clinical and experimental experience with the formulation and it had been optimised
significantly since its initial development. The majority of the evidence for its use in psoriasis was based on results from animal models or in the Chinese population; however, following further evaluation it was determined there was no evidence to suggest it would be unsuitable for use in an Australian mild to moderate severity psoriatic population. Thus, it was determined the PSORI-CM01 formulation would be used in the present Australian RCT.
Chapter 6 – Exploring the biological pathway activity of phytochemicals in principal herb (chi shao) and investigating their potential for psoriasis therapy

This chapter reviews the biological activity of phytochemicals in chi shao, the principal CHM in PSORI-CM01. It compares the phytochemical compositions of the most common botanicals sold as chi shao and evaluates their anti-inflammatory, anti-tumour, anti-viral, antibacterial, antioxidant/prooxidant and glycaemic activity.

6.1 Background

Botanicals have a long history of use in treating diseases or relieving their symptoms, where typically they are administered internally or externally in entire form (Balunas and Kinghorn, 2005, Wachtel-Galor and Benzie, 2011). The active compounds of plants have regularly provided sources for the development of new pharmaceuticals, where their chemical structures are analysed to investigate potential therapeutic activity in target disease (Jones et al., 2006). These active phytochemicals may then undergo in vitro and in vivo experimentation to further elucidate their activity.

Numerous pharmacological drugs or products originate from botanicals, using pharmacogenecy techniques to modify and/or concentrate compounds in order to target and enhance their biological activity (Balunas and Kinghorn, 2005, Jones et al., 2006).

A thorough review of the evidence for pharmacological action of the principal herb, chi shao, in PSORI-CM01, was undertaken (Zaiyou et al., 2013). Chi shao is sourced from Paeonia lactiflora or P. veitchii, so the constituent compounds found in both were classified according to their chemical group and potential biological therapeutic activity.
The aim was to ensure the quality of chi shao product to be utilised in PSORI-CM01 and identify suitable compounds to act as biological markers during processing.

6.1.1 Peony medicinal history

Plants from the genus *Paeonia* have a long history of use in medicine. The genus name comes from a Greek legend in which a student of medicine known as Paeon healed the wound of the god Pluto, who later saved the student from death by turning him into the healing plant commonly known as peony. Early medicinal use was for dissolving bladder and kidney stones (Pickering, 1989). In recent times, constituent compounds of peony have been evidenced to be of medical significance. For example, a group of constituents in *P. lactiflora* known as total glucosides of peony (TGP) exhibit anti-inflammatory action that has seen them approved by the State Food and Drug Administration of China for rheumatoid arthritis (He and Dai, 2011).

6.1.2 Herbaceous peony species used in China

*Paeonia* is the single genus in the family Paeoniaceae, consisting of around 35 species of either tree or herbaceous plant, 11 of which are found in China (Zaiyou et al., 2013). Herbaceous species grow to around three feet in height and are perennial with flowers, often fragrant, which grow to around six inches in diameter (Kamenetski, 2007, Cooperative Extension Service Kansas State University, 1993). A number of Chinese peonies are used in traditional medicine (Chinese Pharmacopoeia Commission, 2005).

The roots of herbaceous peony species are commonly utilised medicinally in China. In the herbal market, peony roots are distinguished by white or red colour. Radix *Paeoniae Alba*, or ‘white peony root’ (*bai shao 白芍*), is generally sourced from *Paeonia lactiflora* Pallas (syn. *P. albiflora*) (*shao yao 芍药*) (Chinese Pharmacopoeia Commission, 2005), but can also be produced from *Paeonia lactiflora* Pallas var. *trichocarpa* Bunge
(mao guo shao yao 毛果芍药), both of which are grown in the north and east of China (State Administration of Traditional Chinese Medicine 'Chinese Materia Medica Committee' (ed.), 1998). Radix Paeoniae Rubra, ‘red peony root’ (chi shao 赤芍), is brownish in appearance and is officially sourced from Paeonia lactiflora Pallas or Paeonia veitchii Lynch (aka Paeonia anomala subsp. veitchii (Lynch) D.Y.Hong & K.Y.Pan) (chuan chi shao 川赤芍), which are from the Sichuan province and other parts of northern and western China (Chinese Pharmacopoeia Commission, 2005, Zhu et al., 2014). In addition, red peony root can be sourced from P. obovata Maxim., P. mairei Levé, P. anomola L. and associated varieties (State Administration of Traditional Chinese Medicine 'Chinese Materia Medica Committee' (ed.), 1998).

Of the geographical varieties of P. lactiflora, a rare form farmed from Duolun has been identified as the variety most characterising red type (chi shao), however it is also considered to be rare (Zhou et al., 2002). As its name suggests, wild P. lactiflora typically has white flowers (Figure 6.1), whereas P. veitchii has red flowers; however, modern cultivars of P. lactiflora can have red, pink or purple flowers (Figure 6.2)(Halda and Waddick, 2010). Consequently, the traditional distinction between white and red peony in China based on flower colour has contributed to the current confusion distinguishing the two types as medicinals (Mikage and Ono, 2009, Hooper, 1929, Zhang and Dai, 2012).
Figure 6.1: Paeonia lactiflora Pallas (Tatyana, 2015)

Figure 6.2: Paeonia veitchii (Smit, 2015)
Traditional Chinese Medicine Materia Medica (an encyclopaedia of herb descriptions, sources, botanical name and known functions) describe a white peony in which the colour of the root when cut is white (Figure 6.3A: Radix Paeoniae Alba) (Zaiyou et al., 2013), compared with another peony in which the colour of the root when cut is pinkish and is known as the red peony (Figure 6.3B: Radix Paeoniae Rubra)(Liang et al., 2014, Chinese Pharmacopoeia Commission, 2005). While white peony root is typically sourced from *Paeonia lactiflora*, there is considerable diversity in the sources of red peony root in the herbal market, although only *P. lactiflora* and *P. veitchii* are considered official (Chinese Pharmacopoeia Commission, 2005). The two species have received considerable research attention regarding their constituents and pharmacological actions (Mikage and Ono, 2009, Hooper, 1929). Due to use of both species as *chi shao* constituent compounds, both herbs were evaluated and significant *in vitro* and *in vivo* evidence of compound pathway activity was reviewed (Zhang et al., 2013a).

**Figure 6.3:** A (left) – sections of root of Radix Paeoniae Alba (cms) (Hempen and Fischer, 2009b) B (right) – sections of root Radix Paeoniae Rubra (cms) (Hempen and Fischer, 2009b)
6.1.3 High-performance liquid chromatography of P. lactiflora and P. veitchii

Chemical classification using high-performance liquid chromatography analysis shows that two subspecies of *P. lactiflora* exist, a northern or southern China species (Zhu et al., 2014, Wang et al., 2014). As yet there is no consistent consensus on which is therapeutically superior. *Paeonia lactiflora* appears to have greater concentration of the principal component paeoniflorin) compared with *P. veitchii* (Zaiyou et al., 2013), yet other research indicates the opposite, paeoniflorin reported to make up 72% of total constituent weight (mg/g) of *P. veitchii* samples, which is greater than 54-65% in *P. lactiflora* samples (Chuang et al., 1996). In *P. lactiflora* samples, a higher concentration of constituent paeoniflorin (65% of total) is reported in decorticated (skin removed) samples than corticated (skin remains) samples (54% of total) (Chuang et al., 1996).

Research also indicates that *P. lactiflora* samples generally contain a greater number of constituents than *P. veitchii* samples (Chuang et al., 1996). Further, samples of decorticated *P. lactiflora* contain higher concentration of the major constituents than corticated samples (Chuang et al., 1996). Similarly, *P. veitchii* has higher constituent content in the root cortex (skin) than the root core, thus it is likely that retention of the cortex is therapeutically important for *P. veitchii* products (Chuang et al., 1996).

Geographical location of farming may affect constituent concentrations of botanicals due to local temperature and rainfall, and even season of harvest can affect concentrations of contained phytochemicals (Jian et al., 2010).

6.1.4 Processing methods

Production methods allow *P. lactiflora* to be sold as white (Radix Paeoniae Alba or *bai shao*) or red (Radix Paeoniae Rubra or *chi shao*) types. Different harvesting and processing procedures for *P. lactiflora* distinguish its type at sale. As *bai shao*, *P.
*lactiflora* is cultivated then the root boiled, peeled and sun-dried (Zhang and Dai, 2012). To further preserve the white appearance, the *P. lactiflora* root it is often fumigated with sulphur dioxide (Wang et al., 2006), so monoterpenic glycoside sulphonated derivatives of many of the constituent compounds are regularly detected in commercial samples of *P. lactiflora* (Wang et al., 2006, Li et al., 2009). Fumigation is not officially sanctioned and the therapeutic effects of the resultant sulphonated compounds are unknown (Luo et al., 2013).

### 6.1.5 Traditional Chinese medicine use of *P. lactiflora* and *P. veitchii*

From a Chinese medicine perspective the two *Paeonia* colours (*chi shao* and *bai shao*) are prescribed for different therapeutic purposes. *Bai shao* is mostly administered for conditions involving menstrual disorder (dysmenorrhoea or menorrhagia) or various painful conditions such as cholecystitis; however, it is also indicated for dysentery, hypertension and spermatorrhoea. Similarly, *chi shao* is also indicated for painful conditions, but is also indicated for infectious conditions that affect the skin, such as measles or chickenpox, in which its action is to treat infection (Hempen and Fischer, 2009b). The therapeutic differences between *chi shao* and *bai shao* suggest possible variation in the constituent compound content of the two types and this has been supported by evidence from high-performance liquid chromatography (Xu et al., 2009).

### 6.2 Methods

A database search was undertaken and key herbal pharmacological encyclopaedia reviewed to identify the known constituents of both botanicals (Zhou et al., 2011). Publications with high performance liquid chromatography (HPLC) results (or other analytic technique) for *P. lactiflora* and *P. veitchii* were compared to encyclopaedia results to ascertain a comprehensive list of the known phytochemicals in each.
Search terms for *P. lactiflora* and *P. veitchii* included their full names *Paeonia lactiflora* and *Paeonia veitchii*. Constituent search terms primarily used the main chemical name of each, however in an instance a constituent had more than one main chemical name a further publication search was conducted.

Using PubChem and PubMed each constituent was then reviewed to identify evidence of their biological activity and then grouped with other similar activity constituents. Where multiple publications were available on the same pathway activity, the original publication identifying the constituents activity for that pathway was used or publications in which the constituent was originally extracted from a paeonia source. Pathway activities of compounds were then grouped under common drug actions which; reduce or modulate inflammation pathways (anti-inflammatory/immunomodulation), reduce proliferation of cells or increase cell apoptosis (cytotoxic/anti-tumour), reduce or prevent viral replication in healthy cells (anti-viral), inhibit bacteria or fungal cell development and replication (anti-bacterial/anti-fungal), influence blood glucose levels (glycaemic), reduce or increase free radical production (anti-oxidant/pro-oxidant) or have activity other than the previous mentioned (other). Within each of the above categories, phytochemical with the highest concentrations are discussed first.

### 6.3 Results

#### 6.3.1 Main phytochemistry and constituents of *P. lactiflora* and *P. veitchii*

Most constituents of *P. lactiflora* and *P. veitchii* are classified as monoterpenoids, triterpenoids, flavonoids, phenols or tannins (Wu et al., 2010, Li et al., 2009). High-performance liquid chromatography shows that paeoniflorin is the most abundant phytochemical in both species (54–65% in *P. lactiflora* and up to 72% in *P. veitchii*), with pentagalloylglucose also found in significant concentrations in both. Albiflorin is
another major phytochemical in *P. lactiflora*, while oxypaeoniflorin is found in significant amounts in *P. lactiflora* (Chuang et al., 1996).

### 6.3.2 Biological pathway activity

**Anti-inflammatory or immunmodulatory activities**

A large number of compounds in both *Paeonia* species have been evaluated as having potential anti-inflammatory or immunmodulatory pathway activity (Table 6.1).

**Total glucosides of peony**

Among the most well studied constituents of *P. lactiflora* is the group known as TGPs. Individually *P. lactiflora* contained monterpene glycosides; paeoniflorigenone, paeonianiin E, paeonidanin A, paeonidanin B and paeonidanin C display inhibitory effects on NO production, reducing the inflammatory response and preventing NO hyper-function tissue damage. When grouped as TGP the anti-inflammatory therapeutic mechanism is likely due to modulation of pro-inflammatory mediators, mediation of cAMP levels and inhibition of synoviocyte proliferation, which in turn decreases production of IL-1, TNF-α and prostaglandin (Xu et al., 2007, Wu et al., 2009b, Deng et al., 2010).

Research has indicated TGP may have potential use in diseases of the kidneys and liver, where they prevent diabetes-associated renal damage through increased expression of nephrin protein and inhibition of diabetic nephropathy progression (Wu et al., 2009b, Wang et al., 2012d, Zhang et al., 2009b, Zhang et al., 2014e, Su et al., 2010a). The anti-inflammatory properties of TGP may also lower blood lipids and inhibit the expression of inflammatory cytokines, subsequently reducing the development of atherosclerotic disease (Li et al., 2011). Potential TGP therapeutic effects include treatment of systemic lupus erythematosus, in which it reduces the use...
of drugs such as prednisone, as well as provides potential hepato-protective effects from drugs such as methotrexate (Zhang et al., 2011a, Chen et al., 2013). Through inhibition of T-cell proliferation and reduction in the maturation of DCs, the TGP group arrests the DCs antigen-presenting ability subsequently reducing the immune-mediated inflammatory response (Zhou et al., 2012b).

**Paeoniflorin**

Paeoniflorin is the constituent with the highest concentration in both species (54-65% in *P. lactiflora* and up to 72% in *P. veitchii*) and is one of the most well studied compounds for potential therapeutic properties (Chuang et al., 1996). It has been shown to reduce chemokine secretion in TNF-α-induced endothelial cells and inhibit TNF-α induced leukocyte migration. Paeoniflorin pre-treatment may also block phosphorylation of IκBα, which requires degradation of its levels to activate NF-κB for the subsequent expression and production of inflammatory chemokines (Chen et al., 2011). Paeoniflorin has been shown to reduce ICAM-1 molecules, which mediate the adhesion of leukocytes. Possibly through inhibiting TNF-α activation pathways of MAP kinases, ERK1/2 and p38, required for the subsequent activation of ICAM-1. Paeoniflorin has also been shown to inhibit the TNF-α stimulated adhesion of monocytes to endothelial cells (Nizamutdinova et al., 2007).

**Albiflorin**

The monoterpene albiflorin (found in both species), has shown minor inhibitory effects on cAMP-PDE activity in neutrophils resulting in a rise in intracellular cAMP (Jiang et al., 2011). (Jiang et al., 2011). This subsequent cAMP rise, increases protein kinase A activity, inhibits the activation of NADPH oxidase and reduces neutrophil release of
oxygen free radicals. These all reduce the activity of neutrophils in an inflammatory response.

**Oxypaeoniflorin and paeoniflorigenone**

The monoterpenic glycoside oxypaeoniflorin and the lesser abundant paeoniflorigenone, which are found in *P. lactiflora*, act through nitric oxide (NO) reduction from lipopolysaccharide-activated macrophages, whereas for the other phytochemicals, NO reduction is via lipopolysaccharide (LPS)-activated N9 microglia (Ding et al., 2012, Duan et al., 2009).

**Gallic acid**

Gallic acid has been shown to act on a similar pathway to paeoniflorin, however with stronger effect (Jiang et al., 2011). It is also known to interfere with polymorphonuclear leukocyte (PMN) functioning, inhibiting the release and activity of myeloperoxidase, scavenging superoxide anions and possibly interfering with active NADPH-oxidase assembly (Kroes et al., 1992).

**Pentagalloylglucose**

Lesser studied is the hydrolysable tannin, (1,2,3,4,6-) pentagalloylglucose, which is considered an ester of gallic acid and found in both *P. lactiflora* and *P. veitchii*. It has an anti-allergic effect, inhibiting IL-4 signal activation in the IgE production pathway. A number of common type-1 hypersensitivity conditions, such as eczema are associated with IgE, and IL-4 is considered the most important cytokine regulating its synthesis (Corry and Kheradmand, 1999, Kim et al., 2013c). It's understood that IL-4 induces expression of ε germline transcript (εGT), which goes on to initiate IgE production.
Daucosterol and \(\beta\)-sitosterol

Acting as an immunorestorative, daucosterol increases human peripheral lymphocyte proliferation and enhances secretion of lymphokine IL-2 and gamma interferon, whilst also enhancing NK-cell activity of lymphocytes. This action shows potential for assisting the inflammatory response of immunodeficient people. Interestingly, by increasing TH1-type helper cells, daucosterol appears to act on lymphokines, whereas TH2-type helper cells are inhibited or remain unchanged, suggesting it might enhance TH-1 pathway activity and/or reduce TH-2 pathway activity (Bouic and Lamprecht, 1999, Lee et al., 2007). Further anti-inflammatory actions of daucosterol have been evidenced through inhibition of both IL-6 and TNF-\(\alpha\) (Bouic and Lamprecht, 1999). Acting similarly to its glucoside (daucosterol), but with greater potency, \(\beta\)-sitosterol acts in the reduction of lipopolysaccharide-induced secretion of IL-6 and TNF-\(\alpha\), requiring much lower concentration for its effect (Ding et al., 2009).

Other

Other phytochemicals found in either botanical but with less significant concentration and function include; hydrolysable tannins 1-O-galloyl-beta-D-glucose, casuariin, pedunculagin, strictinin, and casuarictin; monoterpen glycoside paeoniflorigenone, paeonianein E, paeonidanin A, paeonidanin B and paeonidanin C; galloyl glucoses 1,2,3-Tri-O-galloyl-\(\beta\)-D-glucose and 1,2,6-Tri-O-galloyl-\(\beta\)-D-glucose. Their actions are briefly described in table 6.1.
Table 6.1: Anti-inflammatory or immunomodulatory pathway activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical structure (src. PubChem)</th>
<th>Chemical group</th>
<th>Extended group</th>
<th>Pathway activity</th>
<th>↑ or ↓ pathway</th>
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</thead>
<tbody>
<tr>
<td>Albiflorin (v, l)</td>
<td><img src="image1" alt="Chemical structure" /></td>
<td>Pinnae-type monoterpenes</td>
<td>Monoterpenoid</td>
<td>Neutrophil activation via cAMP-PDE (cyclic adenosine monophosphate – phosphodiesterase) (Jiang et al., 2011)</td>
<td>↓</td>
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<tr>
<td>Daucosterol (beta-Sitosterol glucoside) (v, l)</td>
<td><img src="image2" alt="Chemical structure" /></td>
<td>Phytosterols</td>
<td>Steroid</td>
<td>1. Proliferation of T-cells and natural killer cell activity (Bouic et al., 1996)</td>
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<td>2. Lymphokines belonging to TH1-type (IL-2 and IFN-γ) (Bouic and Lamprecht, 1999, Lee et al., 2007)</td>
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<td></td>
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<td>3. Lymphokines TH2-type helper cells (IL-4 IL-10) (Bouic and Lamprecht, 1999, Lee et al., 2007)</td>
<td>↓</td>
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<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
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<tr>
<td>Oxypaeoniflorin (v)</td>
<td><img src="image1" alt="Chemical structure" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
<td>NO production in lipopolysaccharide-activated-macrophages (Ding et al., 2012)</td>
<td>↓</td>
</tr>
<tr>
<td>Paeoniflorin (v, l)</td>
<td><img src="image2" alt="Chemical structure" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
<td>1.Chemokine mRNA expression in TNF-α-induced Human dermal microvascular endothelial cell -1 cells (Chen et al., 2011)</td>
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<td>2.TNF-α induced leukocyte migration (Chen et al., 2011)</td>
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<td>3.TNF-α-induced NF-κB activation (Chen et al., 2011, Nizamutdinova et al., 2007)</td>
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<td>4.TNF-α-induced phosphorylation of p38 and ERK (Nizamutdinova et al., 2007)</td>
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<tr>
<td>β-Sitosterol (v, l)</td>
<td><img src="image3" alt="Chemical structure" /></td>
<td>Phytosterol</td>
<td>Steroid</td>
<td>LPS-induced secretion of IL-6, as well as TNF-α (Ding et al., 2009)</td>
<td>↓</td>
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<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
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<tr>
<td>Casuariin (l)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>iNOS and cytokine RNA (Kolodziej et al., 2005)</td>
<td>↑</td>
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<tr>
<td>Gallic acid (v, l)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Polyphenol</td>
<td>Others</td>
<td>Superoxide anions (Kroes et al., 1992)</td>
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<td>Myeloperoxidase release and activity (Kroes et al., 1992)</td>
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<td>Neutrophil activation via cAMP-PDE (cyclic adenosine monophosphate – phosphodiesterase (Jiang et al., 2011)</td>
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<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
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<tr>
<td>1-O-galloyl-beta-D-glucose (I)</td>
<td><img src="image1.png" alt="Chemical structure" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Aldose reductase and lipopolysaccharide (LPS)-induced activation of JNK and p38 and lowered reactive oxygen species levels (Yamamoto and Gaynor, 2001)</td>
<td>↓</td>
</tr>
<tr>
<td>Casuarictin (I)</td>
<td><img src="image2.png" alt="Chemical structure" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Antigen-induced activation type I allergies (Yamada et al., 2012)</td>
<td>↓</td>
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<tr>
<td>Oxypaeoniflorin (I)</td>
<td><img src="image3.png" alt="Chemical structure" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
<td>NO production in LPS macrophages (Ding et al., 2012)</td>
<td>↓</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Chemical group</td>
<td>Extended group</td>
<td>Pathway activity</td>
<td>↑ or ↓ pathway</td>
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<tr>
<td>Paeonidanin E (l)</td>
<td><img src="image1.png" alt="Chemical structure" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
<td>NO production in LPS-activated N9 microglia (Duan et al., 2009)</td>
<td>↓</td>
</tr>
<tr>
<td>Paeonidanin A (l)</td>
<td><img src="image2.png" alt="Chemical structure" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
<td>NO production in LPS-activated N9 microglia (Duan et al., 2009)</td>
<td>↓</td>
</tr>
<tr>
<td>paeonidanin B (l)</td>
<td>N/A</td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
<td>NO production in LPS-activated N9 microglia (Duan et al., 2009)</td>
<td>↓</td>
</tr>
<tr>
<td>Paeonidanin C (l)</td>
<td><img src="image3.png" alt="Chemical structure" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
<td>NO production in LPS-activated N9 microglia (Duan et al., 2009)</td>
<td>↓</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Chemical group</td>
<td>Extended group</td>
<td>Pathway activity</td>
<td>↑ or ↓ pathway</td>
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<tr>
<td>Paeoniflorigenone (l)</td>
<td><img src="image1" alt="Chemical structure" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
<td>NO production from LPS-activated macrophages (Ding et al., 2012)</td>
<td>↓</td>
</tr>
<tr>
<td>Palbinone (l)</td>
<td><img src="image2" alt="Chemical structure" /></td>
<td>Triterpene</td>
<td>Diterpenoid</td>
<td>Interleukin-1β (Kadota et al., 1995)</td>
<td>↓</td>
</tr>
<tr>
<td>Pedunculagin (l)</td>
<td><img src="image3" alt="Chemical structure" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Human neutrophil elastase (HNE) (Cryan et al., 2013)</td>
<td>↓</td>
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<td></td>
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<td></td>
<td>Expression of IL-1b mRNA in Langerhans cells, and secretion of IL-1b (Lee et al., 2010)</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NO production (Marzouk et al., 2007)</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Proliferation of T-cells and macrophages (Marzouk et al., 2007)</td>
<td>↑</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Chemical group</td>
<td>Extended group</td>
<td>Pathway activity</td>
<td>↑ or ↓ pathway</td>
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<tr>
<td>1,2,3,4,6-Pentagalloylglucose (l)</td>
<td><img src="image1" alt="Chemical structure" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>IL-4 and antigen-specific IgE production (Kim et al., 2013c)</td>
<td>↓</td>
</tr>
<tr>
<td>Strictinin (l)</td>
<td><img src="image2" alt="Chemical structure" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>IgE class switch (IgE heavy chain germ transcript) of B-cells</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Tachibana et al., 2001)</td>
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<td></td>
<td>Tyrosine phosphorylation of STAT6 (IL-4 pathway) (Tachibana et al., 2001)</td>
<td>↓</td>
</tr>
<tr>
<td>1,2,3-Tri-O-galloyl-β-D-glucose (l)</td>
<td><img src="image3" alt="Chemical structure" /></td>
<td>Polyphenol</td>
<td>Tannin</td>
<td>Advanced glycation end-products, activation of nuclear factor-k B</td>
<td>↓</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>(Lee et al., 2011)</td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Chemical group</td>
<td>Extended group</td>
<td>Pathway activity</td>
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</tr>
<tr>
<td>1,2,6-Tri-O-galloyl-β-D-glucose (I)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Polyphenol</td>
<td>Tannin</td>
<td>Advanced glycation end-products and activation of nuclear factor-k B (Lee et al., 2011)</td>
<td>↓</td>
</tr>
</tbody>
</table>

V, *Paeonia veitchii*; l, *Paeonia lactiflora*; cAMP, Cyclic adenosine monophosphate; ERK, extracellular signal-regulated kinase; IFN-γ, interferon gamma; HNE, human neutrophil elastase; IgE, immunoglobulin E; IL, interleukin; iNOS, nitric oxide synthase; LPS, lipopolysaccharide; mRNA, messenger ribonucleic acid; JNK, c-Jun N-terminal protein kinase; NK-κB, nuclear factor kappaB; NO, nitric oxide; PDE, phosphodiesterase; STAT, signal transducer and activator of transcription; TH, T helper; T-Cells, thymus lymphocytes; TNF-α, tumour necrosis factor-alpha.
Cytotoxic and anti-tumour pathway activity

Numerous compounds have been evaluated as having potential anti-tumour pathway activity (Table 6.2).

Paeoniflorin

Paeoniflorin has demonstrated in vitro, that it possesses anti-proliferative action, inhibiting HT29 colorectal cancer cell growth by as much as 87.3% (Wang et al., 2012c). Such action is understood to be through induction of HT29 cell apoptosis. Paeoniflorin activates initiator caspases, which then further activate effector caspases (caspase-3 and caspase-9), which are important apoptosis moderators (Yamakawa et al., 2000). Further, paeoniflorin presence shows a decreased S phase cell population and at sufficient concentration can lead to cell arrest at the G1 phase. It is likely that increased expression of the pro-apoptotic gene p53 is activated by paeoniflorin and has downstream effects on proteins causing arrest of cell cycle during G1 phase (Wang et al., 2012c). Research on lung cancer A549 cells has shown cell arrest during the same G1 phase, although interestingly, p53 expression was not increased despite a downstream p53 target, p21/WAF1 protein, being enhanced. Also differing is the apoptotic pathway, which in A549 cells is likely triggered by the Fas/Fas Ligand (FasL) system and activation of caspase 8 (Nagata, 1997, Hung et al., 2008).

Pentagalloylglucose

The hydrolysable tannin (1,2,3,4,6-) pentagalloylglucose has been described as a potential chemopreventive. Due to overexpression, oncoproteins (e.g., fatty acid synthase, clusterin) are abundant in carcinoma and pentagalloylglucose can suppress such oncoproteins whilst up-regulating tumour suppressor proteins (e.g., glutathione S-transferase M) (Zhang et al., 2011b). Further, pentagalloylglucose acts to reduce
angiogenesis via inhibition of capillary morphogenesis gene 2a, which is typically up-regulated in endothelial cells undergoing angiogenesis (Cryan et al., 2013). It also reduces proliferation of human prostate cancer cells through inhibition of DNA synthesis in S-phase cells (Cryan et al., 2013).

**Daucosterol**

The phytosterol daucosterol is found in both species and acts on the extrinsic cellular apoptosis pathway. In human breast cancer (estrogen receptor-positive MCF-7) cells, daucosterol increases expression of cell surface death receptor Fas, which leads to activation of caspase-8 and eventual apoptosis. It possibly does so by changing the cell membrane sterol content, in turn affecting Fas expression (Awad et al., 2007).

**Gallic acid**

Gallic acid’s anti-tumour potential lies in its ability to inhibit transcription factor NFκB. Products of NFκB are important for regulating the expression of several genes and cell cycle regulatory components involved in tumour development (Morais et al., 2010). Carcinogens such as cigarette smoke are understood to trigger NFκB, while blocking it with a gallic acid may halt proliferation of tumour cells or sensitise them to anti-tumour agents leading to apoptosis (Yamamoto and Gaynor, 2001). Research into gallic acid as chemotherapy is extensive for a number of different cancer cell types including prostate, lung and colon. A review of potential mechanistic anticancer pathways for gallic acid has been previously conducted and identified: activation of ATM kinase; inhibition of ribonucleotide reductase; inhibition of cyclooxygenase-2 (COX-2); depletion of the antioxidant glutathione; inhibition of UDP-glucose dehydrogenase (UGDH); activation of Fas, FasL and p53 proteins; and a number of other pathways surrounding apoptosis induction.
Another key aspect of tumour growth is angiogenesis, and a number of anti-angiogenic gallic acid pathways have also been identified. Gallic acid’s potential to prevent tumour cell invasion via disturbance of signal transduction pathways indicates why there is so much interest in it as a potential chemotherapy (Verma et al., 2013).

Other

A number of other phytochemicals have been found in the botanicals in lower concentration and likely have weaker cytotoxic actions including hydrolysable tannin tellimagrandin II (eugenin), β-sitosterol, 1,2,3,6-Tetra-O-galloyl-β-D-glucose, 13-methyl tetradecanoic acid, peonin, phenol (carbolic acid) and pedunculagin. Their known activity is briefly described in table 6.2.
Table 6.2: Cytotoxic or anti-tumour pathway activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical structure (src. PubChem)</th>
<th>Chemical group</th>
<th>Extended group</th>
<th>Pathway activity</th>
<th>↑ or ↓ pathway</th>
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</thead>
<tbody>
<tr>
<td>Daucosterol (beta-Sitosterol glucoside) (v, l)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Phytosterols</td>
<td>Steroid</td>
<td>Fas protein and the activity of caspase-8, for apoptosis (Awad et al., 2007)</td>
<td>↑</td>
</tr>
<tr>
<td>Eugeniin (Tellimagrandin II) (v)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>IL-1 beta and tumour cell proliferation (Miyamoto et al., 1993)</td>
<td>↑IL-1beta ↓ tumour cell proliferation</td>
</tr>
<tr>
<td>Paeoniflorin (v)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Monoterpenoid</td>
<td></td>
<td>Active caspase-3 and caspase-9 (Wang et al., 2012c)</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p53 in HT29 cells (Wang et al., 2012a)</td>
<td>↑</td>
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<td></td>
<td>14-3-3ζ protein HT29 cells (Wang et al., 2012a)</td>
<td>↓</td>
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<td></td>
<td></td>
<td>mFasL and sFasL (Hung et al., 2008)</td>
<td>↑</td>
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<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Chemical group</td>
<td>Extended group</td>
<td>Pathway activity</td>
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<tr>
<td>β-Sitosterol (v, l)</td>
<td><img src="image1" alt="Chemical structure" /></td>
<td>Phytosterol</td>
<td>Steroid</td>
<td>Caspase activity resulting in apoptosis (Park et al., 2008)</td>
<td>↑</td>
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<td></td>
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<td></td>
<td>Anticarcinogenic agent changes cell membrane wall fluidity and cell transduction pathways (Awad and Fink, 2000)</td>
<td>↓</td>
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<td></td>
<td></td>
<td>DNA polymerase β lyase activity for repair of DNA (Chaturvedula et al., 2003)</td>
<td>↓</td>
</tr>
<tr>
<td>1,2,3,6-Tetra-O-galloyl-β-D-glucose (Tetragalloylglucos e) (v, l)</td>
<td><img src="image2" alt="Chemical structure" /></td>
<td>Polyphenol</td>
<td>Tannin</td>
<td>Matrix metalloproteinases (Saeki et al., 1999)</td>
<td>↓</td>
</tr>
<tr>
<td>Gallic acid (3,4,5-trihydroxybenzoic acid) (l)</td>
<td><img src="image3" alt="Chemical structure" /></td>
<td>Polyphenol</td>
<td>Others</td>
<td>TNF-α-induced NFκB activation (Morais et al., 2010)</td>
<td>↓</td>
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<td></td>
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<td></td>
<td>ATM kinase signalling (Chaturvedula et al., 2003)</td>
<td>↑</td>
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<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Chemical group</td>
<td>Extended group</td>
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<tr>
<td>13-Methyl tetradecanoic acid [Patent] (l)</td>
<td><img src="image1.png" alt="Image" /></td>
<td>Fatty acid</td>
<td>Fatty acid</td>
<td>Possibly topoisomerase I (Yang, 1999, Lee et al., 1998)</td>
<td>↓</td>
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<tr>
<td>Pedunculagin (l)</td>
<td><img src="image2.png" alt="Image" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Cytotoxic activity against cancer cells (Marzouk et al., 2007)</td>
<td>unsure</td>
</tr>
<tr>
<td>1,2,3,4,6-Pentagalloylglucose (l)</td>
<td><img src="image3.png" alt="Image" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Tumour suppressor proteins (e.g., glutathione S-transferase M (Zhang et al., 2011b))</td>
<td>↑</td>
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<td></td>
<td></td>
<td>Oncoproteins (e.g., fatty acid synthase, clusterin)(Zhang et al., 2011b)</td>
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<td>DNA synthesis in S-phase (Mizushima et al., 2010)</td>
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<td></td>
<td>CMG2 and angiogenesis (Cryan et al., 2013)</td>
<td>↓</td>
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<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Chemical group</td>
<td>Extended group</td>
<td>Pathway activity</td>
<td>↑ or ↓ pathway</td>
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<tr>
<td>Peonin (peonidin-3,5-diglucoside) (l)</td>
<td><img src="image1" alt="Chemical structure" /></td>
<td>Flavonoid</td>
<td>Flavonoid</td>
<td>Of DNA fragments (sub-G1 fraction) (Shin et al., 2009)</td>
<td>↑</td>
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<td></td>
<td>Anti-apoptotic proteins (Shin et al., 2009)</td>
<td>↓</td>
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<tr>
<td>Phenol (Carbolic acid) (l)</td>
<td><img src="image2" alt="Chemical structure" /></td>
<td>Phenol</td>
<td>Others</td>
<td>Coagulation necrosis (Quint et al., 1998, Quint et al., 1996)</td>
<td>↑</td>
</tr>
<tr>
<td>Tellimagrandin I (l)</td>
<td><img src="image3" alt="Chemical structure" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Arachidonate-12-lipoxygenase (Zheng et al., 2012)</td>
<td>↓</td>
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<td></td>
<td>Gap junctional communication (GJIC) and Cx43 gene expression at mRNA and protein levels (Yi et al., 2006)</td>
<td>↑</td>
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<td></td>
<td>Cells in G0/G1 and G2/M phases (Yi et al., 2006)</td>
<td>↓</td>
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<td></td>
<td></td>
<td></td>
<td>Erythroid and megakaryocytic differentiation (Yi et al., 2004)</td>
<td>↓</td>
</tr>
</tbody>
</table>
V, *Paeonia veitchii*; l, *Paeonia lactiflora*; cAMP, Cyclic adenosine monophosphate; ATM, ataxia-telangiectasia mutated; CMG2, capillary morphogenesis gene 2; DNA, deoxyribonucleic acid; ERK, extracellular signal-regulated kinase; FasL, fas ligand; G, gap; GJIC, Gap junctional communication; IFN-γ, interferon gamma; HNE, human neutrophil elastase; HT, Human colon adenocarcinoma cells; IgE, immunoglobulin E, IL, interleukin; iNOS, nitric oxide synthase; LPS, lipopolysaccharide; mRNA, messenger ribonucleic acid; JNK, c-Jun N-terminal protein kinase; NK-κB, nuclear factor kappaB; NO, nitric oxide; PDE, phosphodiesterase; S-phase, synthesis phase; STAT, signal transducer and activator of transcription; TH, T helper; T-Cells, thymus lymphocytes; TNF-α, tumour necrosis factor-alpha.
Anti-viral pathway activity

Three compounds (pentagalloylglucose, gallic acid and tellimagrandin II) have been evaluated as having potential anti-viral pathway activity (Table 6.3).

Pentagalloylglucose

Pentagalloylglucose inhibits NS3 protease, where it shows therapeutic potential against influenza-A virus by reducing plasma membrane accumulation of viral nucleoprotein at the replication stage. Further, by affecting the surface structure of infected cells, release of their virus particles (budding) is reduced (Liu et al., 2011). Strictinin also has potential against influenza-A virus, where it has antioxidant and anti-viral activities. Evidence indicates inoculation with strictinin can inhibit influenza-A virus replication resulting in a reduced number of infected cells. It may also inhibit influenza B virus (IBV) and human parainfluenza virus type-1 (hPIV-1) (Saha et al., 2010).

Gallic acid

Via disruption of viral glycoproteins and detachment of virus-infected cells, gallic acid suppresses expression of viral proteins (ICP27, gC, gD and VP5) in cells infected with the herpes simplex virus; however, it has shown no assistance in inoculation to prevent initial infection with the virus. Similarly, gallic acid has shown to reduce the degree of viral replication of HIV (Kratz et al., 2008).

Tellimagrandin II

Found in P. veitchii, tellimagrandin II (eugeniin) inhibits herpes simplex; however, it also has preference for inhibition of herpes simplex virus-1 DNA polymerase activity over unaffected DNA polymerase activity, leading to an overall reduction in viral DNA synthesis (Kurokawa et al., 1998, Kurokawa et al., 2001). Further evidence suggests tellimagrandin I may also have anti-viral activity towards viruses such as hepatitis C.
where tellimagrandin I prevents invasion of hepatitis C into hepatocytes (Tamura et al., 2010).

Another constituent with potential action on hepatitis C is 1,2,3,6-Tetra-O-galloyl-β-D-glucose. Found in both *Paeonia* species, it targets a common hepatitis C drug pathway inhibiting activity of NS3 protease of the virus’s RNA (Duan et al., 2004).
### Table 6.3: Anti-viral pathway activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical structure (src. PubChem)</th>
<th>Chemical group</th>
<th>Extended group</th>
<th>Pathway activity</th>
<th>→ or ↓ pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eugeniin (Tellimagrandin II) (v)</td>
<td><img src="image.png" alt="Image" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Herpes simplex virus-1 DNA polymerase (Yamakawa et al., 2000, Kurokawa et al., 2001)</td>
<td>↓</td>
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<td></td>
<td>Hepatitis C virus invasion (Tamura et al., 2010)</td>
<td>↓</td>
</tr>
<tr>
<td>1,2,3,6-Tetra-O-galloyl-β-D-glucose (v,l)</td>
<td><img src="image.png" alt="Image" /></td>
<td>Polyphenol</td>
<td>Tannin</td>
<td>Hepatitis C NS3 protease (Duan et al., 2004)</td>
<td>↓</td>
</tr>
<tr>
<td>Gallic acid (l)</td>
<td><img src="image.png" alt="Image" /></td>
<td>Polyphenol</td>
<td>Others</td>
<td>Viral proteins ICP27, gC, gD and VP5 (Kratz et al., 2008)</td>
<td>↓</td>
</tr>
<tr>
<td>Molecule</td>
<td>Type</td>
<td>Type</td>
<td>Effect</td>
<td>Reference</td>
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<tr>
<td>1,2,3,4,6-Pentagalloylglucose (I)</td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Plasma membrane accumulation of NP</td>
<td>Liu et al., 2011</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hepatitis C NS3 protease</td>
<td>Duan et al., 2004</td>
<td></td>
</tr>
<tr>
<td>Strictinin (I)</td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Viral replication</td>
<td>Saha et al., 2010</td>
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<td></td>
<td></td>
<td></td>
<td>HIV reverse transcriptase</td>
<td>Yoshida et al., 1996</td>
<td></td>
</tr>
<tr>
<td>Tellimagrandin I (I)</td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Virus envelope proteins E1 and E2</td>
<td>Tamura et al., 2010</td>
<td></td>
</tr>
</tbody>
</table>

V, *Paeonia veitchii*; l, *Paeonia lactiflora*; DNA, deoxyribonucleic acid; ERK, extracellular signal-regulated kinase; G, gap; HIV, human immunodeficiency virus; HmRNA, messenger ribonucleic acid; NP, nucleoprotein; NS, non-structural protein; S-phase, synthesis phase
Antibacterial and anti-fungal activities

Four *P. lactiflora* compounds (carbolic acid, pyrethrin I, tellimagrandin I and 1,2,3,4,6-pentagalloylglucose) have been evaluated as having potential antibacterial or anti-fungal pathway activity (Table 6.4).

**Pentagalloylglucose**

The most abundant compound with antibacterial activity, pentagalloylglucose, inhibits FabG reductase, which is important for fatty acid biosynthesis and necessary for bacterial growth (Zhang et al., 2008a).

**Carbolic acid**

Carbolic acid (phenol) is used in antiseptics and disinfectants against gram-positive and negative bacteria, acting by denaturing proteins and destroying cell permeability (Martindale, 1996, Hugo, 1978).

**Pyrethrin I**

Pyrethrin I has been shown to inhibit the multiple drug-resistant mycobacterium tuberculosis, as well as protozoal parasites leading to diseases such as African trypanosomiasis, Chagas disease, malaria and leishmaniasis, although the mechanism of these pathways is still not fully understood (Rugutt et al., 1999, Hata et al., 2011).

**Tellimagrandin I**

Tellimagrandin I can reduce drug resistance to antibiotic use and enhance antibacterial action. It has been evidenced to decrease production of penicillin-binding protein 2 (PBP2), which results in a reduction in the resistance level of β-lactams in methicillin-resistant *Staphylococcus aureus* (Shiota et al., 2004). Further evidence suggests
antibacterial activity against *H. pylori*, possibly via its membrane-damaging activity (Funatogawa et al., 2004).

**Benzoic acid**

Found in both *P. lactiflora* and *P. veitchii*, benzoic acid shows anti-fungal activity, hence its common use in juices, food product preservatives and pharmaceuticals. In an acid environment benzoic acid permeates the fungal cell wall until equilibrium inside and outside of the cell is reached, leading to internal cell acidification, which inhibits glycolysis and depletes adenosine triphosphate in the cell, which is necessary for growth (Krebs et al., 1983).
<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical structure (src. PubChem)</th>
<th>Chemical group</th>
<th>Extended group</th>
<th>Pathway activity</th>
<th>↑ or ↓ pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenol (Carbolic acid) (l)</td>
<td><img src="image" alt="Phenol" /></td>
<td>Phenol</td>
<td></td>
<td>Denaturing proteins and destroying cell permeability (Quint et al., 1998, Martingdale, 1996)</td>
<td>↑</td>
</tr>
<tr>
<td>Pyrethrin I (l)</td>
<td><img src="image" alt="Pyrethrin" /></td>
<td>Pyrethrin</td>
<td>Monoterpenoid</td>
<td>Anti-trypanosomal action unknown (Hata et al., 2011, Rugutt et al., 1999)</td>
<td>N/A</td>
</tr>
<tr>
<td>Tellimagrandin I (l)</td>
<td><img src="image" alt="Tellimagrandin" /></td>
<td>Hydrolysable tannin (polyphenol)</td>
<td>Tannin</td>
<td>Penicillin binding protein 2 (2a) (Shiota et al., 2004) Membrane-damaging activity (Funatogawa et al., 2004)</td>
<td>↓, ↑</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Chemical group</td>
<td>Extended group</td>
<td>Pathway activity</td>
<td>↑ or ↓ pathway</td>
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</tr>
<tr>
<td>1,2,3,4,6-Pentagalloylglucose (I)</td>
<td><img src="image1.png" alt="Chemical structure" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>FabG (beta-oxoacyl-ACP reductase) of the fatty-acid-elongation cycle (Zhang et al., 2008b)</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td><img src="image2.png" alt="Chemical structure" /></td>
<td>Carboxylic acid</td>
<td>Others</td>
<td>Glycolysis and ATP production (Krebs et al., 1983)</td>
<td>↓</td>
</tr>
</tbody>
</table>

**Antioxidant or pro-oxidant activities**

Ten compounds, mostly from *P. lactiflora*, have been evaluated as having potential antioxidant or pro-oxidant pathway activity (Table 6.5).

**Albiflorin**

Found more predominantly in the *P. lactiflora* species, the monoterpenoid glycoside albiflorin, has strong antioxidant activity. Albiflorin inhibits abnormal production of mitochondrial superoxide, in turn protecting mitochondria from pro-oxidant reaction activity (Suh et al., 2013).

**Benzoic acid**

A constituent of *P. veitchii*, benzoic acid reduces oxygen radicals, in particular scavenging hydroxyl group radicals, which otherwise enhance arachidonic acid pathway activity, a key pathway implicated in a number of diseases such as psoriasis (Haseloff et al., 1990).

**Gallic acid**

Gallic acid and 2,3-O-(S)-Hexahydroxydiphenoyl-D-glucopyranose are both polyphenol compounds in *P. lactiflora*. Gallic acid has antioxidative activity, which on weight basis is rated as having higher antioxidant potential than vitamin C (Kroes et al., 1992, Kim et al., 2002). Similarly, 2,3-O-(S)-Hexahydroxydiphenoyl-D-glucopyranose shows superoxide-dismutase-like activity and stronger scavenging than gallic acid of 1,1-diphenyl-2-picrylhydrazyl (DPPH) (Haseloff et al., 1990).

**Paeonilactone C**

The monoterpenoid paeonilactone C, found in *P. lactiflora*, also shows antioxidant activity, reducing the highly toxic ROS. Without reduction, these ROS will oxidatively modify
nucleic acid, lipids, sugars and proteins, subsequently forming the cellular toxin H$_2$O$_2$. The resultant cellular inflammation from this toxin can potentiate many diseases such as those of the glial cells in the brain. It is suggested compounds with antioxidant activity such as paeonilactone C may be suitable as a preventive for such disease (Kim et al., 2009b).

**Other**

Other contained antioxidant or pro-oxidant phytochemicals with likely weaker actions include palbinone, pedunculagin, casuarictin and tellimagrandin I. Their potential pathway activity is presented in table 6.5.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical structure (src. PubChem)</th>
<th>Chemical group</th>
<th>Extended group</th>
<th>Pathway activity</th>
<th>↑ or ↓ pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiflorin (v, l)</td>
<td><img src="image1" alt="Albiflorin Chemical Structure" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
<td>Mitochondrial superoxide production (Suh et al., 2013)</td>
<td>↓</td>
</tr>
<tr>
<td>Benzoic acid (v)</td>
<td><img src="image2" alt="Benzoic acid Chemical Structure" /></td>
<td>Carboxylic acid</td>
<td>Others</td>
<td>Hydroxyl radical scavenging (Haseloff et al., 1990)</td>
<td>↑</td>
</tr>
<tr>
<td>2,3-O-(S)-Hexahydroxydiphenoyl-D-glucopyranose (l)</td>
<td><img src="image3" alt="2,3-O-(S)-Hexahydroxydiphenoyl-D-glucopyranose Chemical Structure" /></td>
<td>N/A</td>
<td>Polyphenol</td>
<td>Superoxide anion radical (Fukuda et al., 2003)</td>
<td>↓</td>
</tr>
<tr>
<td>Gallic acid (l)</td>
<td><img src="image4" alt="Gallic acid Chemical Structure" /></td>
<td>Polyphenol</td>
<td>Others</td>
<td>Oxidation (Kim et al., 2002)</td>
<td>↓</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Chemical group</td>
<td>Extended group</td>
<td>Pathway activity</td>
<td>↑ or ↓ pathway</td>
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</tr>
<tr>
<td>Paeonilactone C (l)</td>
<td><img src="image1.png" alt="Image" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
<td>Reactive oxygen species (Kim et al., 2009b)</td>
<td>↓</td>
</tr>
<tr>
<td>Palbinone (l)</td>
<td><img src="image2.png" alt="Image" /></td>
<td>Triterpene</td>
<td>Diterpenoid</td>
<td>Heme oxygenase-1 (Ha et al., 2013)</td>
<td>↑</td>
</tr>
<tr>
<td>Pedunculagin (l)</td>
<td><img src="image3.png" alt="Image" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Radical DPPH and physiological radicals including ROO*, OH*, and O2-*(Marzouk et al., 2007)</td>
<td>↓</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Chemical group</td>
<td>Extended group</td>
<td>Pathway activity</td>
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<tr>
<td>Strictinin (l)</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Linoleic acid peroxidation In micelles, peroxidation of LDL and oxidative haemolysis of red blood cells (Zhou et al., 2004)</td>
<td>↓</td>
</tr>
<tr>
<td>Tellimagrandin I (l)</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Mediated oxidated DNA strand break (Yi et al., 2009)</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mediated plasmid oxidated DNA strand break (Yi et al., 2009)</td>
<td>↓ at low concentration ↑ at high concentrations</td>
</tr>
</tbody>
</table>

V, *Paeonia veitchii*; l, *Paeonia lactiflora*; DNA, deoxyribonucleic acid; DPPH, 2,2-diphenyl-1-picrylhydrazyl; LDL, low-density lipoproteins; O2-, superoxide anion radical; OH, hydroxyl radical; ROO, peroxyl radical.
**Glycemic activity**

Several components of the two *Paeonia* species affect blood glucose (Table 6.6). Through increased expression of nephrin protein in the kidneys of diabetic rats and inhibition of diabetic nephropathy progression, TGP may have potential use in preventing diabetes-associated renal damage (Wu et al., 2009b, Wang et al., 2012d, Zhang et al., 2009b, Zhang et al., 2014e, Su et al., 2010a).

Tellimagrandin II, 8-debenzoylpaoniflorin, gallic acid and palbinone all have anti-glycaemic activity; 8-debenzoylpaoniflorin lowers blood glucose, most likely via an insulin-dependent pathway (Hsu et al., 1997).

Gallic acid may prove to be an important future therapy as it decreases blood glucose and increases insulin in plasma in rats (Punithavathi et al., 2011). This is possibly due to the reduction in oxidation products, an increase in enzymatic antioxidant activity and the stimulation of pancreatic insulin secretion. These actions correlate clinically with a reduction in glycosylated haemoglobin, which when increased is commonly associated with diabetes mellitus (Punithavathi et al., 2011).

Palbinone likely has antiglycemic activity through regulation of gluconeogenesis, the process producing glucose from non-carbohydrate sources in the liver. This gluconeogenesis regulates the plasma glucose levels and is controlled by the activation of AMP-activated protein kinase and stimulation of fatty acid oxidation, and thus increases glucose uptake and glycogen synthesis (Ha do et al., 2009).

Tellimagrandin II inhibits α-glucosidases, in turn reducing the absorption and metabolism of carbohydrates and subsequently preventing rise in blood glucose (Toda et al., 2000).
### Table 6.6: Glycaemic effects

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical structure (src. PubChem)</th>
<th>Action</th>
<th>Chemical group</th>
<th>Extended group</th>
<th>Pathway activity</th>
<th>↑ or ↓ pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-debenzoylpaoniflorin (v, l)</td>
<td><img src="image1" alt="Chemical structure" /></td>
<td>Antiglycemic</td>
<td>Monoterpenoid glucoside</td>
<td>Monoterpenoid</td>
<td>Blood glucose (Hsu et al., 1997)</td>
<td>↓</td>
</tr>
<tr>
<td>Eugeniin (Tellimagrandin II) (v)</td>
<td><img src="image2" alt="Chemical structure" /></td>
<td>Antiglycemic</td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>1. Type III collagen (Tsukiyama et al., 2010)</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Intestinal α-glucosidases (maltase) (Toda et al., 2000)</td>
<td>↓</td>
</tr>
<tr>
<td>Gallic acid (l)</td>
<td><img src="image3" alt="Chemical structure" /></td>
<td>Antiglycemic</td>
<td>Polyphenol</td>
<td>Others</td>
<td>Blood glucose/insulin (Punithavathi et al., 2011)</td>
<td>↓/↑</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Action</td>
<td>Chemical group</td>
<td>Extended group</td>
<td>Pathway activity</td>
<td>↑ or ↓ pathway</td>
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</tr>
<tr>
<td>Palbinone (l)</td>
<td><img src="image" alt="chemical structure" /></td>
<td>Antiglycemic</td>
<td>Triterpene</td>
<td>Diterpenoid</td>
<td>AMPK, GSK-3b, and ACC phosphorylation (Mizushina et al., 2010)</td>
<td>↑</td>
</tr>
<tr>
<td>Paeonia veitchii; l, Paeonia lactiflora; ACC, acetyl-CoA carboxylase; AMPK, 5' adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; CCl 4-, carbon tetrachloride; d-GalN, d-galactosamine; GSK-3b, glycogen synthase kinase 3 beta.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tellimagrandin I (l)</td>
<td><img src="image" alt="chemical structure" /></td>
<td>Hepatoprotective</td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>CCl 4- and d-GalN-induced cell damage (Shimoda et al., 2008)</td>
<td>↓</td>
</tr>
</tbody>
</table>

V, Paeonia veitchii; l, Paeonia lactiflora; ACC, acetyl-CoA carboxylase; AMPK, 5' adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; CCl 4-, carbon tetrachloride; d-GalN, d-galactosamine; GSK-3b, glycogen synthase kinase 3 beta.
**Other phytochemical biological activities**

A number of constituents have activities not within the previous classifications yet still warrant further explanation (Table 6.7). For instance by increasing alkaline phosphatase activity of MC3T3-E1 cell (an osteoblast-like cell) at concentration, albiflorin shows evidence of cytoprotection. The alkaline phosphatase increase is understood to be essential to stimulation of mineralisation and subsequent bone hardening, which may prove beneficial in conditions such as osteoporosis (Yen et al., 2007). Furthermore, albiflorin reduces ROS toxicity in cells and apoptosis, reducing subsequent lactate dehydrogenase leaking and thus increasing the viability of the cells. Overall, albiflorin tends to be able to protect cell mitochondria from oxidative stress and generally improves their function (Suh et al., 2013).

Total glucosides of peony also have protective effects on cells, where in systemic lupus erythematosus they can limit liver damage from drugs such as methotrexate, and reduce the usage of prednisone (Zhang et al., 2011a, Chen et al., 2013).

The chemical structure of daucosterol resembles that of cholesterol, differing only by an extra ethyl group. It’s activity then follows the reduction in the dietary and biliary cholesterol uptake by intestinal cells, subsequently lowering serum total and low-density lipoprotein cholesterol levels (Salen et al., 1970, Jones and AbuMweis, 2009).

Found in both species of *Paeonia*, paeoniflorigenone has potential neuromuscular activity. Paeoniflorigenone has shown *in vivo* evidence it can inhibit acetylcholine chloride contraction of muscle, block muscle twitch response and depolarise the resting membrane potential (Kimura et al., 1984). Paeoniflorigenone, along with three other hydrolysable tannin compounds found in *P. lactiflora* (5-desgalloylstachyurin, casuariin and pedunculagin) also show anticoagulant activity. Paeoniflorigenone is twice as strong as well-known platelet inhibitor acetyl salicylic acid in reducing blood
coagulation (Koo et al., 2010). 5-Desgalloylstachyurin, casuariin and pedunculagin also have in vivo evidence of prolonging blood clotting time, likely inhibiting thrombin from catalysing fibrinogen into clots of fibrin. Likely contributing to this anti-coagulant effect is the ability of the compounds to inhibit factor Xa, important for thrombin activation and a common target of anti-coagulant drugs such as warfarin and heparin (Dong et al., 1998).

Already utilised in the drug bismuth subgallate, gallic acid is commonly utilised for its astringent and haemostatic properties. Commonly utilised in a paste from for surgical operations or conditions such as haemorrhoids, gallic acid activates factor XII and thus accelerates coagulation (Council of Europe, 2005) (Hatton, 2000, Thorisdottir et al., 1988).

Phenol (carbolic acid), has antibacterial activity and is commonly utilised as an antiseptic by pharmaceuticals, however at increased concentration it is understood to take on an analgesic action where it is sometimes administered for conditions such as a sore throat (Martingdale, 1996).

There is research suggesting tellimagrandin II may increase type III collagen production to reduce the effects of skin aging (Tsukiyama et al., 2010). Further, it may be hepato-protective, protecting hepatocytes from carbon tetrachloride (CCl4) damage. Tellimagrandin I has shown a similar effect, although with weaker action (Shimoda et al., 2008).

Pyrethrins have insecticidal qualities, which have been utilised for treatment of skin conditions from parasitic infections such as scabies (Martingdale, 1996). Pyrethrin I and II, both found in P. lactiflora, are believed to have neurotoxic activity, damaging neuron membranes and prolonging sodium channel gate activation (Brown et al., 1995, Kueh et al., 1985, Katsuda, 1999).
**Unknown activity**

A number of constituents are yet to be found in experiment to have any biological activity (Table 6.8).
### Table 6.7: Other constituent pathway activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical structure (src. PubChem)</th>
<th>Action</th>
<th>Chemical group</th>
<th>Extended group</th>
<th>Pathway activity</th>
<th>↑ or ↓ pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiflorin (v, l)</td>
<td></td>
<td>Cytoprotection</td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
<td>ALP activity and calcium deposition in osteoblastic MC3T3-E1 cells (Zhang et al., 2008b)</td>
<td>↑</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oxidative stress and ATP production in mitochondria (Suh et al., 2013)</td>
<td></td>
</tr>
<tr>
<td>Daucosterol (beta-Sitosterol glucoside) (v, l)</td>
<td></td>
<td>Anti-cholesterol</td>
<td>Phytosterols</td>
<td>Steroid</td>
<td>Serum total and LDL-cholesterol (Jones and AbuMweis, 2009)</td>
<td>↓</td>
</tr>
<tr>
<td>Paeoniflorigenone (v, l)</td>
<td></td>
<td>1. Anti-coagulant</td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
<td>Platelet aggregation and blood coagulation (Koo et al, 2010)</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Neuromuscular blocking</td>
<td></td>
<td></td>
<td>Acetylcholine induced contraction and muscle twitch response (Kimura et al., 1984)</td>
<td>↓</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Action</td>
<td>Chemical group</td>
<td>Extended group</td>
<td>Pathway activity</td>
<td>↑ or ↓ pathway</td>
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</tr>
<tr>
<td>5-Desgalloylstachyurin (I)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Anticoagulant</td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Thrombin and Factor Xa (Dong et al., 1998)</td>
<td>↓</td>
</tr>
<tr>
<td>Casuariin (I)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Anticoagulant</td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Thrombin and Factor Xa (Dong et al., 1998)</td>
<td>↓</td>
</tr>
<tr>
<td>Pedunculagin (I)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Anticoagulant</td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Thrombin, fibrinogen and Factor Xa (Dong et al., 1998)</td>
<td>↓</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Action</td>
<td>Chemical group</td>
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<td>Pathway activity</td>
<td>↑ or ↓ pathway</td>
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</tr>
<tr>
<td>Phenol (Carbolic acid) (l)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Anaesthetic (Chloraseptic® and Carmex®)</td>
<td>Phenol</td>
<td>Others</td>
<td>Paralysis of the free nerve endings (Martindale, 1996)</td>
<td>N/A</td>
</tr>
<tr>
<td>Pyrethrin I (l)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Insecticide</td>
<td>Pyrethrin</td>
<td>Monoterpenoid</td>
<td>Voltage-gated sodium channels (Wolansky and Tornero-Velez, 2013, Brown et al., 1995)</td>
<td>↓</td>
</tr>
<tr>
<td>Pyrethrin II (l)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Insecticide</td>
<td>Pyrethrin</td>
<td>Monoterpenoid</td>
<td>Voltage-gated sodium channels (Wolansky and Tornero-Velez, 2013, Brown et al., 1995)</td>
<td>↓</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Action</td>
<td>Chemical group</td>
<td>Extended group</td>
<td>Pathway activity</td>
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</tr>
<tr>
<td>Tellimagrandin I (l)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Hepatoprotective</td>
<td>Hydrolysable tannin</td>
<td>Tannin</td>
<td>Carbon tetrachloride (CCl₄-) and d-galactosamine (d-GalN)-induced cell damage (Shimoda et al., 2008)</td>
<td>↓</td>
</tr>
</tbody>
</table>

V, *Paeonia veitchii*; l, *Paeonia lactiflora*; ALP, alkaline phosphatase; ATP, adenosine triphosphate; CCl₄, carbon tetrachloride; d-GalN, d-galactosamine; LDL, Low-density lipoprotein
Table 6.8: Unknown pathway activity constituents

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical structure (src. PubChem)</th>
<th>Chemical group</th>
<th>Extended group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactiflorin (v)</td>
<td><img src="image" alt="Lactiflorin" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
</tr>
<tr>
<td>(Z)-(1S,5R)-β-Pinen-10-yl-β-vicianoside (v)</td>
<td><img src="image" alt="Vicianoside" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
</tr>
<tr>
<td>Albiflorin R1(l)</td>
<td>N/A</td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
</tr>
<tr>
<td>Benzoylpaeoniflorin (l)</td>
<td><img src="image" alt="Benzoylpaeoniflorin" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Chemical group</td>
<td>Extended group</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------------------</td>
<td>----------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>3-O-Galloylquinic acid (l)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Polyphenol</td>
<td>Tannin</td>
</tr>
<tr>
<td>4-O-Galloylquinic acid (l)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Polyphenol</td>
<td>Tannin</td>
</tr>
<tr>
<td>Paeonilactone A (l)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
</tr>
<tr>
<td>Compound</td>
<td>Chemical structure (src. PubChem)</td>
<td>Chemical group</td>
<td>Extended group</td>
</tr>
<tr>
<td>----------------------------------</td>
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<td>----------------</td>
</tr>
<tr>
<td>Paeonilactone B (I)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
</tr>
<tr>
<td>Paeonidanin D (I)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Monoterpene glycoside</td>
<td>Monoterpenoid</td>
</tr>
<tr>
<td>1,3,6-Trigalloyl-β-D-glucose (I)</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Polyphenol</td>
<td>Tannin</td>
</tr>
</tbody>
</table>

V, *Paeonia veitchii*; I, *Paeonia lactiflora*; N/A, not available
6.3.3 Toxicity

Despite the possible efficacy of herb botanicals, the identified active pathways may also provide potential risks of therapy. There are reports of toxicity associated with oral herb intake, and any research involving repeated doses are recommended to consider appropriate and timely testing of liver and kidney function among others if there is known or suspected toxicity (Perharic et al., 1993, Graham-Brown, 1992).

There is little published toxicity evidence for either of the *Paeonia* botanicals, with major pharmacopoeia identifying only a precaution not to administer either botanical with veratrum root or rhizome (rhizome et Radix veratri bot. *Veratrum nigrum* L.; *lilu*). This incompatibility has been likely known for thousands of years, where *Veratrum nigrum* is documented in major pharmacopoeia as toxic and requires caution for its prescription. Research confirms this classical view, with trembling, convulsions and spasms developing in mice following intragastric administration of the combined solution resulting in death in 5–10 minutes (Zhang et al., 2014f). In this experiment, the mortality of female mice decreased as the concentration of *P. lactiflora* increased; however, the pattern was less obvious in male mice. Interestingly, *P. lactiflora* had a neuroprotective effect against the toxicity of *Veratrum nigrum* (Zhang et al., 2014f). This antitoxic activity has been supported in other research where *P. lactiflora* has shown to be hepato-protective, assisting the liver to excrete toxins (Du, 1989, Sun et al., 2008).

The US National Institute of Health lists peony as well tolerated with occasional gastrointestinal upset and allergic skin reactions reported, the latter more common when applied topically. As such, dietary supplements do not require extensive pre-marketing approval from the US Food and Drug Administration (United States National Institute of Health (NIH), 2013). Despite little evidence suggesting the entire botanicals
to be of any significant toxicity, there is evidence that the constituents individually have some potential toxicity. For example, phenol and pyrethrin I dose toxicity in rats has shown development of tremors, spasms and eventual death from respiratory failure, likely due to nervous tissue voltage-dependent sodium channels having a prolonged open state (Industrial Bio-test Laboratories Inc, 1973, Verschoyle and Barnes, 1972, Wolansky et al., 2006). In contrast, potential anti-fungal benzoic acid has been recognised as safe by the US Food and Drug Administration for use in foods (Nair, 2001).

6.4 Discussion

Although there are constituents in common between *P. lactiflora* and *P. veitchii*, there are also many that are only found in one of the species. Improved scientific analysis techniques such as HPLC will continue to fine-tune the identification and concentrations of contained phytochemicals, and may also identify new compounds. The phytochemical variation between the two species indicates their biological activity likely differs when administered in their entire form.

For rigorous scientific studies, correct identification of botanicals is vital to ensure processed extracts contain the correct phytochemicals for the disease being targeted. For psoriasis, most disease activity is associated with inflammation and proliferation of cells, so botanical constituents with potential activity on these pathways warrant further investigation. Both *P. lactiflora* and *P. veitchii* constituents contain activity relevant to psoriasis. For instance, monoterpenoids, albiflorin and paeoniflorin found in both botanicals have anti-inflammatory activity evidenced in psoriasis. Albiflorin has the ability to reduce activation of neutrophils, while paeoniflorin acts by reducing chemokine expression in endothelial cells, as well as down-regulating numerous TNF-α inflammatory induction activities.
Studies on constituent activity, however, are not necessarily undertaken in psoriasis models, and as such much of the activity can only be theorised to have effect on psoriasis. Thus, *in vitro* and *in vivo* study of constituent activity is needed in psoriasis-specific models to investigate how the actual constituent activity impacts psoriatic disease.

It appears the function of constituents in *P. lactiflora* and *P. veitchii* match their indication by Chinese medicine for psoriasis therapy. For instance, historic usage of *Paeonia* for kidney and liver disorders matches scientific evidence for TGP activity in these organs (Pickering, 1989, Wu et al., 2009b, Li et al., 2011). Further investigation of constituents from each botanical in PSORI-CM01 may provide further indication of correlation between scientific biological disease activities and indicated Chinese medicine therapeutic use.

*Bai shao* and *chi shao* products found in the marketplace are manufactured and processed from a variety of botanicals and geographic areas. It is therefore difficult for consumers to distinguish which botanical variety they are being sold. Usage of incorrect product, may not only impact on therapeutic outcomes for consumers, but may also increase risk of adverse events caused by a constituent activity not indicted for their disease.

Toxicity of both species in entire form appears to be low; however toxicity of individual constituents varies considerably. More research is needed to evaluate the toxicity of constituents prior to utilising a compound as an individual therapeutic. Further, pharmacogenics research is also needed to understand interactions and any potential synergism or antagonism between constituents, which may impact therapeutic and/or toxic outcomes.
6.5 Conclusion

It is evident that while some constituents are common between *P. veitchii* and *P. lactiflora* many also unique to each. Such difference needs to be considered when administering either botanical in their whole form, to ensure the intended therapeutic effect matches the intended biological activity. Phytochemical variation between the species may support traditional medicine theory and recommendations of each botanical for different diseases. Anti-inflammatory, anti-tumour and antioxidant agents make up the majority of phytochemical actions in both species.

Scientific research evidence indicates that activity of *Paeonia* phytochemicals match traditional Chinese medicine usage of the botanicals. For instance, historic usage of the *Paeonia* species for kidney and liver disorders matches evidence for TGP in diseases of these organs (Pickering, 1989, Wu et al., 2009b, Li et al., 2012b). However, some traditional medicine uses for each species are as yet unable to be explained molecularly, such as their historic analgesic use. Such function may be explained by the large number of phytochemicals with anti-inflammatory activity present in both species, however more research is needed.

Based on the biological activity of each botanical and historical Chinese medicine usage of both peony species, *chi shao* produced from *P. veitchii* appears to be the most appropriate form for the proposed clinical trial formulation. While *P. lactiflora* contains more known constituents, many of these do not appear to be relevant to psoriasis disease activity. Paeoniflorin was determined to be the biological marker of choice given its relatively high available concentration in *P. veitchii* and the multiple activity pathways it has on TNF-α. As discussed, anti TNF-α is one of the key targets for many psoriatic pharmaceuticals.
Chapter 7 – Development of a pilot randomised, placebo-controlled parallel design study: Oral Chinese herbal medicine plus topical standard conventional care (Calcipotriol cream) vs. oral placebo plus standard conventional care (Calcipotriol cream) for mild–moderate adult psoriasis vulgaris

This chapter details development of a protocol for a pilot RCT to investigate oral CHM PSORI-CM01 combined with conventional medicine. It explains how the pilot’s design was determined and details its aims and methodology. Full details are presented on participant recruitment, screening, randomisation and blinding. Intervention/placebo administration and dosage are detailed along with the assessment time points and investigated outcome measures. Potential psoriasis related blood markers, regulatory aspects of the pilot and the safety measures in place for participants are described. Lastly handling procedures for participant data and its proposed statistical analysis methods are described.

7.1 Background

Following literature review of psoriasis phenotypes, their prevalence, aetiology, pathogenesis, severity measures and treatments, results were used to establish the basis for design of further clinical study of CHM. Further discussion and literature review was needed to determine the most suitable methodology for the study. The two main approaches to clinical studies are either a pragmatic design in which methodological aspects of the protocol are flexible, or an explanatory style in which these aspects are more fixed. Both designs were explored to evaluate their pros and cons, and aspects from each were utilised to develop a clinical trial protocol that would sufficiently investigate the efficacy of PSORI-CM01 for vulgaris type psoriasis.
7.2 Methods of clinical trial design

The design of a study is important as it can assist or hinder analysis of its data, as well as influence potential bias of any results and impact on significance any outcomes may have for researchers, physicians, policymakers and sufferers. Pragmatic design studies tend to more accurately reflect real life scenarios of a condition; however, as data are often quite varied and difficult to classify analysis becomes complicated. Explanatory design studies provide much clearer data that can be more simply grouped, as they provide data that are repeated or similarly grouped, which can then be compared with some level of statistical confidence. Unfortunately, the specificity of explanatory data generally means results are only transposable to populations with the same characteristics as those targeted in the study. Both approaches have their benefits and drawbacks, and ideally study designers should consider aspects from both approaches to ensure subsequent development of a study protocol is rigorous, has low risk of bias and is likely to provide clinically relevant data.

7.2.1 Explanatory study design

Very few trials investigating interventions are purely pragmatic or explanatory in design with some aspects of an explanatory study often beyond the investigators’ control (Thorpe et al., 2009). Commonly considered the gold standard for assessing the efficacy of an intervention, the RCT is predominantly explanatory in style. There is, however, criticism that RCT results do not provide sufficient clinically relevant data. A key contributing aspect of the explanatory nature of RCTs is the screening of participants, where inclusion and exclusion criteria are used to determine the characteristics of the sample. For example, a study might exclude people with a worse prognosis, or include participants with a better prognosis, subsequently limiting the
generalizability of the RCT results and reducing their potential clinical value (McKee et al., 1999). Randomised controlled trials may have great internal validity for the studied population, but external validity of differing race, age, co-morbidities etc. is often reduced (Kovesdy and Kalantar-Zadeh, 2012). Due to these limitations, researchers and health policymakers have shifted towards pragmatic style studies (Zwarenstein and Treweek, 2009, Foster and Little, 2012, Kovesdy and Kalantar-Zadeh, 2012).

### 7.2.2 Pragmatic study design

Pragmatic trials provide a greater level of external validity to the general population, and as a result clinical applicability usually reflects more closely the clinical reality of the disease population (Black, 1999). A pragmatic design provides greater measurement and analysis of the synergistic effects a population may experience if exposed to the intervention. While pure pragmatic study would identify and collecting sample characteristics such as severity and concomitant drug use, it would not exclude people due to such characteristics. A treatment protocol may be provided to guide pragmatic style studies; however, a true pragmatic study would allow other treatments to be added at the researchers’ or indeed the participants’ discretion. Frustrated medical specialists are now campaigning for researchers to follow pragmatic methods to investigate interventions (Kovesdy and Kalantar-Zadeh, 2012).

### 7.2.3 Explanatory vs. pragmatic for development of CHM studies

Chinese herbal medicine physicians treating in clinical scenarios are able to individually adjust patient treatment strategies based on syndrome differentiation. Typically, the more rigid explanatory design of RCTs prevents pragmatic approaches being utilised. As a result, CHM RCTs are often too direct in their approach, where a set intervention is used in a set population of a set condition type to measure the effect of the intervention
on a set outcome. Taking a more pragmatic approach may involve multiple interventions in a diverse population with numerous condition types to measure different effects of interventions to known and unknown outcomes. Such a pragmatic approach may provide data that reflect real life scenarios well; however, obtaining enough data to draw statistical and clinical significance requires very large sample sizes. Explanatory design studies can dramatically reduce the sample size required to evaluate an intervention.

The scientific model and explanatory nature of a RCT clearly suits evaluation of an explanatory style intervention such as a pharmaceutical drug, where there is often a known dosage and mechanism of action for a target group. In CHM, however, it is not uncommon that the intervention is a formulation consisting of numerous ingredients and subsequently containing countless compounds with many biological modes of action. Further difficulties in CHM standardisation arise due to the variability in constituents of herbal compounds, which vary depending on growing conditions and manufacturing process among other factors (Lu et al., 2014b). Review has found standardisation of CHM and reporting in RCTs is poor and it has been recommended future RCTs should utilise CHM interventions that have been produced according to good agricultural and manufacturing practice (Leung et al., 2006).

Clinically, CHM practitioners have the flexibility to vary their use of CHM based on the suitability of the substance for each patient’s syndrome type. Explanatory designed studies make intervention flexibility difficult as any change to the intervention would create a new dataset group that, if not separately analysed, would add heterogeneity to the results and, if separated, would require an increase in the sample size to show statistical significance (Nahin and Straus, 2001).
For CHM research of a specific condition, achieving the most efficacious results using a pure explanatory approach would require the most efficacious CHM be utilised for a specific syndrome type (condition). This, theoretically, should provide the greatest likelihood of statistically significant treatment effects. Selection of such a CHM, however, is not straightforward, nor is defining syndrome type, as the previous literature reviews indicated (see Chapters 2 and 3).

A more pragmatic approach may simplify such selection where aspects such as syndrome type, although somewhat restricted, may vary. Data may also be collected at various points throughout the trial by independent blinded assessors not associated with the care of the patient, as explanatory studies dictate, yet reflect the effects of multiple interventions for which pragmatic style studies such as observational studies would usually be utilised.

A pragmatic style study enables flexibility of eligibility criteria and inclusion of a wider range of psoriasis types. Such results would assist in assessing the impact of the CHM more broadly on psoriasis and help evaluate the feasibility of CHM in a more explanatory designed RCT. Such mixed style studies could lead to development of more pure explanatory style studies where researchers have greater confidence in the intervention for the disease in the targeted sample (Hennekens and Buring, 1993). However, there may also be occasions when results from a pragmatic trial are so strong and dramatic (positive outcomes, no change or reduced outcomes) that they provide enough evidence to validate an intervention and skip RCT explanatory investigation altogether (Black, 1999).
7.3 Proposed study design

Initial trial design was developed using a pragmatic approach then following further collaboration with study investigators with previous expertise an explanatory design was developed. This section details the initial design method and the finalised protocol methods.

7.3.1 Comparing and evaluating explanatory and pragmatic methods using the pragmatic–explanatory continuum indicator summary

An assessment tool known as the pragmatic–explanatory continuum indicator summary is able to help evaluate the degree of pragmatic versus explanatory design in a study. It is designed to aid researchers in the development of a protocol suitable to the research questions it intends to answer (Thorpe et al., 2009). The pragmatic–explanatory continuum indicator summary was utilised in the current study to guide the development of a protocol investigating PSORI-CM01 for psoriasis vulgaris. We determined that the study would be predominantly explanatory in style to maintain the rigour of the study results, but would also contain pragmatic aspects to ensure clinical relevance of results. Elements of pragmatism would also ensure that the sample characteristics would be varied enough to reach sample size targets yet specific enough for data to be grouped for analysis. If the sample characteristics varied too much, results would show high heterogeneity.

The pragmatic–explanatory continuum indicator summary covers 10 domains that are used to distinguish explanatory style from pragmatic style studies based on four key aspects of a clinical study: participants; intervention/s and expertise; follow-up and outcomes; participant compliance and adherence; and analysis of results. The domains covering theses are:
(1) the eligibility criteria for trial participants;

(2) the flexibility with which the experimental intervention is applied;

(3) the degree of practitioner expertise in applying and monitoring the experimental intervention;

(4) the flexibility with which the comparison intervention is applied;

(5) the degree of practitioner expertise in applying and monitoring the comparison intervention;

(6) the intensity of follow-up of trial participants;

(7) the nature of the trial’s primary outcome;

(8) the intensity of measuring participants’ compliance with the prescribed intervention, and whether compliance-improving strategies are used;

(9) the intensity of measuring practitioners’ adherence to the study protocol, and whether adherence-improving strategies are used; and

(10) the specification and scope of the analysis of the primary outcome.

For each of these domains the pragmatic and explanatory design was considered then the style was determined for the present psoriasis study (Table 7.1). For eligibility criteria we decided that the explanatory method was preferred. Restricting the selection of participants (vulgaris type only, of mild–moderate severity, without significant health risk) would be important to ensure the sample would be appropriate for the intervention. Pragmatic style would be utilised for syndrome type, as the prevalence of syndrome types unknown for the Australian population. This would also help us reach recruitment targets. While syndrome type would not determine eligibility, all participants would still be assessed for syndrome type.
As the formulation for the current study already had significant evidence of its efficacy for psoriasis, the main purpose of the study was to evaluate it under controlled conditions, so we decided dosage, administration and formulation would be purely explanatory, that is, fixed. We decided that any efficacy of the experimental intervention should be able to be easily evaluated with little impact from any related co-founders. It was decided records should be kept of each participant’s use of the experimental interventions (daily administration recording with reasoning provided for non-compliance). As the study was designed as a direct comparison between PSORI-CM01 plus calcipotriol versus placebo plus calcipotriol the same explanatory approach was required for the comparison intervention domain.

In relation to the expertise of the practitioner administering the experimental intervention we decided, for the safety of participants and to ensure consistent administration of interventions, only registered (Australian Health Practitioner Regulation Authority) CHM practitioners would dispense the experimental medication. The same explanatory approach was utilised for the practitioner expertise of the comparison intervention domain, in this case the calcipotriol plus placebo. The researchers were to be blind to participant intervention at all stages and as the placebo was to be manufactured as close as possible to match the appearance and taste of the CHM intervention it was important the dispenser gave the same instructions and had the same qualifications and training as dispensers of the experimental interventions. Similarly, as both groups would also be receiving calcipotriol, the dispenser needed to follow dosage and administration instructions provided by the manufacturer and according to treatment guidelines (Leo Pharmaceutical Products Ltd A/S, 2002, Dermatology Expert Group, 2004, Callen et al., 2003).
Of the two follow-up and outcome domains the first evaluates the ‘follow-up intensity’ where a pragmatic approach does not require direct follow-up with participants to evaluate data measures, instead existing datasets are searched for the required data to assess outcomes. For the proposed intervention study, participants needed regular follow-up to assess their symptoms and monitor adverse events. One of the proposed outcomes was evaluation of changes to cytokines, which would also require strict follow-up to ensure blood was collected correctly and stored appropriately. This degree of follow-up is explanatory, yet the frequency is still comparable with that seen clinically so for this domain there was little reason to take a pragmatic approach.

For the domain surrounding the primary trial outcome a pragmatic approach would utilise an outcome that is clinically relevant to the participant. For the proposed study it was important the outcomes could be compared with those of other studies in order to evaluate the effectiveness of PSORI-CM01. Other studies commonly use PASI and DLQI and we decided to utilise these same instruments complimented by appropriate use of other validated instruments such as the SKINDEX29. Outcome measures were selected for assessment of symptom severity and QoL based on guideline recommendations (The Australian Government, 2004). We determined wherever possible to use validated instruments and scales. The majority of these have already shown some level of reliability and are considered to be relevant to psoriasis sufferers ensuring that although the study is taking an explanatory approach to this domain the outcomes would still have clinical relevance.

The next two domains cover compliance and adherence, to the intervention and the protocol. As the proposed study is a pilot study designed to investigate intervention feasibility and the protocol design for a larger study, it makes sense to monitor the
compliance of participants. Such monitoring may provide insights into difficulties participants had with the intervention. Taking this explanatory approach we decided that the intervention should be provided in a form that is easy to administer, in this case a granulated extract that can simply be mixed with water and drunk. Providing it in a raw formulation would likely reduce compliance due to the preparation involved to cook the herbs. Providing formulation in pill form, while likely improving ease of administration, would require multiple pills in order to consume the therapeutic dosage required. An antihistamine to ease pruritus was also included. All study interventions would be measured to evaluate compliance with intervention administration instructions through the treatment phase and a daily diary completed by participants would detail further reason for lack of compliance to interventions.

Adherence to the study protocol by practitioners is an important domain to consider. For the proposed study it was important any potential bias was limited and for the safety of participants the protocol needed to be adhered to carefully. To ensure this, a standard operating procedure was proposed. The standard operating procedure would ensure all aspects of the study were undertaken according to pre-defined instructions and enhance consistency in all aspects of implementation. This approach is solely explanatory in design.

The last domain to consider in the design of the study was the analysis of the data. For the proposed study, both pragmatic and explanatory approaches to analysis were chosen. This would allow for analysis of the overall results and would also allow for subgrouping of data to evaluate other specific interests such as what impacts syndrome type may have on outcome measures. While standard outcomes such as the efficacy of the intervention had to be evaluated and comparisons between groups, researchers could conduct further analyses suiting the final data.
<table>
<thead>
<tr>
<th>Participants</th>
<th>Eligibility criteria</th>
<th>Pragmatic style</th>
<th>Explanatory style</th>
<th>Psoriatic trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants who have the condition of interest are enrolled, regardless of their anticipated risk, responsiveness, co-morbidities or past compliance</td>
<td>Stepwise selection criteria are applied that (a) restrict study individuals to those previously shown to be at highest risk of unfavourable outcomes, (b) further restrict these high-risk individuals to those who are thought likely to be highly responsive to the experimental intervention and (c) include just those high-risk, highly responsive study individuals who demonstrate high compliance with pre-trial appointment-keeping and mock intervention</td>
<td>Participants with the diagnosis of mild–moderate psoriasis vulgaris but of any CM syndrome type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventions and expertise</td>
<td>Experimental intervention: Flexibility</td>
<td>Instructions on how to apply the experimental intervention are highly flexible, offering practitioners considerable leeway in deciding how to formulate and apply it.</td>
<td>Inflexible experimental intervention, with strict instructions for every element</td>
<td>Intervention is a fixed dosage oral CHM and topical conventional therapy</td>
</tr>
<tr>
<td>Experimental intervention: Practitioner expertise</td>
<td>The experimental intervention typically is applied by the full range of practitioners and in the full range of clinical settings, regardless of their expertise, with only ordinary attention to dose setting and side effects.</td>
<td>The experimental intervention is applied only by seasoned practitioners previously documented to have applied that intervention with high rates of success and low rates of complications, and in practice settings where the care delivery system and providers are highly experienced in managing the types of patients enrolled in the trial. The intervention often is closely monitored so that its ‘dose’ can be optimised and its side effects treated; co-interventions against other disorders often are applied.</td>
<td>Registered practitioners of CHM, regardless of their level of expertise, will administer the intervention.</td>
<td></td>
</tr>
<tr>
<td>Comparison intervention: Flexibility</td>
<td>'Usual practice' or the best alternative management strategy available, offering practitioners considerable leeway in deciding how to apply it</td>
<td>Restricted flexibility of the comparison intervention; may use a placebo rather than the best alternative management strategy as the comparator.</td>
<td>Comparison is placebo plus conventional therapy (calcipotriol) With a standard recue therapy for all participants (anti-histamine)</td>
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<td></td>
</tr>
<tr>
<td>Comparison intervention: Practitioner expertise</td>
<td>The comparison intervention typically is applied by the full range of practitioners and in the full range of clinical settings, regardless of their expertise, with only ordinary attention to their training, experience and performance.</td>
<td>Practitioner expertise in applying the comparison intervention(s) is standardized to maximize the chances of detecting whatever comparative benefits the experimental intervention might have.</td>
<td>The same practitioners at the experimental intervention to limit potential bias will apply comparison.</td>
<td></td>
</tr>
<tr>
<td>Follow-up and outcomes</td>
<td>Follow-up intensity</td>
<td>No formal follow-up visits of study individuals. Instead, administrative databases (e.g., mortality registries) are searched for the detection of outcomes.</td>
<td>Study individuals are followed with many more frequent visits and more extensive data collection than would occur in routine practice, regardless of whether patients experienced any events.</td>
<td>Telephone follow-up and face to face assessments at various time points where extensive symptom measures, quality of life measures and blood tests will be performed as well as health resource utilisation collected to assess intervention effect and monitor safety</td>
</tr>
</tbody>
</table>

**Assessment**—Explanatory
<table>
<thead>
<tr>
<th><strong>Primary trial outcome</strong></th>
<th>The primary outcome is an objectively measured, clinically meaningful outcome to the study participants. The outcome does not rely on central adjudication and is one that can be assessed under usual conditions (e.g. special tests or training are not required).</th>
<th>The outcome is known to be a direct and immediate consequence of the intervention. The outcome is often clinically meaningful but may sometimes (e.g., early dose finding trials) be a surrogate marker of another downstream outcome of interest. It may also require specialised training or testing not normally used to determine outcome status or central adjudication.</th>
<th>Primary outcome is a clinically meaningful outcome with reduction in PASI as suggested by the Therapeutic Goods Association and relevant treatment guidelines. Outcomes measures require training of PASI calculation. <strong>Assessment</strong>–explanatory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participant compliance with 'prescribed' intervention</strong></td>
<td>There is unobtrusive (or no) measurement of participant compliance. No special strategies to maintain or improve compliance are used.</td>
<td>Study participants' compliance with the intervention is monitored closely and may be a prerequisite for study entry. Both prophylactic strategies (to maintain) and 'rescue' strategies (to regain) high compliance are used.</td>
<td>Compliance will be recorded according to measurement of remaining study drugs. A rescue therapy is being utilised to aid compliance rates. <strong>Assessment</strong>- explanatory</td>
</tr>
<tr>
<td><strong>Practitioner adherence to study protocol</strong></td>
<td>There is unobtrusive (or no) measurement of practitioner adherence. No special strategies to maintain or improve adherence are used.</td>
<td>There is close monitoring of how well the participating clinicians and centres are adhering to even the minute details in the trial protocol and 'manual of procedures.'</td>
<td>All deviations from the protocol and standard operating procedure will be recorded, as well as details of distribution of study drugs as well as timely follow-up. <strong>Assessment</strong> – explanatory</td>
</tr>
</tbody>
</table>

IMPPS, integrative medicine for psoriasis pilot study
Table 7.2 compares characteristics of the two methodological designs that were discussed prior to determining the final trial protocol. Initially a pragmatic designed study was developed to optimise treatment effects of CHM intervention (Method A). Psoriasis of any type, severity and duration was considered. Effect optimisation would permit modification of the intervention based on Chinese medicine syndrome type and disease characteristics such as severity. Method A consisted of an observation period (3 months) where treatment was prescribed and administered as per treating physician instructions followed by an intervention period (3-6 months) where CHM is administered alongside standard care. Treatment would cease and follow up would begin when participants achieved complete clearance of psoriasis or following 6 months CHM.

Table 7.2 Comparing pragmatic and explanatory study designs

<table>
<thead>
<tr>
<th>Design characteristics</th>
<th>Method A (primarily pragmatic)</th>
<th>Method B (primarily explanatory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant target group</td>
<td>Psoriasis any phenotype</td>
<td>Psoriasis vulgaris only</td>
</tr>
<tr>
<td>Psoriasis severity</td>
<td>Any severity</td>
<td>Set severity range (i.e. based on PASI)</td>
</tr>
<tr>
<td>Psoriasis duration</td>
<td>No limits on duration</td>
<td>At least 12 months history of psoriasis</td>
</tr>
<tr>
<td>Investigative intervention</td>
<td>Can be modified with addition or subtraction of other CHM at any time point of the study.</td>
<td>CM is fixed for the duration of the study</td>
</tr>
<tr>
<td>- Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Placebo</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>- Dosage</td>
<td>Can be adjusted as disease worsens or improves</td>
<td>Fixed dosage for duration of the study</td>
</tr>
<tr>
<td>Control</td>
<td>No control participant can use any psoriasis related medication</td>
<td>Control is fixed and identical for each participant</td>
</tr>
<tr>
<td>- Type</td>
<td>No control participant can use any psoriasis related medication</td>
<td></td>
</tr>
<tr>
<td>- Dosage</td>
<td>Can be adjusted as disease worsens or improves</td>
<td>Adjusted according to recommended treatment guidelines for severity</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>No restriction of use</td>
<td>Cease all psoriasis related medication for the duration of the study</td>
</tr>
<tr>
<td>Use of CM syndrome differentiation</td>
<td>Used for determination of intervention ingredients and dosage</td>
<td>Can be assessed but has no impact on intervention selection or dosage</td>
</tr>
</tbody>
</table>
Study length | 3 months of standard care (observation period) followed by 3 months of study drugs (intervention period). Those achieving full clearance would then commence a 3 month follow up phase. Participants not achieving clearance would continue treatment for a further 3 months then undergo their 3 month follow up phase. | 2 week run-in phase followed by 3 months treatment and 3 months follow up. |

Blinding | Assessors would be blinded to treatment ingredients however would know all participants are taking CM | Participants and assessors would be blinded to their treatment allocation throughout the duration of the study |

Outcomes | Severity change (%PASI), relapse rates, syndrome change, dosage and ingredient change, adverse events, inflammatory marker change and health resource utilization | PASI 75 rate, severity change (%PASI), adverse events, inflammatory marker change and health resource utilization |

CM, Chinese medicine; PASI, psoriasis area severity index

7.3.2 Discussion on study design

While the importance of conducting clinically relevant studies is clear, such studies still need to be rigorous in their design to ensure results have low bias. For CHM studies to be published in high impact journals, taking an explanatory approach to reduce risks of bias is needed. With such rigorous design there is no reason why CHM studies could not be published alongside conventional pharmacological studies (Sheehan et al., 1992).

Randomisation of the sample is an important aspect of explanatory designed studies reducing risk of bias. Without randomisation, non-treatment or low efficacy treatment groups may preference allocation to more efficacious groups leading to poor compliance, increased dropouts and/or false reporting of outcomes (Brewin and Bradley, 1989). Incorporating the same conventional medicine intervention in both the control and intervention arms of the trial and using an apparently identically placebo
will provide explanatory design for the study yet allow for efficacy outcomes to be measured and maintain blinding to reduce risk of potential bias.

Participant-specific inclusion criteria can make study results more specific to the intervention; however they need to be weighed up against participant availability. Choosing too specific a sample reduces eligibility of the population to participate, making recruitment sample targets more difficult and increases the time to reach these targets. Thus, for the proposed study, inclusion criteria deemed most important to evaluate the intervention were selected and after discussion with specialists those deemed less important for evaluation of the intervention were disregarded. The purpose was to ensure the included sample population accurately reflected the population yet had suitable characteristics (mild–moderate psoriasis vulgaris) for the proposed interventions.

**7.3.3 Conclusion on study design**

Research suggests transcribing explanatory RCT data is difficult and expensive, and to improve clinical best practice observational pragmatic designed study data should complement it (1992, Black, 1996). For the proposed study, previous clinical and laboratory evidence supporting PSORI-CM01 already exists, however rigorous, low bias research is lacking. It was determined by the research team an explanatory style pilot trial should be conducted allowing for minor pragmatic aspects such as syndrome diagnosis. With an explanatory approach forefront, a protocol was developed to further investigate the efficacy of PSORI-CM01.

**7.4 Aims and objectives of the pilot study**

The aim of this study is to evaluate of the efficacy and safety of a CHM formulation (PSORI-CM01) combined with standard conventional treatment (calcipotriol) in the
management of mild–moderate psoriasis vulgaris via a randomised, double-blinded, placebo-controlled clinical trial.

Using primarily an explanatory approach the following protocol was developed according to recommendations from the publication ‘Standard Protocol Items: Recommendation for International Trials’ (Chan et al., 2013) to investigate:

- Whether the combination of oral CHM formula PSORI-CM01 and pharmacotherapy (calcipotriol) is more effective than the combination of CHM placebo and pharmacotherapy (calcipotriol), in terms of psoriasis vulgaris symptom control (assessing the change in PASI score in treatment phase).

- Whether the combination of oral CHM formula PSORI-CM01 and pharmacotherapy (calcipotriol) is more effective than the combination of CHM placebo and pharmacotherapy (calcipotriol), in terms of psoriasis vulgaris patients’ QoL (assessing the change in dermatology life quality index score and Skindex 29 score in treatment phase) (Appendix 4 and 5).

- Whether the combination of CHM formula PSORI-CM01 and pharmacotherapy (calcipotriol) is safe for the treatment of psoriasis vulgaris (monitoring adverse events in treatment and follow-up phases).

- Whether the combination of oral CHM formula PSORI-CM01 and pharmacotherapy (calcipotriol) provides significant psoriasis symptom relief beyond the treatment phase (assessing change in PASI score, relapse rate in follow-up phase).

- Whether the oral CHM formula PSORI-CM01 is an acceptable form of treatment for people with psoriasis vulgaris (assessing the acceptability, willingness to repeat ratings in treatment phase).
7.5 Pilot RCT methodology

The study is a randomised, double-blinded, placebo-controlled parallel trial of conventional topical treatment (calcipotriol) plus oral CHM (PSORI-CM01) versus conventional topical treatment (calcipotriol) plus oral CHM placebo.

7.5.1 Participants

Sample size

The study will be a pilot trial involving 30 participants designed to test the feasibility and assist calculation of the sample size required for a large-scale RCT. Post hoc power analysis via effect size estimation of the pilot study data will be used to determine sample size for the full-scale trial.

Sample population

Thirty participants over the age of 18, with at least a 12-month history of psoriasis vulgaris (physician-diagnosed), meeting specific inclusion criteria will be recruited. Participants are to be sourced from Bundoora, Victoria, Australia and its surrounding suburbs. A participant shortfall will see a second China site commence recruitment at Guangdong University and Provincial hospital using the same batch of study drug.

The inclusion criteria are:

- aged between 18 and 70 years;
- at least 12 months of psoriasis vulgaris symptoms;
- patient-informed consent;
- PASI score ≥7 and ≤12.

The exclusion criteria are:

- pregnant or breast-feeding women;
- type of psoriasis other than vulgaris;
- systemic drugs or phototherapy for psoriasis within 4 weeks of screening;
- topical drugs for psoriasis within 2 weeks of screening;
- other severe disorders;
- known disorders of calcium metabolism (high blood calcium levels);
- known kidney function disorders;
- taking calcium, vitamin D supplements or vitamin D-like medicines;
- known sensitivity to Chinese herbs;
- known sensitivity to calcipotriol;
- unwilling or unable to cease other topical and systemic psoriasis-related medication for the duration of the trial.

Recruitment

Recruitment will be via poster advertisements in hospitals, health clinic waiting rooms and around university campus. Further recruitment will be through newspaper advertisements, email newsletters and Internet advertisements (Appendix 6). Patients may also be referred to the trial by their doctor (general practitioner, dermatologist or immunologist).

Informed consent

Informed consent will be sought from the participants at their initial assessment prior to a run-in period and randomisation. Written information (plain language statement) and verbal explanation of the study will be provided prior to consent (Appendix 7). Questions that arise will all be answered prior to the signing of informed consent. Written consent will be required from the participants in the presence of a witness. The witness will be someone who is not involved in the clinical trial. The responsible investigator will record the date, time and location of the provision of informed consent.
Withdrawal of participants

Participants are permitted to withdraw at any time during the trial, with or without reason provided. All withdrawn cases that have received the intervention will be contacted eight weeks after withdrawal to obtain information regarding their condition.

7.5.2 Blinding and randomisation

Blinding

Participants, researchers and outcome assessors will all be blinded to group allocation. PSORI-CM01 and placebo will be packaged identically and labelled with a code directly corresponding to the generated randomisation sequence required for identification of the allocation group. Packaging and labelling will be conducted by persons independent of the research team and the randomisation sequence sealed and stored in a locked filing cabinet separate from any participant data and accessible only to those who generated the randomisation sequence. Testing of participant blinding to allocation will be done at various timepoints throughout the duration of the trial.

Randomisation and allocation concealment

Participants will be randomly allocated to the intervention group (PSORI-CM01 plus calcipotriol) or control group (placebo plus calcipotriol) in equal ratio (1:1). The randomisation numbers will be generated by computer program into blocks (blinded block number). The randomisation numbers will be kept in sealed envelopes and the envelopes will be opened sequentially for each participant only after participant details are written on the outside of the envelope. A code inside the envelope will correspond with a package number that will contain 12 weeks of either PSORI-CM01 or placebo granules.
7.5.3 Data management

Data will be collected at initial assessment (~2 weeks), mid-treatment assessment (6 weeks), post-treatment assessment (12 weeks) and post-follow-up assessment (24 weeks) (Appendix 8). Assessors and participants will be trained for data recording prior to commencement. Personnel blinded to group allocation will enter all data into a pre-designed, password-protected file. Data entry will be performed continuously throughout the study. Double-checking of entered data will be performed to ensure accuracy, with any correction or changes of written data in patient files documented and dated. Randomisation codes will only be broken after the data validation and editing processes are completed, or if a serious adverse event (SAE) occurs.

7.5.4 Study intervention description

Conventional treatment

The topical drug calcipotriol 0.005% (50 μ g/g) cream (30g tubes) will be administered as pharmacotherapy. Calcipotriol is a moderate action first line therapy drug commonly used and recommended in treatment guidelines, with little risk of side effects and proven efficacy in people with mild to moderate psoriasis symptoms (Pearce et al., 2006). The drug is listed on the Australian pharmaceutical benefit schedule for psoriasis. Calcipotriol is a vitamin D3 derivative that decreases proliferation and induces differentiation of keratinocytes, with a strong immunomodulation effect reducing the levels of pro-inflammatory cytokines (Tiberio et al., 2009, Fenton and Plosker, 2004). It was favoured over the use of corticosteroids in the current study as it does not cause atrophy of skin and is less messy than topically applied tars or anthralin (Nagpal et al., 2001). Rescue therapy will be provided to all participants, at no cost, for intolerable itch in the form of an antihistamine (lortadine).
**Chinese herbal medicine**

The herbal formula has been developed based on pre-clinical research and clinical experience (see Chapter 5). The ingredients and ratios of formula PSORI-CM01 are: *chi shao* (1.5), *hong tiao zi cao* (2.5), *gan cao* (1), *wu mei* (2.5), *jiu jie cha* (2.5), *cu e zhu* (1.5) and *tu fu ling* (2.5). Details of each herb are listed in Table 5.3. The granules of PSORI-CM01 and placebo will be produced by a manufacturer that holds a good manufacturing practice certificate. For the PSORI-CM01 granule, the manufacture procedure is:

- combine raw herbs of *chi shao* 265kg, *hong tiao zi cao* 441kg, *gan cao* 177kg, *wu mei* 441kg, *jiu jie cha* 441kg, *cu e zhu* 265kg, *tu fu ling* 441kg and add 10 times the amount of water;
- bring to the boil and cook for 1.5 hours; filter out the liquid;
- add eight times the amount of fresh water;
- bring to the boil and cook for 1 hour; filter out the liquid;
- combine the extracted liquids;
- pressure spray dry the mixed liquid extraction to form a granulated extract;
- package granules in small sachets (9.5cm × 9.5cm in size) each weighing 5.5g (one dose).

**Placebo**

The placebo will be produced by the same manufacturer as the PSORI-CM01 granules and will consist of starch with no active ingredients. It will be matched as closely as possible to the appearance and taste of the PSORI-CM01 granules. Colour will be made identical by adding artificial pigment while taste will be adjusted by adding medicine intermediate D-(-)-Cellobiose octaacetate. Dosage and administration instructions for the PSORI-CM01 and placebo groups will be identical (Figure 7.2, 7.3 and 7.4).
7.5.5 Intervention administration and dosage instructions

Instructions for drug administration for both participant groups will be identical and will include a starting dosage for the calcipotriol cream.

Treatment group

The intervention group will receive PSORI-CM01. Dosage of CHM granules will be 5.5g per sachet administered twice daily for 12 weeks. The calcipotriol cream will be administered daily to affected body surface areas for 12 weeks according to American Academy of Dermatology guidelines (1% surface area coverage=0.5 fingertip unit) (Table 7.3 and Figure 7.1) or until complete clearance of the lesions. The maximum dose should not exceed 100g per week as per consumer medicine information for Daivonex® (calcipotriol)(Leo Pharmaceutical Products Ltd A/S, 2002) (Appendix 9).

Table 7.3: American Academy of Dermatology recommendations for topical medication use (one fingertip unit=approx. 500 mg) (Menter et al., 2009)

<table>
<thead>
<tr>
<th>Area to be treated</th>
<th>No. of fingertip units</th>
<th>Approximate body surface area (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Face and neck</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>One hand (front and back) including fingers</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>One entire arm including entire hand</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Elbows (large plaque)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Both soles</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>One foot (dorsum and sole), including toes</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>One entire leg including entire foot</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Buttocks</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Knees (large plaque)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Trunk (anterior)</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Trunk (posterior)</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Genitalia</td>
<td>0.5</td>
<td>1</td>
</tr>
</tbody>
</table>
**Figure 7.1:** One fingertip unit

**Control group**

The control group will receive placebo granules identical in appearance and as close as possible in taste to the PSORI-CM01. In preparation of the placebo people unassociated with the research study were approached to compare the taste, smell and appearance of each when in solution. The placebo was further adjusted with addition of starch and colour until it was indistinguishable from the PSORI-CM01 by taste. Dosage of 5.5g of placebo granules (one sachet) will be administered twice daily for 12 weeks, identical to the dosage for the PSORI-CM01. The calcipotriol cream of the control group will be administered according to the same methods and dosage guidelines as the intervention group (Figure 7.2, 7.3 and 7.4).

**Figure 7.2:** Packaged satchets of PSORI-CM01 and placebo (blind as to A and B allocation)
Figure 7.3: Granulated PSORI-CM01 and placebo (blind as to A and B allocation)

Figure 7.4: Solution of PSORI-CM01 and placebo (blind as to A and B allocation)

7.5.6 Adverse events and risk to participants

Monitoring of adverse effects

Potential adverse effects of the calcipotriol are considered minor and may consist of skin irritation (including peeling or rash), a change in the colour of the skin and/or sensitivity to light (Leo Pharmaceutical Products Ltd A/S, 2002). For the PSORI-CM01, the herbal constituents are used commonly in clinical practice with no reported risk. Six herbs of the PSORI-CM01 formulation are TGA approved in Australia and another herb (zhong jie feng) has been proven safe by research (Guo-qing Ying et al., 2007; Sun et al., 2003). Minor side effects of CHM are possible, such as nausea and or diarrhoea, but these are not identified as specific to the investigated herbal substances (MacPherson and Liu, 2005). If participants develop any minor side effects as a result of either intervention they will be advised to seek medical advice from their GP and cease the
interventions if they become intolerable. As there have been previous reports of toxicity with use of CHM (e.g. phosphatase and gamma-glutamyltransferase, alanine aminotransferase and aspartate aminotransferase, not specific to the herbs investigated here), blood tests for liver and kidney function will be collected at weeks 6, 12 and 24, and if any results become abnormal during treatment it will be ceased and documented as an AE (Graham-Brown, 1992). Liver and kidney function will also be assessed at screening (week -2) to identify any pre-existing liver and kidney disorder and if found requires physician permission to continue in the study. Central aortic blood pressure as well as systolic and diastolic pressure will also be monitored before and during the treatment period at weeks –2, 0, 6 and 12 to evaluate any change treatment may have. If increased abnormally, treatment will cease and participants will be advised to seek medical advice from their doctors as to their safe continuation in the study.

Risk management

The clinical trial will consist of a research team with qualifications in Chinese medicine herbal prescription, medical dermatology, statistics and clinical trial operation. Only Chinese medicine registered practitioners will provide the packaged herbs or placebo to the participant. The manufacturing and production of the CHM and placebo capsules will be by a GMP-certified company for quality control.

Early termination of the trial

All ingredients of PSORI-CM01 are used routinely in Chinese medicine daily practice; if SAE become apparent, the trial will be discontinued. Participants in their daily diary will record all reactions, including AEs (Appendix 10). Serious adverse events will be judged according to TGA criteria (The Australian Government, 2004) and recorded on the SAE form as “Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing
hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is a medically important event or reaction” (Appendix 11). See ‘Potential risks associated with treatments’ for description on what physiological safety monitoring measures are in place. A Data Safety Monitoring Board will be established consisting of independent specialists in clinical pharmacology, statistics, medical dermatology and traditional Chinese medicine dermatology. The Data Safety Monitoring Board will periodically review and evaluate the study data for safety and study conduct then make recommendations regarding the continuation, modification or termination of the study. Any SAEs will be reported to the relevant human research ethics committee and the Therapeutic Goods Administration (TGA). Any dropouts will be reported on an “end of study form” with reason provided and placed in the relevant case record file (Appendix 13).

Procedures for breaking codes

Emergency 24-hour access to the participant ID and treatment codes will be made available to authorised personnel at the study site. Should the need to unmask the treatment code arise, the authorised personnel will have access to the treatment code upon request of the principal investigator. The details of AEs and the unmasking of the treatment code will be documented by the investigator with endorsement from the principal investigator.

Ethics and trial registration

The trial protocol was assessed and subsequently approved by the RMIT University Human Research Ethics Committee (HREC) in accordance with the Australian Government’s National Statement on Ethical Conduct in Human Research (National Health and Medical Research Council et al., 2007). The HREC reviewed the risks and assessed the strategies proposed to negate them. The proposed research was also
reviewed to ensure potential vulnerable participants were protected from harm and that the target population was appropriate for the proposed research. The patient informed consent form was also reviewed to ensure it contained all relevant study details such as time requirements, tests involved and potential risks of participation (Appendix 7).

The HREC also reviewed the storage of results to ensure it protected the privacy of individuals and approved dissemination of results for publication and conference presentation when available. Methods of specimen collection and their use were also reviewed by the HREC, as well as the ingredients of all interventions, to ensure they were appropriate for the outcomes being investigated. Lastly, the HREC ensured the potential benefits of the study outweighed the potential risks for participants before it was ethically approved (Appendix 14).

The trial was filed with the TGA under the Clinical Trial Notification scheme and registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR): ACTRN12614000493640 (Appendix 15). The trial will be undertaken in accordance with the National Health and Medical Research Council’s National Statement of Ethical Conduct in Human Research (National Health and Medical Research Council et al., 2007) and the TGA’s guidance in good clinical practice (Therapeutic Goods Administration, 2000).

**Financing and insurance**

This clinical trial is part of the project funded by China-Australia International Research Centre for Chinese Medicine. The project is covered by RMIT University, Broadform Public and Product Liability Insurance.
Publication policy

No individual identifiable information of participants will be reported or published. To avoid individual participant identification data will be published in group form and presented in such a way that identifiable data is removed.

7.7.7 Outcome measures

For the developed study in an Australian population it was most appropriate to use instruments and scales suggested by Australian medical and Therapeutic Goods Association guidelines (Baker et al., 2013, The Australian Government, 2004). After review of guidelines and consideration of other symptom instruments, PASI and BSA were selected to measure psoriasis lesion severity. The majority of published clinical trials utilise these two primary outcomes and with considerable research existing of their reliability and validity, both are recommended widely.

As discussed, the PASI does still have deficiencies, a major one being no consideration of pruritus in calculation of severity, evidenced to be as prevalent as 80% of cases (Stinco et al., 2014). For the present study, there was addition of a separate scale measuring participant itch.

To measure QoL for the pilot study, dermatology life quality index and Skindex 29 were selected. Again, therapeutic guidelines commonly recommend dermatology life quality index, hence its selection, whereas Skindex 29 is reported as the most validated QoL measure available. Further, Skindex 29 has been reported most sensitive to change in milder psoriasis patients, which is important as they are the target population for the pilot trial.
Primary outcome measures

Complete clearance of psoriasis symptoms is usually not achievable, so recommended treatment success is considered a reduction in PASI score of 75% (PASI 75) or greater. Treatment failure is regarded as a reduction in PASI score of 50% (PASI 50) or less. For scores falling between 50% and 75% the dermatology life quality index is used to determine if the current treatment should continue or be modified (Mrowietz et al., 2011). The Australian Therapeutic Goods Administration recommends standard outcomes PASI 75, PASI 50 and BSA to assess product efficacy for psoriasis (The Australian Government, 2004). The primary outcome measure will be PASI change (mean) from baseline to mid-treatment (week 6), end of treatment (week 12) and end of follow-up (week 24) (see Table 7.6). The scoring method for PASI will be based on the training and reference provided at http://www.pasitraining.com. Researchers are experienced in psoriasis assessment and assessors are trained in conducting PASI. Only registered Chinese medicine practitioners of dermatologists will conduct outcome assessments. Initially two researchers will conduct the assessments to ensure consistency in evaluation then one researcher at a time will continue to assess lesions.

Secondary outcome measures

- PASI 75 (the proportion (%) of patients achieving a PASI improvement of 75%) (week 12);
- PASI 50 (the proportion (%) of patients achieving a PASI improvement of 50%) (week 12);
- relapse rate (defined as return of the rash to 50% of the area it involved before treatment (Rogers et al., 1979));
- BSA score change (%) (week 12);
- dermatology life quality index score change (%) (week 12);
- Skindex 29 score change (%) (week 12);

- questions on acceptability of treatment and willingness to repeat treatment (week 12);

- blood test (full blood test, and kidney and liver function tests, blood glucose and lipids);

- reported AEs and SAEs;

- Chinese medicine syndrome type change (weeks -2, 0, 6, 12 and 24);

- Body mass index (BMI) change (%) (week 12);

- health resource utilisation data (GP visits, hospital visits and use of medication).

**Psoriasis severity**

The psoriasis area severity index 75, 50 and body surface area (BSA) are recommended by TGA as standard outcome achievement goals to assess a product’s efficacy for psoriasis (The Australian Government, 2004). The dermatology life quality index instrument is recommended by both by the TGA and the Australian College of Dermatologists to evaluate psoriasis severity and patient QoL. It is a validated and well recognised instrument used in psoriasis research. The Skindex 29 has been evidenced for psoriasis as the most sensitive scale with the greatest applicability and is the most validated QoL instrument for dermatological conditions (Bronsard et al., 2010, Fernandez-Penas et al., 2012). Photos of the major lesion area will be taken at weeks 2, 6, 12 and 24. Photos will be taken in a way that they do not reveal the identity of the participant.

**Acceptability of treatment and willingness to repeat**

Acceptability will be measured on an ordinal scale from 0 to 10 where 0 equals very dissatisfied and 10 equals very satisfied with the treatment. Willingness to repeat the treatment will be measured at each assessment on a Likert scale with a choice of
responses. Adverse events will be measured daily by the participant and by blinded assessors at each assessment.

**Safety**

Safety will be assessed according to the number and types of adverse events reported by participants and assessors’ observations then classified if they are likely related to the CHM or pharmacotherapy. Psoriasis related hospitalisation and physician visit data will be collected to evaluate any increased risk from study interventions. Blood tests at weeks –2, 6, 12 and 24 for full blood count, and liver and kidney function will be evaluated for any significant change (Table 7.6).

**Biological markers**

**Cytokine concentrations**

Numerous cytokines have been identified as being involved in psoriasis disease progression. A sample of serum is to be stored for further investigation of key cytokines levels using BioPlex (weeks –2, 12 and 24). Thus, the cytokines in Table 7.4 will be analysed using BioPlex for concentration change during the study.

**Table 7.4: Bio-Plex Pro Human cytokine measurements**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>IL-2</th>
<th>IL-10</th>
<th>MCP-1 (MCAF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eotaxin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGF basic</td>
<td>IL-4</td>
<td>IL-12 (p70)</td>
<td>MIP-1α</td>
</tr>
<tr>
<td>G-CSF</td>
<td>IL-5</td>
<td>IL-13</td>
<td>MIP-1β</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>IL-6</td>
<td>IL-15</td>
<td>PDGF-BB</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>IL-7</td>
<td>IP-10</td>
<td>RANTES</td>
</tr>
<tr>
<td>IL-1β</td>
<td>IL-8</td>
<td>IL-17 and 17A</td>
<td>TNF-α</td>
</tr>
<tr>
<td>IL-1ra</td>
<td>IL-9</td>
<td>IL-23</td>
<td>VEGF</td>
</tr>
</tbody>
</table>
By comparing cytokine concentrations with those of healthy skin, there is greater understanding of differences. Surprisingly evidence indicates systemic chemokine levels of psoriatic people don’t tend to differ greatly from unaffected people (Lima et al., 2014). There is though significant research for a number of key cytokines involved in psoriasis. This section reviews these cytokines and provides justification for the selection of the final group to be analysed for concentration change during the study.

**IL-1**

Appearing to mainly be a linking cytokine in the immune response, evidence suggests IL-1 is raised in psoriasis sufferers, however its specific role in psoriasis is unclear (Bebes et al., 2014).

**IL-2**

With the administration of IL-2 in high doses shown to exacerbate or induce psoriasis, *in vivo* and *in vitro* studies confirm its increased production in psoriatic lesional skin (Lee et al., 1988).

**IL-4**

Increased IL-4 receptor expression is evident in psoriasis, likely the body physiologically attempts to increase IL-4 production, as IL-4 presence will subsequently down-regulate a number of cytokines implicated in aggravation of psoriasis (Hart et al., 1989).

**IL-6**

Expressed in the transitional epidermis zone of psoriatic lesions, and corresponding with expanding regions of plaques, IL-6 is increased in psoriasis. Secreted by macrophages, endothelial cells and epithelial cells, IL-6 concentration is shown to
decrease following effective treatment. Increased levels are linked to increases in key psoriatic inflammatory cytokine IL-23 (Olaniran et al., 1996, Lindroos et al., 2011, Paquet and Pierard, 1996). It is understood IL-6 is responsible for promotion of keratinocyte hyperplasia and cellular influx of macrophages and T-cells (Grossman et al., 1989). Psoriatic keratinocytes are reported to be more sensitive to growth-promoting effects of IL-6 than healthy keratinocytes. Also implicated with TGF-beta, IL-6 is important for the differentiation of naïve T-cells into pathogenic Th17 cells, a prominent psoriasis pathway (Bettelli et al., 2006). Also key to regulating the levels of C-reactive protein, IL-6 may be a factor linking psoriasis with co-morbidities in which C-reactive protein is pathogenically implicated such as obesity, diabetes and cardiovascular disease.

*IL-7*

Produced by keratinocytes and monocytes, IL-7 synergises with IL-12 to induce T-cell proliferation, increase IFN-γ production and stimulate cytotoxic activity, all relevant activity to psoriasis (Borger et al., 1996). Higher IL-7 levels have been observed in lesional samples compared with non-lesional skin and serum of healthy samples (Bonifati et al., 1997).

*IL-8*

Research indicates neutrophils and upper layer keratinocytes of lesional epidermis are the main producers of IL-8 (Gillitzer et al., 1991, Gillitzer et al., 1996). Enhancing angiogenesis, IL-8 is evidenced to be a potent chemo-attractant for neutrophils and T-cells, as well as a promoting factor for keratinocyte proliferation. Elevated levels are found in psoriatic skin (Nickoloff et al., 1994, Barker et al., 1991, Tuschil et al., 1992).
Likely IL-8 contributes to the epidermal hyperplasia phenomenon observed in psoriasis (Kemeny et al., 1994).

**IL-11**

Predominately inhibiting production of IL-12 from monocytes and macrophages, IL-11 has shown to also inhibit production of TNF-α, IL-6 and IL-1beta, which may have effect on psoriasis (Leng and Elias, 1997).

**IL-12**

Found in lipopolysaccharide-stimulated macrophages, IL-12 has increased synthesis in psoriatic skin possibly following physiological attempt of the body to reduce the inflammatory cascade of psoriasis (Leng and Elias, 1997). Also likely secreted by dendritic cells, IL-12 enhances production of Th1 line cells, further producing TNF-α and INF-γ and continuing further activation of keratinocytes with subsequent progression of psoriasis inflammatory loop pathways (Nwe et al., 2013). Efficiency of ustekinumab (see 2.7.3 Interleukin-12 and interleukin-23 inhibitors) in psoriasis in a phase III clinical trial is believed to target the gene p40, producing IL-23 and IL-12 which may explain its efficacy (Papp et al., 2008).

**IL-15**

Produced by monocytes, macrophages, dendritic cells and T-cells, IL-15 can induce angiogenesis, immune cell recruitment and activation of keratinocytes (McInnes and Gracie, 2004). Further, highly expressed in psoriatic skin, *in vitro* study has shown IL-15 inhibits apoptosis of keratinocytes, which may associate it with the increased proliferation of skin cells seen in psoriasis (Ruckert et al., 2000).
**IL-17**

A pro-inflammatory cytokine, IL-17 acts on keratinocytes increasing expression of chemokines and attracting neutrophils, Th17 cells and dendritic cells to the inflammatory site (Girolomoni et al., 2012). Levels of IL-17 are significantly increased in lesional compared with non-lesional skin and recent drug development has centred on targeting it (Frleta et al., 2014, Gisondi et al., 2014). Being down-regulated by IL-23 and subsequent TH17 pathway activation, IL-17 is now considered one of several central cytokines in psoriasis pathogenesis and it is recognised as an important target due to it inducing inflammation genes known to contribute to psoriasis (Malakouti et al., 2014, Chiricozzi and Krueger, 2013). Evidence suggests neutrophils and mast cells are also further sources of IL-17, which may indicate why biologics targeting IL-17 have such dramatic efficacy for psoriasis (Schon, 2014).

**IL-18**

Inducing production of IFN-γ, increased IL-18 plasma concentrations common to psoriatic people are correlated with increasing psoriasis severity. Subsequent psoriasis treatments see IL-18 concentrations reduce with coinciding reduction in symptom severity. This indicates the likely involvement of IL-18 in the pathogenesis of psoriasis (Rasmy et al., 2011). Research suggests links between genetic variation in components of the intracellular protein complex NLRP1 inflammasome and increasing IL-18. The NLRP1 inflammasome is likely initially activated in individuals by pathogens and subsequent cell death (Ekman et al., 2014).

**IL-21**

Cytokine expression of IL-21 is increased in psoriasis plaques and serum, where its presence is understood to aggravate presence of hyperplasia and inflammation in
psoriasis (He et al., 2012). In a mouse model, blockade of IL-21 with an antibody has seen subsequent improvement in hyperplasia and reduction in expression of Th1 and Th17 inflammatory pathways (Botti et al., 2012).

**IL-22**

Promoting proliferation of keratinocytes, IL-22 is active in skin inflammation of psoriasis (Sa et al., 2007) (Ma et al., 2008). With increased levels of IL-22 found in psoriatic sufferers, transcription of IL-22 appears to be triggered by IL-23 as well as expressed by mast cells of skin (Benham et al., 2013, Mashiko et al., 2015). Interestingly, a study determined IL-22 is not central to psoriasis and that, in mice at least, its absence might still see psoriasis develop via the IL-23 pathway (Takaishi et al., 2013).

**IL-23**

Overproduced by keratinocytes and dendritic cells in psoriatic skin lesions, IL-23 when injected has been shown to induce hyperkeratosis (Piskin et al., 2006). Presence of IL-23 stimulates increased proliferation of Th-17 cells, which has an important psoriatic downstream role producing IL-17 (see above). A key pathway recognised as involved in psoriatic inflammation. As a result of its significance, many newer developed biologics now target this pathway (Sonnenreich, 2013). Targeting IL-23 is theorised as one of the more sensitive, selective and effective mechanisms for treating psoriasis (Chiricozzi et al., 2014). The IL23R R381Q gene variant has shown to be protective of psoriasis development, likely due to reduction in IL-23’s ability to produce IL-17A (Di Meglio et al., 2011). Research has investigated blocking thymic stromal lymphopoietin, to suppress IL-23 production from dendritic cells (Volpe et al., 2014).
**IL-33**

Understood to be expressed in psoriatic skin by presence of TNF-α, IL-33 is dependent on a stimulus invoking it. It acts primarily by alarming or activating either the Th1 or Th2 inflammatory pathways. Interestingly, it appears to be expressed more in psoriasis (predominantly more Th1 type disease) than in Th2 acting diseases such as atopic dermatitis (Balato et al., 2014).

**Growth factors**

In psoriasis, several studies have indicated deregulation of keratinocyte epidermal growth factor (EGF) receptor-ligand system and increased expression of EGF receptor, as well as ligands TGF-α and amphiregulin in lesional epidermis (King et al., 1990).

**Endothelin-1 (ET-1)**

Different studies have indicated that molecule ET-1 levels are increased in patients with psoriasis, with increasing serum levels correlating with increasing PASI scores (Trevisan et al., 1994, Cecchi et al., 1994, Bonifati et al., 1998). Its action on psoriasis may be due to monogenic and neutrophil chemo-attractant properties associated with participation in inflammation and keratinocyte hyper-proliferation. It may also counterbalance the vasodilatory action of raised reactive nitrogen intermediates from vasoconstrictive activity (Wright et al., 1994).

**TNF-α**

Inducing maturation of Langerhans cells and up-regulating T-Cell production, TNF-α has also shown it stimulates synthesis of prostaglandin and leukotrienes (Terajima et al., 1998). Langerhans cells have been shown in vivo to be anti-inflammatory and immunosuppressive of psoriatic lesions (Glitzner et al., 2014). The TNF-α induces keratinocyte proliferation and vascular endothelial growth factor (Kimber et al., 2000).
Further, TNF-α induces synthesis of other pro-inflammatory cytokines including IL-1, IL-6, IL-8, transforming growth factor-α, granulocyte macrophage-colony stimulating factor and leukaemia inhibitory factor (Wakefield et al., 1991). It may also increase plasminogen activator inhibitor type 2 (PAI-2), which is key to inhibition of apoptosis absent in psoriasis and further aggravating the proliferation of keratinocytes (Wang and Jensen, 1998).

**NF-κB**

Thought to be a key pathway mediator in psoriasis pathogenesis, genetic studies have associated a number of genes with activation of transcription factor NF-κB, leading it to translocate and bind with DNA (Gupta et al., 2014). Many treatments aimed at cytokines also impact on NF-κB signalling, having an effect of up-regulating or down-regulating key cytokine production pathways such as IL-17 and TNF-α. NF-κB concentration levels have shown to decrease significantly following successful psoriasis treatment, yet some drugs increase its levels, suggesting the pathways are quite complex (Goldminz et al., 2013).

**Prolactin**

Increased serum levels of prolactin have been observed in psoriatic patients, with increase also associated with greater psoriasis severity (Keen and Hassan, 2014). The precise mechanism of prolactin’s involvement is not yet clear, however research theorises it may inhibit T-cell suppression, increase keratinocyte proliferation as well as T-cell IFN-γ production, and promote angiogenesis (Lowes et al., 2007).

**Chinese medicine syndrome**

Given the present study was designed not to provide individualised Chinese medicine treatments, a syndrome differentiation instrument was developed to provide data that
can be utilised for subgroup analysis of Chinese medicine syndrome groups in the sample (see Chapter 4). One instrument that showed potential was the traditional East Asian medicine structured interview, traditional Chinese medicine version (Schnyer et al., 2005). The uniqueness and appeal of the instrument is it can be adjusted to suit any health condition; however, after further discussion with the creator its suitability was deemed low for the present study. Limitations for use in our study included the considerable time requirements to complete, modify and validate the instrument, and potential restrictions due to intellectual property rights.

Without a suitable syndrome differentiation instrument available for psoriasis, a short instrument was developed for the trial following translation of Chinese guidelines for psoriasis which list three syndromes for psoriasis (blood heat, blood stasis and blood deficiency) and detail the physiological, emotional, tongue and pulse features of each syndrome (China Academy of Chinese Medicine, 2011). From this, a simple tick box questionnaire was developed with the three syndromes grouped into their key features (Appendix 1).

*Other secondary outcomes*

Although the current study is just a pilot to evaluate the feasibility of a large-scale study it will collect health resource utilisation such as non-trial related pharmacotherapy use (psoriasis related only) and the number of GP and hospital visits. Data will also be collected on body mass index to evaluate any change with treatment as psoriasis and obesity have a strong correlation (Tobin et al., 2014). To explore co-morbidities such as cardiovascular disease and diabetes, blood tests at weeks 0, 12 and 24 will analyse blood glucose and lipid level change.
7.5.8 Study procedures

Participants will undergo an initial screening, followed by pre-treatment assessment, a two week run-in phase, baseline assessment, randomisation to treatment, six weeks treatment, fortnightly compliance and safety assessments, mid treatment assessment, a further six weeks treatment period, end of treatment assessment, twelve week follow up period and a final end of follow-up period assessment (Figure 7.2). All face to face data will be recorded in the participant’s case record forms (CRFs) (Appendix 7). This section outlines the study procedures in full.

Figure 7.5: Flowchart of study procedure
**Screening and pre-assessment (week –2)**

The initial assessment will consist of screening for inclusion and exclusion criteria (see 6.4.2), informed consent and assessment measures including psoriasis area severity index (PASI) and body surface area (BSA), which is calculated based on lesion skin surface coverage (Menter et al., 2009), dermatology life quality index (Appendix 4), Skindex 29 (Appendix 5) and Chinese medicine syndrome differentiation diagnosis (Appendix 3).

**Run-in period (week –2 to week 0)**

Following screening, participants will undergo a two-week run-in period. During this period all psoriasis-related medications and herbal supplements will be restricted from use. Participants will be provided with sorbolene cream during this period, which they may apply as required to assist symptom discomfort until the treatment period commences. Sorbolene or QV cream was recommended by specialists for use as a moisturiser due their unlikeliness to have any therapeutic action on the psoriasis. Of these, Sorbolene was selected for use in the study as it contains the least ingredients of the two, thus further reducing the chance of any therapeutic effect (Table 7.5).

**Table 7.5: Ingredients of QV cream and Sorbolene**

<table>
<thead>
<tr>
<th>Aqua (14 ingredients)</th>
<th>Sorbolene (8 ingredients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butylparaben</td>
<td></td>
</tr>
<tr>
<td>Paraffinum liquidum</td>
<td>Cetearyl Alcohol</td>
</tr>
<tr>
<td>Glycerin</td>
<td>Ceteareth-20</td>
</tr>
<tr>
<td>Petrolatum</td>
<td>Glycerin</td>
</tr>
<tr>
<td>Cetearyl alcohol</td>
<td>Methylparaben</td>
</tr>
<tr>
<td>Squalane</td>
<td>Mineral Oil</td>
</tr>
<tr>
<td>Dimethicone</td>
<td>Petrolatum</td>
</tr>
<tr>
<td>Ceteth-20</td>
<td>Propylparaben</td>
</tr>
<tr>
<td>Glyceryl stearate SE</td>
<td></td>
</tr>
<tr>
<td>Stearic acid</td>
<td></td>
</tr>
</tbody>
</table>
Baseline assessment

After the run-in period, participants will undergo baseline assessments (week 0: Table 7.6 – PASI, BSA, dermatology life quality index, Skindex 29, and Chinese medicine syndrome diagnosis) as well as full blood count, and kidney and liver function tests. Photos of the lesion areas will be taken, coded and placed in the patient’s case record file.

Twelve-week treatment phase week 1 to week 12

After baseline assessments participants will be randomly allocated to the intervention of placebo group. The first six weeks’ worth of medication will be dispensed to participants along with administration instruction (Appendix 9). During this period, psoriasis symptoms will be recorded in participants’ daily diary using self-administered assessments (Appendix 10). A consultation will be scheduled during the treatment phase at weeks 6 and 12, at which data will be collected to measure symptom severity, safety, dosage used and repeat the physiological tests done at baseline (Table 7.6). Phone calls will be made to participants at weeks 2, 4, 8 and 10 to check adherence to the dosage guidelines. At week 6 assessments the second 6 weeks’ worth of dosage of trial medications or placebo will be allocated to participants.

Administration of calcipotriol will continue until the end of the treatment period. Calcipotriol dosage can be reduced from the initial dosage at the participant’s discretion as the symptoms reduce. Participants in their daily diary will record any reduction in dosage with reasoning. Participants will be instructed to recommence prescribed dose
of calcipotriol if their symptoms return at any stage during the follow-up period. The CHM therapy and CHM placebo initial dosages will be continued to the end of the 12-week course regardless of complete psoriasis rash clearance. Any unused trial medications will be collected at the end of treatment assessment. Participant lesion areas will be photographed and coded with the participant’s identity masked.

**Twelve-week follow-up phase (week 13 to week 24)**

For the remaining 12-week post-treatment phase participants will continue to record symptoms in their daily/weekly diaries as well as utilisation of any health resources (including drug therapy use). At the end of this 12-week follow-up period (week 24) participants will attend the trial clinic for the end of follow-up assessment (fifth visit). Final photos of the lesion areas will be taken, coded and added to the patient’s case record file. The end of study form will be completed at this time and the participant’s involvement in the study will end.

**7.5.9 Data analysis and security**

**Data analysis**

All data will be processed and analysed by an independent statistician. The Statistical Package for the Social Sciences (SPSS) software version 21.0 for Windows (SPSS Inc., Armonk, New York, USA) will be used for data analysis. Baseline demographic characteristics on categorical variables such as gender will be assessed for balance between the two treatment groups via the chi-square test. Continuous or interval variables (e.g. age) will be assessed for equivalence between the treatment groups by t-test. Intention-to-treat analysis will be applied to outcome data to minimise bias due to withdrawals, all missing data will be replaced using the last observation carried forward. Continuous data will be presented as means and standard deviation (SD), or 95%
confidence interval (CI). All dichotomous data such as the percentage of participants achieving PASI 75 will be presented as risk ratio (RR) and 95% CI. Other outcomes (e.g. severity and QoL) will be assessed for equivalence in the two groups. Effects with P-values <0.05 will be considered statistically significant.

Reporting of results will be in accordance of the recommendations provided by the Consolidated Standards of Reporting Trials (CONSORT) (Schulz et al., 2010) and extensions of the CONSORT for both herbal interventions (Gagnier et al., 2006a) and pragmatic trials (Zwarenstein et al., 2008).

**Data security**

Information of the participants, including the administration of PSORI-CM01, instrument measures, AEs, laboratory reports and other relevant data will be documented in or attached to the case record form (CRF) and stored in the participant’s file in a locked filing cabinet. The filing cabinet will be accessible only to the researchers involved in the study. All corrections made to the CRF must be personally signed and dated by the person responsible. On all documents participants will be identified only by their study ID code. An end of study form will be completed for all participants in the study when they finish their final assessment or withdraw from the trial for any reason. Data from the participant files will be entered into a database on a password-protected computer accessible only to the researchers involved in the trial. Upon request of a regulatory authority or RMIT University HREC, the investigator will make available direct access to the source data and other trial-related records.
Table 7.6: Assessment measures and time points

<table>
<thead>
<tr>
<th></th>
<th>PASI</th>
<th>BSA</th>
<th>DLQI 29</th>
<th>Skindex 29</th>
<th>CM syndrome diagnosis</th>
<th>Medication and Health utilisation</th>
<th>Blood tests</th>
<th>Compliance</th>
<th>AEs of CHM and calcipotriol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre assessment (Visit 1/Week 0)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline assessment (Visit 2/Week 1)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliance assessment phone call (Week 2 and 4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Daily/weekly self-assessment during eight weeks treatment (Weeks 1-12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Mid-treatment assessment (Visit 3/Week 6)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Compliance assessment phone call (Week 8 and 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>End of treatment assessment (Visit 4/Week 12)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Daily/weekly self-assessment during eight weeks follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>End of follow-up assessment (Visit 5/Week 24)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

PASI, psoriasis area and severity index; BSA, body surface area; DLQI, dermatology life quality index; CM, Chinese medicine; AEs, adverse events.
7.5.10 Blood samples

The collection of blood samples from participants will occur at screening (−2 weeks), mid-treatment (6 weeks), post-intervention phase (12 weeks) and at the end of the follow-up period (24 weeks). Blood samples will undergo full blood count analysis, lipid levels, glucose levels as well as kidney and liver function. From the blood collected a sample will have the plasma separated and will be frozen for future assay measure of relevant cytokines showing possible involvement in psoriasis pathogenesis (see 7.6.8)(Michalak-Stoma et al., 2013). The sample results in the treatment group will be compared for each participant for each time point for any significant changes to concentrations. Similarly, the control group samples for each participant will be compared for any concentration changes between the three time points. Assay will be conducted using Bio-Plex® multi assay plexed kits and analysis will use Bio-Plex Data Pro™ software. Assays will be performed according to recommended protocols supplied by Bio-Plex®.

7.5.11 Clinical trial compliance

The clinical trial will be conducted according to the following guidelines:

- CPMP/ICH, Note for Guidance on Good Clinical Practice – Annotated with Therapeutic Goods Administration (TGA) comments (CPMP/ICH/135/95);
- CPMP/ICH, General Considerations for Clinical Trial (CPMP/ICH/291/95);
- CPMP/ICH, Statistical Principles for Clinical trial (CPMP/ICH/363/96);
- National Health and Medical Research Council, National Statement on Ethical Conduct in Research Involving Humans;
The clinical trial will be registered with the Australian New Zealand Clinical Trial Registry (ANZCTR) as well as under the TGA’s Clinical Trial Notification scheme.
Chapter 8 – Pilot study: operation, experience, baseline and preliminary safety data results

This chapter provides a summary of the operation of the pilot study to date, including issues encountered, potential implications and limitations of results, adverse events and future study plan. Future improvements to CHM studies are discussed as well as the preliminary feasibility of the pilot study design for repeat in a large-scale study. Resources such as study personnel, equipment and site location are discussed in relation to budget and planning for a large-scale study.

Due to the duration of treatment and follow-up required for each participant (6 months), the pilot study was still ongoing at the time of thesis preparation. Full result analyses were not available at the time of thesis submission and nor were there any interim efficacy results due to the blinded nature of the study. When all participants have completed study requirements, the data will be analysed and a manuscript reporting results prepared for publication in a peer-reviewed journal.

8.1 Recruitment

It was determined early in the study that email response to people’s email enquiries about the study rarely had a response back from interested participants, so instead they were phoned to discuss the trial further and screen for suitability. Throughout the recruitment phase, enquiry from potential participants was possible 24 hours 7 days a week; however, to ease scheduling and monitoring of participants, face-to-face assessments were only offered over six time periods (cohorts). Each of these face-to-face assessment periods spanned a week and potential participants were able to book a convenient day and time for screening during that week. This method meant relevant
assessments coincided at each time point, which eased tracking and follow-up and simplified the management of assessments. For example, to spread the workload, screening was done in a week when mid-treatment or end of treatment assessments of other cohorts was not required.

Following phone and/or face-to-face assessment there were two modes of exclusion possible:

1) Permanent: Those who were clearly not eligible due to inclusion/exclusion criteria were documented with exclusion reason and no further evaluation was required.

2) Temporary: Those who had potential to be eligible at future screening after change or clarification of their condition (see below) remained eligible for future participation and were invited to contact the research team when their condition may be suitable for inclusion.

Temporary exclusion was granted if: disease severity was too severe or too mild; topical, systemic or UVA/UVB therapy had recently been used; previous liver function disorder required physician consultation and clearance for inclusion; psoriasis vulgaris had not yet been medically diagnosed. This meant in some instances potential participants were screened on multiple occasions, either face-to-face or via phone during the recruitment period.

Face-to-face screening for the first cohort commenced on March 16th 2015 and the sixth and final cohort was screened on July 21st 2015. During this time there were 107 enquiries to participate. Cohort numbers gradually declined as trial recruitment period progressed, with the final cohort booking only three people. Of the 107 enquiries, 25 were unable to be reached for further screening, were uninterested in undergoing
further screening, or missed their screening appointment and were lost to further follow-up. The remaining 82 were screened further via phone and/or face-to-face assessment. Of these, 68 were excluded with the main reasons because: psoriasis symptoms were too mild (n=22); the location of the study site was too far (n=16); psoriasis was not vulgaris type (n=7); or they were unwilling or unable to stop current psoriasis-related medication (n=7) (Figure 8.1).

Fourteen participants were deemed eligible for the study and commenced the run-in phase. All fourteen participants had blood samples collected to assess their liver and kidney function. Of the fourteen, five returned abnormal liver function results and were referred to their treating physician for advice prior to continuing involvement in the study. After discussion with their physician, three of these participants withdrew during the run-in phase. After the run-in phase and baseline assessment, the remaining 11 were randomised and commenced their treatment phase. There were two dropouts during treatment phase, one before the week 6 mid-treatment assessment (due to work commitments and lack of time), the other was lost before the week 12 end of treatment assessment (Figure 8.1).

8.1.1 Advertisement

To attract participants during the recruitment period, various advertisement methods were employed. Initially a webpage was set up through the RMIT University website (Appendix 6), which provided a brief overview of the study and contact information for those interested in involvement. The webpage aimed to be an information source available to the public 24 hours a day. Advertisements were then arranged for local newspapers, RMIT staff newsletters, Google ad words and via link to webpage on a number of social network applications (Facebook, Twitter and LinkedIn) (Appendix 6).
A press release was provided by RMIT University's Marketing and Communication department, which was picked up by SBS radio and an online source providing further free exposure. An interview for SBS radio attracted a small influx of interest (n=3), however these were not located in the local area so were unable to participate.

Overall, there were nine enquiries from Internet advertisements and other online sources, however again they were typically not from the local area. Further free exposure was gained through a number of local newsletters. Recruitment posters were also printed and displayed at RMIT University Bundoora and Melbourne city campuses, with tear-off tabs detailing email, phone and website link for further details about the study (see Table 8.1) (Appendix 10).
Where possible, on first contact participants were asked how they heard about the study. The majority did not supply further information or were unsure (n=48); however,
of those who did respond, newspaper advertisement (n=22) and recruitment posters (n=17) proved to be most effective. Five newspaper advertisement campaigns were run over the recruitment period targeting a variety of regional papers. Newspapers closest to the study site provided half the enquiries (n=9) with the remaining three campaigns attracting the rest.

Table 8.1: Trial advertising strategy recruitment numbers

<table>
<thead>
<tr>
<th></th>
<th>Newspaper</th>
<th>Social media</th>
<th>Posters</th>
<th>SBS radio</th>
<th>Other</th>
<th>Unsure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of enquiries received</td>
<td>22</td>
<td>9</td>
<td>17</td>
<td>3</td>
<td>10</td>
<td>46</td>
<td>107</td>
</tr>
<tr>
<td>Number of potential eligible volunteers</td>
<td>11*</td>
<td>2*</td>
<td>10*</td>
<td>0</td>
<td>4*</td>
<td>10*</td>
<td>37*</td>
</tr>
<tr>
<td>Number of final included participants</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>14</td>
</tr>
</tbody>
</table>

*Booked for face-to-face screening

8.2 Monitoring

Participants were regularly monitored for relevant efficacy and safety assessment throughout the study, with communication at least fortnightly. Further communication between allocated assessments occurred via phone and email, with participants free to contact the study co-ordinator at any time. Before each face-to-face assessment participants were sent an email containing relevant information regarding their upcoming assessment, including appointment booking date, time and location as well as preparation instructions prior to assessment, such as fasting and completion of study diaries. A mobile phone text message reminder was also sent to participants the day before their assessment, ensuring appointment attendance and to remind them to bring their study diary, remaining medication, and/or fast for the 12 hours prior to their visit.
Regular monthly reports were prepared for study investigators informing them of recruitment numbers, dropouts and adverse events. Study investigators were contacted in instances where the protocol and/or standard operating procedures were breached to determine any necessary action. As discussed, participants who returned abnormal liver function pathology results were referred to their GP, who assessed their safe continuation in the study and monitored their follow-up blood tests (weeks 6, 12 and 24).

8.3 Adverse events

Adverse events were self-reported daily in participant study diaries, as well as over the phone during compliance and safety assessments and fortnightly to assessors at face-to-face assessments. At this stage no serious adverse events or incidences threatening participant safety have occurred, in which case information would be sent to the study investigators then, if deemed necessary, forwarded to the Data & Safety Monitoring Committee for recommended action, such as sending a report to the RMIT HREC and TGA (National Health and Medical Research Council, 2009).

Adverse events were reported by participants during both the run-in phase and treatment phase (Table 8.2). Only two people rated their adverse event as severe, one during the run-in phase reporting severe stress for two days and another who reported instance of severe itch during the treatment phase that lasted one day, but did not require medical intervention. Itch was the most common AE reported by participants (n=4). Incidence of itchy rash may be related to the calcipotriol as it is indicated as a potential side effect of its use (Leo Pharmaceutical Products Ltd A/S, 2002).
Both participants who reported nausea experienced it in weeks 1 or 2 of treatment, with one reporting it moderate severity, however there were no further reported incidents of nausea during the treatment phase. Due to previous review of AE reports in CHM (see chapters 3 and 4), investigators considered the nausea could possibly be associated with the PSORI-CM01 intervention. Runny nose was reported by one participant that then progressed to hayfever symptoms. Participant report indicated all adverse events to be relatively short term and only one participant requiring medical intervention as a result of an adverse event. This participant reported a moderate burning skin sensation after applying calcipotriol for the first time however the symptoms subsided and did not reoccur with further calcipotriol use.

At this stage, due to the blinded nature of the study it is unclear whether adverse events are related to PSORI-CM01 or the placebo group.

Table 8.2: Number of participants reporting adverse events during the run-in and treatment phase

<table>
<thead>
<tr>
<th>Reported adverse event</th>
<th>Run-in phase (week -2 to week 0)</th>
<th>Treatment phase (Week 1 to week 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>3 (2 mild, 1 moderate)</td>
<td>3 (2 mild, 1 moderate)</td>
</tr>
<tr>
<td>Stress</td>
<td>1 severe</td>
<td>-</td>
</tr>
<tr>
<td>Itch</td>
<td>2 mild-moderate</td>
<td>4 (2 mild, 1 moderate, 1 severe)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 mild</td>
<td>3 mild</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 mild</td>
<td>1 mild</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 mild</td>
<td>-</td>
</tr>
<tr>
<td>Abdomen pain</td>
<td>1 mild</td>
<td>-</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 mild</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>2 (1 mild, 1 moderate)</td>
</tr>
<tr>
<td>Runny nose</td>
<td>-</td>
<td>1 mild</td>
</tr>
<tr>
<td>Hayfever</td>
<td>-</td>
<td>1 mild-moderate</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>-</td>
<td>1 mild</td>
</tr>
<tr>
<td>Tiredness</td>
<td>-</td>
<td>2 mild</td>
</tr>
<tr>
<td>Thirst</td>
<td>-</td>
<td>1 mild</td>
</tr>
<tr>
<td>Sensation of burning skin</td>
<td>-</td>
<td>1 moderate</td>
</tr>
</tbody>
</table>
8.4 Current progress report and ongoing operation

Currently nine participants have completed the follow-up phase and all eleven participants have completed treatment phase. In November the Guangdong Provincial Academy of Chinese Medical Sciences commenced operation of a second site and will recruit remaining participant numbers. The protocols remain the same for the Guangdong site and data will be pooled for analyses. Participants will continue in the study until the last participant completes their follow-up phase, at which point data will be sent to a statistician who is blinded to group allocation for analysis. Blood samples will be further analysed for concentration changes in cytokines using the Bio-Plex® MAGPIX™ Multiplex Reader. Once all data have been analysed a manuscript reporting results of the study will be prepared and submitted to a peer-reviewed journal for publication.

8.4.1 Participant characteristics at screening (week -2) and baseline (week 0) assessments

Characteristics of participants assessed as eligible who undertook the run-in phase and those that continued on to randomization are shown in table 8.3. The average age of participants screened as suitable was 44.7±14 years of age and the male to female was 50:50, with majority of participants being born in Australia (n=9) and one each from South Africa, South Korea, China, Malaysia and India. The average BMI of included participants at screening was 25.7±4.1. This BMI is classified by the WHO as overweight (World Health Organization, 2006). Mean systolic and diastolic blood pressure was 130/82, which place the participant mean in to the prehypertension range according to NIH recommendations (National Institute of Health, 2015) (Table 8.3).
For psoriasis severity the mean PASI score at screening was 8.7±1.3 and BSA was 9.1±4, and at the end of the run-in phase PASI mean had risen to 9±2.4 whilst BSA had decreased to 7.8±3.3 Photographic examples of a participant’s lesion change are shown at screening (week -2), baseline (week 0), mid treatment (week 6) and end of treatment (week 12) in figure 8.2.

**Figure 8.2:** Example lesion change photos  
A, Week -2; B, Week 0; C, Week 6; D, Week 12
The average age of onset at screening was 22.4±14.4 years of age, with the age of psoriasis diagnosis on average similar at 23.4±15 years. For QoL mean DLQI was 8.7±1.3 at screening compared to 9±2.4 at week 0. For Skindex 29 the mean domain for symptoms reduced (week-2 = 398 vs. week 0 = 377) whilst means increased for both the emotions (487->507) and functioning (377->463) domains.

Of the 14 participants screened as eligible, 10 had previously used Chinese medicine and of these seven had utilized it for their psoriasis. Of the 10 who had previously used Chinese medicine three had utilized acupuncture, two CHM and four had used a combination of the two modalities. Eight of the 14 eligible had no previous family history of psoriasis and eight had no previous history of smoking. Both family history and smoking have significant evidence to indicating they increase the likelihood of psoriasis development (Mahil et al., 2015) (Armstrong et al., 2013). Almost all the participants consumed alcohol (n=12) and five of these indicated 2-3 days per week or more alcohol consumption. Six of the eligible stated they had 3 or more standard drinks on each occasion of alcohol consumption. Three people reported having more than four standard drinks in a day at least once per week or more. Excessive alcohol consumption has also been linked to psoriasis development and symptom exacerbation (Richard et al., 2013).

<p>| Table 8.3: Participant characteristics at screening and baseline assessments |
|-------------------------------------------------|-----------------|-----------------|
| <strong>Screening (week -2)</strong> | <strong>Baseline (week 0)</strong> |
| Age (mean±SD) | 45±13.9 | 45±14.4 |
| Gender M/F | 7/7 | 6/5 |
| Country of birth | Au=9, SA=1, SK=1, C=1, MA=1 | Au=6, SA=1, SK=1, C=1, MA=1 |
| Weight (kg) (mean±SD) | 73.8±9.4 | 73.3±9 |
| Height (cm) (mean±SD) | 170±7.8 | 171±7.3 |
| Blood pressure systolic (mean±SD) | 130±12.9 | 127±10.8 |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SD</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure diastolic (mean±SD)</td>
<td>82±8.6</td>
<td>81±9.3</td>
</tr>
<tr>
<td>Aortic systolic pressure (SP) (mean±SD)</td>
<td>113±31.3</td>
<td>117±10.6</td>
</tr>
<tr>
<td>Aortic diastolic pressure (DP) (mean±SD)</td>
<td>83±9.4</td>
<td>82±9.6</td>
</tr>
<tr>
<td>Aortic mean arterial pressure (MAP) (mean±SD)</td>
<td>99±9.4</td>
<td>96±9.7</td>
</tr>
<tr>
<td>Aortic pulse pressure (PP) (mean±SD)</td>
<td>37±6.5</td>
<td>34±7.1</td>
</tr>
<tr>
<td>Aortic heart rate (HR) (mean±SD)</td>
<td>71±7.7</td>
<td>74±11.7</td>
</tr>
<tr>
<td>Aortic augmented pressure (AP) (mean±SD)</td>
<td>12±4.8</td>
<td>9±6.5</td>
</tr>
<tr>
<td>Aortic augmentation index (Alx) (mean±SD)</td>
<td>32±9.1</td>
<td>25±15.8</td>
</tr>
<tr>
<td>Body Mass Index (BMI) (mean±SD)</td>
<td>26±4.1</td>
<td>25±3.5</td>
</tr>
<tr>
<td>Psoriasis Area Severity Index (PASI) (mean±SD)</td>
<td>8.7±1.3</td>
<td>9±2.4</td>
</tr>
<tr>
<td>Body Surface area (BSA) (mean±SD)</td>
<td>9.2±4.1</td>
<td>7.9±3.3</td>
</tr>
<tr>
<td>Dermatology Life Quality Index (DLQI) (mean±SD)</td>
<td>8.3±5.6</td>
<td>10±7.6</td>
</tr>
<tr>
<td>SKINDEX 29 - Symptoms</td>
<td>398±125</td>
<td>377±125.7</td>
</tr>
<tr>
<td>- Emotions (mean±SD)</td>
<td>487±232</td>
<td>507±234.8</td>
</tr>
<tr>
<td>- Functioning (mean±SD)</td>
<td>377±284.1</td>
<td>463±301.1</td>
</tr>
<tr>
<td>Previous use of Chinese medicine (Yes/No)</td>
<td>10/4</td>
<td>8/3</td>
</tr>
<tr>
<td>If yes, was it for psoriasis (Yes/No)</td>
<td>7/3</td>
<td>5/3</td>
</tr>
<tr>
<td>Previous form of Chinese medicine (ACU/CHM/Both)</td>
<td>3/2/4</td>
<td>3/2/3</td>
</tr>
<tr>
<td>Age of onset of psoriasis (mean±SD)</td>
<td>22.4±14.4</td>
<td>22.4±13.6</td>
</tr>
<tr>
<td>Age of diagnosis of psoriasis (mean±SD)</td>
<td>23.4±15</td>
<td>23.5±14.4</td>
</tr>
<tr>
<td>Family history of psoriasis (Yes/No)</td>
<td>6/8</td>
<td>3/8</td>
</tr>
<tr>
<td>Smoking status (Never/previous/current)</td>
<td>8/3/3</td>
<td>6/2/3</td>
</tr>
<tr>
<td>Drinks alcohol (Yes/No)</td>
<td>12/2</td>
<td>10/1</td>
</tr>
<tr>
<td>Drinking frequency (Daily or most days/2 – 3 days per week/Once per week/2 – 3 days a month/Less often)</td>
<td>2/3/1/1/5</td>
<td>2/2/1/1/4</td>
</tr>
<tr>
<td>Average drinks per drinking occasion (5 or more/3 – 4 /1– 2)</td>
<td>2/4/6</td>
<td>2/3/4</td>
</tr>
<tr>
<td>Over the last 12 months or so, how often had more than 4 standard drinks in a day? (Daily or most days/2 – 3 days per week/Once per week/2 – 3 days a month/Less often)</td>
<td>0/2/1/2/7</td>
<td>0/2/1/2/5</td>
</tr>
</tbody>
</table>

Au, Australia; C, China; cm, centre mitre; F, female; kg, kilogram; M, male; MA, Malaysia; SA, South Africa; SD, standard deviation; SK, South Korea;
8.4.2 Medication use at screening and during the run-in phase

At screening three included participants were taking other non-psoriasis related medication. One person was taking coveram 10mg per day and eutroxsig 150mg per day which are commonly prescribed for high blood pressure and hypothyroidism (Servier Research International, 2013, Therapeutic Goods Administration, 2015) However this participant dropped out during the run-in phase prior to randomization. Another person was taking anti-seizure (topomax 50mg per day) (JANSSEN-CILAG Pty Ltd, 2015), anti-depressant (lovan 60mg per day) (Alphapharm Pty Limited, 2013), antacids (zantac 120mg per day and pantorazole 40mg per day) (Aspen Pharmacare Australia Pty Ltd, 2012, Amneal Pharma Australia Pty Ltd, 2015). A third participant was taking thyroxine 75mg per day for hypothyroidism.

Other medications used during the run-in phase included analgesics paracetamol, ibuprofen and codeine but were not administered for psoriasis related symptoms. Two participants utilized topical psoriasis related therapy during the run-in phase despite instruction not to. One applied hydrocortisone acetate 0.5 fingertips (day 11) to the face and groin area due to unhappiness with the appearance and another applied a combination of 50% topical corticosteroid with 50% savlon at day 6 (two fingertips), 7 (three fingertips) and 8 (three fingertips) to groin area where skin was causing discomfort from cracking.

During the run-in phase, prior to randomization and administration of any study drug, participants experienced various symptoms. One person reported difficulty sleeping but did not rate the severity, whilst another also reported difficult sleeping on one occasion due to pruritus. This same person reported pruritus regularly on various limbs throughout the run-in phase, which was reported as mild to moderate in severity. Other mild symptoms reported included headache by three people, diarrhoea by one
person and dizziness by one person. Only one person reported any abnormal symptoms as severe, reporting stress on days one and two of the run-in phase.

8.4.3  Pathology results for blood samples at screening

All participants assessed as eligible at screening had three blood samples collected. One sample had plasma separated and stored, to be analysed at a later date for cytokine concentrations. The other two samples were sent to a pathology laboratory where blood examination was undertaken, as well as examination of fasting glucose, liver function and kidney function. Results are presented in Table 8.4. Lipid concentrations were also assessed to evaluate cholesterol levels, as well as triglyceride, HDL, LDL, non-HDL and the cholesterol to HDL ratio (Table 8.5).

Blood tests at screening identified one participant diagnosed with mild anaemia at screening (Haemoglobin: 12.9, RCC: 4.38, MCHC: 31.2), but no added risk to participation was identified so they continued to randomization. Another participant was diagnosed with mild eosinophilia (eosinophils 1.2), but was also randomized following the run-in phase. Blood test results of five out of the 14 people reported abnormal liver function. Three of these became dropouts, which after discussing their abnormal liver function results with their treating physician elected not to continue in the study. However two participants after discussion with their physician continued the study to the randomization phase. All three dropouts during the run-in phase were due to abnormal liver function results.

Table 8.4: Blood pathology analyses of participants at screening (week -2) (mean±SD)

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean (standard deviation)</th>
<th>Test</th>
<th>Mean (standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>141 mmol/L (2.4)</td>
<td>Glucose mmol/L (fasting)</td>
<td>5.2 (0.4)</td>
</tr>
<tr>
<td>Test</td>
<td>Value</td>
<td>Reference Range</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>4 mmol/L (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>105 mmol/L (2.1)</td>
<td>WCC (x10⁹/L) 6.6 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>30 mmol/L (1.7)</td>
<td>Platelets (x10⁹/L) 269 (46.3)</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>5 mmol/L (1.4)</td>
<td>PCV (%) 44 (3.9)</td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>89 mL/min (2)</td>
<td>RCC (x10¹²/L) 4.9 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>66 umol/L (14.9)</td>
<td>MCV (fL) 90 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>11 umol/L (3.6)</td>
<td>MCH (pg) 29.8 (1.3)</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>27 U/L (14)</td>
<td>MCHC (g/dL) 33 (0.8)</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>24 U/L (5.5)</td>
<td>RDW (%) 13.6 (0.8)</td>
<td></td>
</tr>
<tr>
<td>ALP</td>
<td>79 U/L (26.4)</td>
<td>Neutrophils (x10⁹/L) 3.8 (1.2)</td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td>34 U/L (30)</td>
<td>Lymphocytes (x10⁹/L) 2.1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Total protein</td>
<td>72.6 g/L (3.1)</td>
<td>Monocytes (x10⁹/L) 0.5 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>45.8 g/L (2)</td>
<td>Eosinophils (x10⁹/L) 0.2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Globulin</td>
<td>27 g/L (2.1)</td>
<td>Basophils (x10⁹/L) 0.0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

ALP, Alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; MCH, Mean corpuscular haemoglobin; MCHC, Mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; PCV, packed cell volume; RCC, red cell count; RDW, red cell distribution width; WCC, white cell count.

Shown increasing evidence in recent years is a greater risk in psoriasis sufferers to metabolic disease comorbidities such as cardiovascular disease (Puig et al., 2014). Cholesterol was measured at screening for eligible participants to evaluate if cholesterol levels were within recommended levels. Mean total cholesterol was 5.6 (0.9) well above the recommended limit for primary cardiovascular disease prevention (<4.0) (Tonkin et
al., 2005), means were also elevated for LDL 3.3 (0.9) (<2.0) and Non-HDL 3.9 (1.0) (<2.5). Only HDL 1.7(0.4) was in the recommended range for primary prevention (≥1.0) (Tonkin et al., 2005)(Table 8.5).

Table 8.5: Blood lipid analyses of participants at screening (week 0) mmol/L (mean±SD)

<table>
<thead>
<tr>
<th>Total Chol</th>
<th>Triglyceride</th>
<th>HDL</th>
<th>LDL</th>
<th>Non-HDL</th>
<th>CHOL/HDL (Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6 (0.9)</td>
<td>1.3 (0.6)</td>
<td>1.7 (0.4)</td>
<td>3.3 (0.9)</td>
<td>3.9 (1.0)</td>
<td>3.6 (1.3)</td>
</tr>
</tbody>
</table>

Chol, cholesterol; HDL, high-density lipoproteins; LDL, low-density lipoproteins

8.4.4 Preliminary analysis of Th-17 pathway cytokines

As the study is ongoing not all participant plasma samples are yet collected. At the time of preparing this thesis the baseline samples had been analysed for the 11 participants randomised to date.

Sample preparation involved collection of a 5mL blood sample collected in an ethylenediaminetetraacetic acid (EDTA) coated vacutainer. The vacutainer was stood at room temperature for 30 minutes before being centrifuged at 1000 revolutions per minute (rpm) at four degrees Celsius (C) for 15 minutes with deceleration set to six. The sample was then separated from the palate using a pipette into a sterile centrifuge tube and centrifuged again at 4C but for 10 minutes at 3000 rpm and deceleration 6. The plasma was then again separated from the palate using a pipette this time into 2mL cryovial tube where they were stored in the freezer at -80C until day of assay (Figure 8.3).
The assay was run in a 98 well Bio-Plex® 4-plex according to the Bio-Plex® protocols supplied with the assay kit. Samples were thawed, vortexed and kept on ice then 50 μL of each sample was pipetted to be run at three concentrations (1:1, 1:2 and 1:4). Eight standards were used to develop the standard curve and two non-disease samples were used as controls, again at the three concentrations. Each standard, unknown and control was assayed in duplicate. The 4-plex consisted of Th17 pathway cytokines IL-17F, IL-21, IL-23 and IL-31.

Wash step used the Bio-Plex Pro™ Wash Station and once plate shaking and incubation was complete results were read using MAGPIX™ Multiplex Reader and analysed using Bio-Plex Manager software using a detection target of 50 beads (Figure 8.4).
Figure 8.4: Serum sample analysis using Bio-Plex® MAGPIX™ Multiplex Reader and Bio-Plex Manager software

Any points from the standard curve that had accuracy outside 70-130% range were excluded. Using the software's optimization setting the curve was set to the standards (Figures 8.5 A-D).

![Graph showing standard curve of sample results for IL-17F](image)

Figure 8.5A: Standard curve of sample results for IL-17F
- **Standard**
- **Partial Outlier**
- **Outlier**
Figure 8.5B: Standard curve of sample results for IL-21

- **Standard**
- **Partial Outlier**
- **Outlier**

---

Figure 8.5C: Standard curve of sample results for IL-23

- **Standard**
- **Partial Outlier**
- **Outlier**
Bead count for all samples was well over the required 50 with the mean bead count of the unknown samples 388 (87). All unknown samples had concentrations detected of the target cytokines at the lower end of their standard curves.

For IL-17F two participant samples (both 1:1 concentration) presented an observed concentration over 100, remaining samples all had observed concentrations under 50 (Figure 8.6A). Three samples showed observed concentrations over 100 for IL-21 the rest were under 100 with two samples not reported having concentration within range. Only one sample had a concentration within detectable range at a 1:4 dilution (Figure 8.6B). Two samples had observed concentrations above 100 for IL-23, whilst three samples did not have detectable observed concentrations (Figure 8.6C). All samples detected a relatively low observed concentration of IL-31, however no samples were outside the detected range at a 1:1 dilution ratio (Figure 8.7D).

Figure 8.5D: Standard curve of sample results for IL-31
- Standard
- Partial Outlier
- Outlier
**Figure 8.6A:** Observed concentration of IL17F in plasma samples IMPPS, study ID; C, control

**Figure 8.6B:** Observed concentration of IL-21 in plasma samples IMPPS, study ID; C, control
Figure 8.6C: Observed concentration of IL-23 in plasma samples
IMPPS, study ID; C, control

Figure 8.6D: Observed concentration of IL-31 in plasma samples
IMPPS, study ID; C, control
8.5 Feasibility of the trial protocol

Full assessment of feasibility awaits conclusion of the pilot study, however early indication for large-scale study scope is positive. This section evaluates feasibility of the study to date.

8.5.1 Advertising methods for recruitment and feasibility of inclusion/exclusion criteria

Advertisement

Advertisement for the pilot appeared suitable to attract interest, with the number of enquiries exceeding the target sample size by more than three times. It should be noted, though, that the enrolment rate (13%) was lower than anticipated, estimated on previous experience of psoriasis severity. To recruit 30 participants using the current protocol would require 231 enquiries. Like the pilot, a future large-scale study would best utilise a mixture of advertisement types, in particular local newspaper advertisements near to study sites, online social media and poster display at study site locations.

Inclusion and exclusion

The pilot study indicated restrictions (exclusion) and requirements (inclusion) for participant involvement in the study did not appear to greatly affect participants’ willingness to participate. However, for the majority of interested participants, inclusion/exclusion criteria were limiting factors, deeming many ineligible. For the 14 who did remain eligible, over one-third (n=5) returned abnormal liver function results, and although two of the five were cleared to continue, in a large-scale study such liver function results would impact (on 20% of recruited participants) on retention and should be factored into sample size calculations.
There is concern over the current PASI severity for inclusion as discussed in more
detail in 8.6: Study limitations and further improvement. To reach a larger sample
target it is likely the PASI inclusion would need to be lowered slightly.

8.5.2 Feasibility of the study protocol

Study length and participant continuation

With the addition of the follow-up period, participation in the study required
participant commitment of over six months. So far from pilot assessment, long-term
study commitment does not appear to be a factor reducing willingness to participate or
impact retention, indicating the duration of the pilot is feasible. Assessment frequency
and timing of such assessments also appear to be acceptable to participants.
Throughout the pilot, in instances when participants were expected to be unavailable
for assessment, their commencement and assessment dates were adjusted. A large-scale
study should similarly allocate assessment dates early in the study so participants can
arrange their work and holiday schedules around these dates.

Tolerance of PSORI-CM01 and its placebo

The granulated powder forms of PSORI-CM01 and placebo have been well tolerated
through the study thus far. Some participants expressed mild distaste of the allocated
oral formulation on initial consumption. The pilot is still currently blind, so we do not
know which group these people were allocated to. Distaste, however, has not prevented
participants from consuming their allocated oral formulations and generally after less
than a week participants reported no further issue.

Feasibility of the control

Use of calcipotriol as the control for the study has not resulted in any withdrawals or
refusals to therapy. The topical conventional therapy (calcipotriol) has been well
tolerated and appears to be suitable for future large-scale study use. There were some participants who expressed initial lack of confidence using calcipotriol, informing the dispenser that due to previous lack of efficacy in use they doubted it would have sufficient efficacy. Despite doubts, no participant refused calcipotriol use, and most applied it according to supplied instructions for recommended dosage and administration.

It was noted during the study that sufferers commonly had psoriasis plaques located on their scalp and as calcipotriol cream is unsuitable for scalp application these lesions did not receive conventional treatment in either group. A large-scale study might consider addition of a scalp-suitable form of calcipotriol or another suitable intervention for participants affected by scalp lesions. However, the limitation of calcipotriol use did not impact on compliance, retention or willingness to participate.

*Feasibility of chosen outcome measures*

The instruments utilised by the pilot to measure outcomes were administered without issue; however, a full-scale study might consider inclusion of other secondary outcomes for psoriasis severity. While collection of plasma samples for analysis of cytokine changes was possible for the pilot, for a full-scale study the costs of running such a large analysis would restrict samples from undergoing the same level of assessment. A full-scale study would need to receive considerable funding to carry out the same range of cytokine assessments as the pilot study. The solution may be to reduce the number of cytokines being measured, from the broad cytokine analysis in the pilot to one or two targeted cytokines evidenced from the pilot to have further investigation promise.

*Feasibility of cytokine testing*

Baseline assay results indicate a 1:4 dilution is not necessary due to the low concentrations of cytokines. Future assay of plasma should utilize 1:1 or 1:2 dilutions in
the assay. Due to the low concentrations 7-8 standards is most likely sufficient for the sample type and cytokine concentrations. Future assay should consider further centrifuge of the plasma samples after thawing with pipette separation prior to being added to the assay.

8.5.3 Feasibility of trial operation, equipment and resources

Site location and equipment

The study site location, RMIT University School of Health Sciences Research Hub, Bundoora, Victoria, has been a suitable site location, having the necessary equipment and facilities to conduct the pilot. A private room was available to assess psoriasis severity and conduct assessments, with equipment on site to measure blood pressure, height, weight and to draw blood. It is unlikely a multiple-site, large-scale study would have the same level of facilities available at all sites, so logistics would need to be considered to ensure minimal inconvenience to participants and study staff at assessment time points. Considering the current pilot has only one site, additional study sites at other locations would attract greater participant numbers.

If any physicians showed interest in being involved in the research, a large-scale study might consider potential study site extension to include dermatology and/or GP clinics. Such sites also have the potential to provide a further source of participants and could provide trained on-site staff with the skills required to undertake many of the study tasks. Chinese medicine clinics may also be considered as potential site recruitment and assessment centres.

A second site at Guangdong University and Provincial hospital is being implemented to recruit the remaining subject numbers. Same protocol will be implemented at China site and all outcome measures will be identical. Sub group
analysis will be conducted to evaluate any site difference prior to pooling of data. A site visit will also be conducted at the China site to ensure it operates consistently with the Australian site and data is recorded correctly. Data from both sites will be merged into the same excel template.

**Study personnel**

Primarily, one research assistant performed all tasks for the current pilot study. Due to the amount of work required for phone follow-ups, face-to-face assessments, screenings, blood processing and other study-related activity, it is estimated that if there were 20 or more participants enrolled at any one point extra staff would be required. For a large, multi-site study, further research staff would be required based on the target sample and recruitment rate. Required skills of these additional staff would depend on the requirements of staff at each given site, which would relate to equipment available at and activities performed, i.e. venepuncture, blood centrifugation and transfer, medication dispensing.

Some activities such as blood collection may be outsourced to external facilities such as pathology centres. Indeed, external site blood collection has occurred on occasion during the pilot. For example, if a participant forgot to fast or bloods were unable to be withdrawn at the time of assessment, participants were referred to their local pathology collection centre for blood drawing and results sent back to the research team. Assessment of each study visit takes between 1 and 2 hours, and blood sample separation and processing requires a further 1–2 hours. This reduces the number of participants a research assistant can process to approximately 2–3 per day.

**Budget feasibility**

The current pilot study has thus far been conducted below the anticipated budget, mostly due to the reduced sample size. So far there have been no unexpected costs,
however advertising budget was increased slightly to attract further suitable participants. However, advertisement costs could be minimised if screening inclusion criteria for PASI were adjusted to include more potential participants.

8.5.4 Conclusion of feasibility

When the study is complete, further assessment of pilot data will be undertaken; however, preliminary findings suggest modifications to inclusion/exclusion criteria and an increase in staffing levels and site locations for full-scale study feasibility.

8.6 Study limitations and further improvement

The main limitation encountered during this study was difficulty achieving the recruitment target (n=30). While there was high interest and number of enquiries, the majority of those screened were not eligible. The most common reason for exclusion (n=27) was a failure to meet the required PASI score range (7–12), most (n=22) being too mild. Had this criterion been adjusted and the study open to all PASI score levels, the recruitment target would have been met with an enrolment rate of 38% (n=41). Allowing for 20% dropout, this would still have supplied the required target (n=32).

In fact, during face-to-face screening, it became apparent that the sensitivity of PASI for mild conditions was poor, with many sufferers with substantial size lesions on one or two regions of the body not meeting the PASI minimum (PASI 7) required. Sufferers with large lesions on visible areas such as the lower arms or hands scored lower PASI than those with small, more hidden lesions on multiple body regions such as the back, upper legs and scalp. It was clear in some instances that sufferers with PASI scores not reaching the required threshold still had significant psoriasis severity. Further, it was noted that people more commonly presented with lesions on one body region than with smaller lesions on multiple body regions.
The required PASI range (7–12) appeared to be very sensitive, yet PASI lacked the same sensitivity below 7, with erythema, induration and scaling having less effect on overall PASI score. The sensitivity of the PASI 7–12 range seemed to make inclusion difficult, as changes in same symptoms had too great an effect, pushing people above the range. While PASI 12 seemed to be an appropriate maximum severity cut-off for this study intervention, minimum severity would have been more appropriately set to around PASI 4, as people with this score tended to report psoriasis impact similar to people in the PASI 7–12 range. For example, the most characteristic presentation of psoriasis vulgaris is plaques on the extensor surfaces of elbows and knees; however, such location with moderate to severe severity was not sufficient in PASI score to be included in the current pilot study (see Figure 8.7 example).

Figure 8.7: Example PASI score of typical psoriasis located on elbows and knees with moderate to high scores for erythema, induration and scaling
Chapter 9 – Summary of main findings and discussion

This chapter summarises the main findings of each chapter of the thesis. It details a summary first of the systematic review findings and their implications for clinical practice and research. It then provides a summary of conducting the pilot study to date and the implications of the study’s strengths and weaknesses for further research.

9.1 Main findings of the systematic reviews

9.1.1 Findings of systematic review one: oral CHM vs. placebo

Results from the first systematic review indicated that oral CHM might bring mild to moderate improvement to psoriasis symptoms when compared with placebo. The general quality of the reviewed studies was low and reporting was poor. It was difficult to determine how each CHM intervention was selected and which were most effective. The most common CHM ingredients utilised in reviewed studies were salvia miltiorrhiza, angelica sinensis and rehmannia glutinosa. Use of oral CHM alone appears to be safe, with predominantly minor adverse events reported and moderate side effects rare. There was little follow-up data available to evaluate long-term effects of oral CHM for psoriasis.

9.1.2 Findings of systematic review two: oral CHM combined with conventional therapy vs. conventional therapy

The second systematic review and meta-analysis revealed an enhanced effect of oral CHM on psoriasis when combined with conventional therapy. The majority of trials investigating combined therapy utilised systemic drug acitretin or topical vitamin D analogue calcipotriol. Compared with conventional therapy alone, CHM appeared to increase therapeutic effects and reduce adverse effects. The most common herbs used
in combination with conventional therapy were *rehmannia glutinosa (shu di/di huang)*, *salvia miltiorrhiza (dan shen)* and *lithospermum erythrorhizon (zi cao)*. Chinese herbal medicine ingredients varied significantly and made it difficult to determine which have the greatest efficacy for psoriasis. Certain herbs (*salvia miltiorrhiza (dan shen)*, *angelica sinensis (dang gui)* and *rehmannia glutinosa (shu di/di huang)*) were utilised more often than others in interventions, indicating these herbs may have greater therapeutic effect than others. There was considerable variation between the reported participant syndrome types amongst the reviewed studies, but many studies did not stipulate how they determined syndrome, so results for syndrome efficacy had to be considered with caution.

The review indicated that in some instances oral CHM has potential to impact liver function, with degree of risk likely dependent on the type of CHM being utilised. It was unclear from results which CHM ingredients have greatest risk. Otherwise, adverse event risk is mild to moderate and evidence suggests oral CHM may act as a preventative of side effects for some conventional therapies.

**9.1.3 Implications of the reviews for clinical practice**

Generally, there appears a benefit of adding CHM to conventional therapy and physicians should consider integrating oral CHM with ongoing conventional therapy. For instance, to enhance outcomes for patients, physicians who prescribe systemic drug acitretin or topical calcipotriol should consider referral for oral CHM therapy. Until long-term safety data are available, clinicians utilising oral CHM should consider short-term (8–12 weeks) administration in patients for psoriasis. Similarly, until further toxicity data are available, physicians of psoriasis sufferers with decreased liver function should carefully consider use of specific CHM to minimise additional impact on
the liver. Where possible, through blood pathology, physicians are encouraged to monitor liver function and evaluate any changes, especially for people with a history of long-term use of systemic psoriasis treatments, such as methotrexate, which is known to directly damage liver function.

9.1.4 Implications of the reviews for further research

The quality of design of the reviewed studies was generally low, thus more high quality studies are needed. In addition, variation in outcome measures between studies meant some were unable to be pooled for meta-analysis. Future research studies should determine methodological design according to CONSORT recommendations to ensure repeatability of studies, minimise risk of bias and allow for meta-analysis. Only some conventional therapies combined with CHM have sufficient data to evaluate their efficacy and safety, highlighting the need for more research to evaluate further conventional therapies combined with oral CHM.

The findings of the systematic reviews may help researchers identify previous CHM formulations that warrant further investigation for psoriasis for example Dai 2014’s Yinxieling formulation, which in meta-analyses results compared to placebo had the strongest effect size of the CHM (Dai et al., 2014b). In addition, repeat studies of CHM interventions would aid pooling of results data for comparison. Such data comparisons may provide evidence to support or refute previous findings, and may eventually lead to broad conclusive findings and recommendations for oral CHM therapy in psoriasis.
9.2 Preliminary findings of the pilot study

9.2.1 Findings from development of an oral CHM formulation for psoriasis vulgaris and the biological activity of its constituents

While the first developed formulation had theoretical basis to support its use, it had no RCT trial clinical evidence indicating its potential benefits for psoriasis. Investigation of the constituent compounds confirmed the ingredients had biological actions with potential anti-psoriatic activity. Considering the limited available resources and unknown prevalence of Chinese medicine syndrome types in the target population, rather than restrict sample size on such basis, the formulation was made to be suitable for all syndrome types. However, consultation with experts yielded recommendations to use an existing formulation that has substantial clinical and laboratory evidence of its efficacy for psoriasis.

Thus, the pre-existing formulation PSORI-CM01 was chosen for the pilot study intervention. Again, investigation of constituent compounds present in the seven included ingredients indicated potential actions similar to those of conventional anti-psoriatic therapies. The chief herb, chi shao, is sourced predominantly from two peony species, *P. lactiflora* and *P. veitchii*. The Radix Paeoniae Rubra (*chi shao*) produced from *P. veitchii* was found to be the form needed for the proposed formulation. The primary Chinese medicine actions of *chi shao* are to cool heat, cool blood and move blood. The conventional medical benefits of *chi shao* relevant to psoriasis are that it inhibits epithelial cell mitosis, reduces proliferating cell nuclear antigen expression, promotes epidermal cell differentiation, and acts as a sedative, analgesic, antipyretic, anti-inflammatory and vasodilator.
Ongoing conjecture exists surrounding the correct botanical source of PSORI-CM01’s principal CHM, *chi shao*. Furthermore, *bai shao* is often sold in the marketplace as *chi shao*, so distinguishing between each can be difficult. A review of the two common botanicals processed and sold as *chi shao*, *P. lactiflora* and *P. veitchii*, revealed they have some but not all constituents in common. Variation between the two species may have an intrinsic basis and/or be caused by environmental differences in the geographical regions of cultivation. The constituents of both botanicals showed evidence of anti-inflammation, anti-tumour, antibacterial, anti-viral and antioxidant-like activity, which are all pathways that have been implicated in psoriasis pathogenesis. Historical records and constituent features both suggested *P. veitchii* should be the source for *chi shao* in the PSORI-CM01 formulation.

9.2.2 Implication of the pilot study for further research

Although the pilot study results may impart some insights into clinical use of CHM alongside conventional treatments, the primary aim of the pilot is to inform a future adequately powered study. Thus, the current, ongoing pilot study is in the process of evaluating the feasibility and practicality of a larger study. After completion of data collection and analysis, results are hoped to help predict resources, equipment and methodology for a subsequent study. Improvements already suggested include modifying PASI score (to PASI 4–12 to improve targeting of mild-moderate symptoms, and also allow inclusion of more participants, thus increasing chances of reaching sample size targets. Similarly, increasing the number of study site locations may improve recruitment success.

Further research which might be prompted by the present pilot study results, include blood cytokine change with PSORI-CM01 treatment. Further scientific
investigation into the psoriasis-related biological pathway effects of cytokines may lead to development of new psoriasis drug treatments.

Further research is also needed into the effects of the sulphurisation process during bai shao processing. Evidence suggests that it does alter the constituent compounds; however, investigation is needed into how these changes affect the therapeutic and biological activity of bai shao for psoriasis disease, as well as safety to consumers. While a number of botanical species and interspecies variants have been evaluated for chi shao, research should continue to compare and evaluate botanical species for psoriasis efficacy. Further in vitro and in vivo investigation of botanical species may provide further indication of which is of most benefit to key psoriatic disease aspects such as inflammation and proliferation. There is also scope for investigating the potential benefits of these constituents for other diseases sharing similar pathways. Future studies should also investigate both granulated extracts and raw herb decoction to compare the efficacy and safety of each.

Another area of research that warrants further research is the effect of syndrome type on psoriasis treatment selection and efficacy. The PSORI-CM01 formulation was originally developed to be applicable to all syndrome types. Indeed, there is no current reliable and validated Chinese medicine syndrome instrument available for psoriasis. Development of such an instrument, plus more investigation into the effect of syndrome type on efficacy and safety of various CHM interventions are needed.

9.2.3 Strengths and limitations of the pilot study

The double-blinded, randomised, placebo-controlled trial study design is the most rigorous method to evaluate an intervention with low risk of bias. The present pilot study attempted to match the look, taste and smell of CHM and placebo treatments to
ensure participant blinding throughout the study. Thus far, participants have reported their perceived treatment group allocation is based on change or lack of change to clinical symptoms, not the features of the provided granules.

For CHM interventions, such rigorous RCT design can restrict potential efficacy of the intervention and may not reflect actual clinical effects. Allowing for syndrome in the study design allows Chinese medicine clinical relevance to be applied to results at analysis. Ideally, syndrome would be utilised to determine both CHM ingredient selection and dosage for each participant. With a much larger sample size and funding to develop and manufacture a range of formulations, such a study may be possible while maintaining rigour and minimising bias.

Another feature of the pilot study is that there is no change to intervention during the treatment period, which keeps participants and dispensers blinded and reduces potential risk of bias to treatment allocation. However, this design may limit the potential efficacy of the oral CHM, as Chinese medicine theory indicates maximum efficacy requires ongoing formula modification according to disease and syndrome change. While such a design would provide maximum efficacy of CHM treatment, it would also increase risk of bias through treatment allocation.

9.3 Conclusions

The current study and its protocol development were based on a culmination of systematic review findings. Literature reviews were undertaken in Chinese medicine and conventional psoriasis disease and treatment, CHM plus conventional treatment for psoriasis, and biological activity of common CHM constituents in psoriasis. The reviews indicated that oral CHM has benefit for psoriasis, particularly when combined with conventional therapy. Deficiencies in the quality of previous research meant that
findings could not be considered conclusive. Safety data, although limited, indicated low risk of adverse events, however long-term data are lacking.

Mild–moderate severity psoriasis vulgaris is the most common type and has limited oral therapeutic options. Here, an oral CHM evidence-based intervention (PSORI-CM01) was combined with conventional therapy calcipotriol in a randomised, double-blinded, placebo-controlled pilot study designed according to the most rigorous methods possible. The pilot study is ongoing; however, preliminary reports indicate the study design is well suited for use in a full-scale study.


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Appendices

Appendix 1 – Chinese medicine syndrome differentiation instrument

**CHINESE MEDICINE SYNDROME DIFFERENTIAL DIAGNOSIS QUESTIONNAIRE** (to be completed by a Chinese medicine practitioner)

<table>
<thead>
<tr>
<th>Differentiation of psoriasis Syndrome</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Wind-heat with Blood dryness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Plaques are in bright red colour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Plaques are currently in emerging stage (recent exacerbation of the plaques)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Increased erythema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Skin lesions appear at the site of irritation (Koebner phenomenon)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Irritability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Dry mouth and thirsty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Dry stool</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Dark colour urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(B) Blood Deficiency with Wind-dryness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Plaques are in pale red colour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Plaques may be in remission stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Large amount of scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Dry mouth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Dry stool</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C) Blood stasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Skin hypertrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Plaques are in dark red/purple colour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Plaques are prolonged</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tongue</th>
<th>(A) Red tongue body, yellow or greasy tongue coating</th>
<th>(B) Pink tongue body, thin and white tongue coating</th>
<th>(C) Purple or dull tongue body, with dark purple patches or spots</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse</td>
<td>(A) Taut and slippery or rapid pulse</td>
<td>(B) Thin and slow pulse</td>
<td>(C) Unsmooth/hesitant/choppy pulse or thin and slow pulse.</td>
</tr>
</tbody>
</table>

**Differentiation (please tick one of the three syndromes):**

(A) Wind-heat with Blood dryness
(B) Blood Deficiency with Wind-dryness
(C) Blood Stasis
Appendix 2 - Chinese database search strategy

Search strategy for psoriasis

CNKI

1. Condition

银屑病 牛皮癣 白庀 白庀 鬱风 庀风 松皮癣

2. Intervention

中医 中医治疗 中医临床 中医辨证 中医干预 祖国医学 辨证施治 中西医 中西医学 中西医结合 中西医治疗 中西医结合治疗 中西医结合疗法 中西医结合方法

草药 中草药 中医药学 中医药 中医药治疗 中医药疗法 中医药防治 中医药研究 中医中药治疗 中草药治疗应用

传统医学 传统医药 传统治疗 中国传统医学

3. Study type

随机临床观察 随机临床试验 临床随机研究 临床随机试验 临床观察 临床研究 临床疗效

随机试验 疗效观察随机 随机 对照 单盲 双盲 系统评价 Meta 分析

4. Strategy

(SU% 银屑病 or SU% 牛皮癣 or SU% 白庀 or SU% 松皮癣) and (SU% 中医 or SU% 中医临床 or SU% 中医辨证 or SU% 祖国医学 or SU% 辨证施治 or SU% 中西医 or SU% 中西医结合 or SU% 中西医结合疗法 or SU% 草药 or SU% 中草药 or SU% 中医药 or SU% 中医药治疗 or SU% 中医药防治 or SU% 中医药研究 or SU% 传统医学 or SU% 传统医药 or SU% 传统治疗) and (SU% 临床观察 or SU% 随机临床试验 or SU% 临床随机研究 or SU% 临床随机试验 or SU% 临床研究 or SU% 临床疗效 or SU% 随机试验 or SU% 系统评价)
CQVIP:

Keyword_C= ((银屑病+牛皮癣+白疕+松皮癣)*(中医+中医临床+中医辨证+祖国医学+辨证施治+中西医+中西医结合+中西医结合疗法+草药+中草药+中医药+中医中药+中药治疗+中医药防治+中医药研究+传统医学+传统医药+传统治疗)*(临床观察+随机临床试验+临床随机研究+临床随机试验+临床研究+临床疗效+随机试验+系统评价))

Title_C= ((银屑病+牛皮癣+白疕+松皮癣)*(中医+中医临床+中医辨证+祖国医学+辨证施治+中西医+中西医结合+中西医结合疗法+草药+中草药+中医药+中医中药+中药治疗+中医药防治+中医药研究+传统医学+传统医药+传统治疗)*(临床观察+随机临床试验+临床随机研究+临床随机试验+临床研究+临床疗效+随机试验+系统评价))
Appendix 3 – Literature search list of Chinese herbs utilized for psoriasis

<table>
<thead>
<tr>
<th>Herb</th>
<th>Herb name (Pinyin)</th>
<th>Scientific/botanical name</th>
<th>Herb</th>
<th>Herb name (Pinyin)</th>
<th>Scientific/botanical name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Huang qi</td>
<td>Astragali radix</td>
<td>59</td>
<td>Bai zhi</td>
<td>Angelicae dahuricae radix</td>
</tr>
<tr>
<td>2</td>
<td>Dang shen</td>
<td>Codonopsis radix</td>
<td>60</td>
<td>Fu ling</td>
<td>Poria cocos</td>
</tr>
<tr>
<td>3</td>
<td>Dan shen</td>
<td>Salviae miltiorrhizae radix</td>
<td>61</td>
<td>Bai zhu</td>
<td>Atractylodis macrocephalae rhizoma</td>
</tr>
<tr>
<td>4</td>
<td>Chi shao</td>
<td>Paeoniae radix rubra</td>
<td>62</td>
<td>Dong gu or xiang gu</td>
<td>Lentinus edodes</td>
</tr>
<tr>
<td>5</td>
<td>Chuan xiong</td>
<td>Rhizoma ligustici chuanxiong</td>
<td>63</td>
<td>Shui fei ji</td>
<td>Fructus silybum marianum</td>
</tr>
<tr>
<td>6</td>
<td>Di long</td>
<td>Pheretima aspergillum</td>
<td>64</td>
<td>Jiang huang</td>
<td>Curcumae longae rhizoma</td>
</tr>
<tr>
<td>7</td>
<td>Niu xi</td>
<td>Aechyranthis bidentatae radix</td>
<td>65</td>
<td>Jiang can</td>
<td>Bombyx batrycatus</td>
</tr>
<tr>
<td>8</td>
<td>Zi cao</td>
<td>Arnebiae/lithosperm i radix</td>
<td>66</td>
<td>Cha ye</td>
<td>Camellia sinensis</td>
</tr>
<tr>
<td>9</td>
<td>Gan cao</td>
<td>Glycyrrhizae radix</td>
<td>67</td>
<td>Ling xiao hua</td>
<td>Campsisitis flos</td>
</tr>
<tr>
<td>10</td>
<td>Ma huang</td>
<td>Ephedrae herba</td>
<td>68</td>
<td>She chuang zi</td>
<td>Cnidii fructus</td>
</tr>
<tr>
<td>11</td>
<td>Fu zi</td>
<td>Aconiti radix lateralis praeparata</td>
<td>69</td>
<td>Huang lian</td>
<td>Picrorrhizae rhizoma</td>
</tr>
<tr>
<td>12</td>
<td>Bai jie zi</td>
<td>Sinapis albae semen</td>
<td>70</td>
<td>King rat snake</td>
<td>Elaphe carinata</td>
</tr>
<tr>
<td>13</td>
<td>Rou gui</td>
<td>Cinnamomi cassiae cortex</td>
<td>71</td>
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<td>Dai mao fen</td>
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</table>
Appendix 4 – Dermatology life quality index instrument

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: ........................................... Date: ..........................
Name: ...................................................... Score: ..........................
Address: ................................................... Diagnosis: ........................

The aim of this questionnaire is to measure how much your skin problem has affected your life
OVER THE LAST WEEK. Please tick (✓) one box for each question.

1. Over the last week, how itchy, sore, painful or stinging has your skin been?
   Very much  ❑
   A lot  ❑
   A little  ❑
   Not at all  ❑

2. Over the last week, how embarrassed or self-conscious have you been because of your skin?
   Very much  ❑
   A lot  ❑
   A little  ❑
   Not at all  ❑

3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?
   Very much  ❑
   A lot  ❑
   A little  ❑
   Not at all  ❑
   Not relevant  ❑

4. Over the last week, how much has your skin influenced the clothes you wear?
   Very much  ❑
   A lot  ❑
   A little  ❑
   Not at all  ❑
   Not relevant  ❑

5. Over the last week, how much has your skin affected any social or leisure activities?
   Very much  ❑
   A lot  ❑
   A little  ❑
   Not at all  ❑
   Not relevant  ❑

6. Over the last week, how much has your skin made it difficult for you to do any sport?
   Very much  ❑
   A lot  ❑
   A little  ❑
   Not at all  ❑
   Not relevant  ❑

7. Over the last week, has your skin prevented you from working or studying?
   Yes  ❑
   No  ❑
   Not relevant  ❑

   If "No", over the last week how much has your skin been a problem at work or studying?
   A lot  ❑
   A little  ❑
   Not at all  ❑

8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?
   Very much  ❑
   A lot  ❑
   A little  ❑
   Not at all  ❑
   Not relevant  ❑

9. Over the last week, how much has your skin caused any sexual difficulties?
   Very much  ❑
   A lot  ❑
   A little  ❑
   Not at all  ❑
   Not relevant  ❑

10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?
    Very much  ❑
    A lot  ❑
    A little  ❑
    Not at all  ❑
    Not relevant  ❑

Please check you have answered EVERY question. Thank you.

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Note: Used with permission Dr Faraz Mahmood Ali (on behalf of Prof. Andrew Finlay)
Appendix 5 – Skindex 29 Instrument

Skindex29
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These questions concern your feelings over the past 4 weeks about the skin condition that has bothered you the most. Tick the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?

<table>
<thead>
<tr>
<th>Statement</th>
<th>NEVER</th>
<th>RARELY</th>
<th>SOMETIMES</th>
<th>OFTEN</th>
<th>ALL THE TIME</th>
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</thead>
<tbody>
<tr>
<td>1. My skin hurts</td>
<td>□ 1</td>
<td>□ 2</td>
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<td>2. My skin condition affects how well I sleep</td>
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<td>3. I worry that my skin condition may be serious</td>
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<td>4. My skin condition makes it hard to work or do hobbies</td>
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<td>5. My skin condition affects my social life</td>
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<td>6. My skin condition makes me feel depressed</td>
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<td>7. My skin condition burns or stings</td>
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<td>8. I tend to stay at home because of my skin condition</td>
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<td>9. I worry about getting scars from my skin condition</td>
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<td>10. My skin itches</td>
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<td>11. My skin condition affects how close I can be with those I love</td>
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<td>12. I am ashamed of my skin condition</td>
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<td>13. I worry that my skin condition may get worse</td>
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<td>14. I tend to do things by myself because of my skin condition</td>
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<td>15. I am angry about my skin condition</td>
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<td>16. Water bothers my skin condition (bathing, washing hands)</td>
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<td>17. My skin condition makes showing affection difficult</td>
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<td>18. I worry about side-effects from skin medications / treatments</td>
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<td>19. My skin is irritated</td>
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<td>20. My skin condition affects my interactions with others</td>
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Please turn to the next page
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<th>SOMETIMES</th>
<th>OFTEN</th>
<th>ALL THE TIME</th>
</tr>
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<td>21. I am embarrassed by my skin condition</td>
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<td>26. I am humiliated by my skin condition</td>
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<td>27. My skin condition bleeds</td>
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<td>29. My skin condition interferes with my sex life</td>
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<td>30. My skin condition makes me tired</td>
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Note: User agreement signed with MAPI research trust for SKINDEX 29 use
Appendix 6 – Study recruitment advertisements and recruitment poster

Chinese herbal medicine for psoriasis study

Volunteers are invited to participate in a study that will investigate the use of Chinese herbal medicine to relieve and improve psoriasis symptoms.

Do you or someone you know suffer from psoriasis?

Psoriasis is a skin condition consisting of rough, raised and often red rash areas known as plaques on the surface of the skin. Commonly found on the extensor areas such as the knees and elbows it can also be found in large or small amounts on the torso or other areas of the body. The rash is usually unsightly and unfortunately there is currently no cure.

Chinese herbal medicine has been used to treat psoriasis for 100s of years. Recent research suggests it may improve psoriasis symptoms complementary to current standard care.

Study recruiting now

We are recruiting volunteers to participate in the trial between March and December 2015.

RMIT University is undergoing a double blind randomised placebo controlled trial, which is considered the gold standard for evaluating an intervention. See the Australia New Zealand Clinical Trial Registry for details of the study.

The study will investigate the addition of a Chinese herbal medicine extract to topical standard care treatment for the relief of psoriasis symptoms and improvements in quality of life.

The study will include treatment over 12 weeks, followed by a further 12 week follow up phase. 30 people with plaque type (vulgaris) psoriasis between the ages of 18 and 70 will participate.

Register your interest

If you or someone you know may be interested in participating or would like more information, please contact the trial coordinator Shefton Parker on email psoriasis.trial@rmit.edu.au.

Source RMIT Univeristy website (https://www.rmit.edu.au/.../chinese-herbal-medicine-for-psoriasis-study/)
New study on psoriasis participants needed.
Shefton Parker

Do you or someone you know suffer from psoriasis?

RMIT University is currently undertaking a clinical trial investigating the integration of Chinese Herbal Medicine and a conventional standard care topical therapy (calcipotriol) for plaque type psoriasis. The study will take place at RMIT’s Bundoora West Campus in the School of Health Sciences new “Research Hub”. We are currently collecting interest from people with psoriasis who may like to participate. The study is ethics approved by the RMIT Human Research Ethics Committee and registered with the Australia New Zealand Clinical Trial Registry.

If you or someone you know may be interested please pass on the link to our webpage which contains more information http://www.rmit.edu.au/healthsciences/psoriasis-trial

Phone: 03 9925 7741

Source: Linked In (https://www.linkedin.com/)

Life News magazine
Do you have psoriasis?

If you are over 18 and have psoriasis (plaque/vulgaris type) you may be eligible to participate in a research study conducted by RMIT University investigating integrative medicine by combining conventional treatment with herbal medicine.

If you would like further information please contact:

Shefton Parker Ph:  
email: psoriasis.trial@rmit.edu.au

www.rmit.edu.au/healthsciences/psoriasis-trial
Clinical Studies for Psoriasis and Eczema

Volunteers needed

RMIT University is conducting two clinical trials to evaluate the effectiveness of Chinese herbal medicine to reduce and improve psoriasis symptoms and itching in atopic eczema.

Children (8-16 years) who suffer from itching and skin rash due to atopic eczema (AD) or atopic dermatitis (AD) are invited to participate in the eczema study.

The psoriasis study is looking for volunteers aged between 16 and 70 who suffer from plaque type (psoriasis) psoriasis.

Both studies will be conducted at RMIT University's Brunswick West campus.

To find out more on the psoriasis study phone
To find out more on the eczema study phone

www.rmit.edu.au/healthsciences

Source: Example newspaper advertisement published in the Moreland Leader newspaper
Appendix 7 – Patient information and consent form

INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

PARTICIPANT INFORMATION

Project Title: Integration of Chinese Herbal medicine and conventional medical therapy for psoriasis vulgaris: a randomised, placebo controlled trial.

Investigators:

Prof Charlie Xue, BMed, PhD; Registered Chinese medicine practitioner
Head of School of Health Sciences, RMIT University
charlie.xue@rmit.edu.au

Dr Tony Zhang, BMed, MPH, PhD; Registered Chinese medicine practitioner
Head of Discipline of Chinese Medicine, RMIT University
tony.zhang@rmit.edu.au

Dr Claire Zhang, BMed, PhD; Registered Chinese medicine practitioner
Discipline of Chinese Medicine, RMIT University
claire.zhang@rmit.edu.au

Prof Chuanjian Lu, MD, PhD
Dermatologist, Guangdong Provincial Hospital of Chinese Medicine
Luchuanjian888@vip.sina.com

A/Prof. Greg Goodman MBBS (HONS), GRADDIPLINEPI FACD
Dermatologist, Dermatology Institute of Victoria

Mr Shefton Parker, BHSc, BAppSc; Registered Chinese medicine practitioner
PhD Candidate, RMIT University
psoriasis.trial@rmit.edu.au
Dear Sir/Madam,

You are invited to participate in a research project being conducted by RMIT University in co-ordination with the Dermatology Institute of Victoria and funded by RMIT University in conjunction with the China-Australia International Research Centre for Chinese Medicine. Please read this sheet carefully and be confident that you understand its contents before deciding whether to participate. If you have any questions about the project, please ask one of the investigators.

Who is involved in this research project? Why is it being conducted?

The research study is being conducted by collaboration between RMIT University and the Dermatology Institute of Victoria. The research is part of Mr Shelton Parker’s PhD project and the [aggregated] results will be presented in conference presentations and journal publication. This is a pilot study of a large size clinical trial.

The project has been approved by RMIT Human Research Ethics Committee and supported in part with funding from RMIT University and support from Guangdong Provincial Hospital of Chinese Medicine and Guangdong Provincial Academy of Chinese Medical Sciences.

Why have you been approached?

You have been approached to participate as you have been previously diagnosed with psoriasis of vulgaris (plaque) type and have previously given verbal consent for the Dermatology Institute of Victoria (DIV) or RMIT researchers to contact you with further details about this research study. You may otherwise have contacted us from a recruitment poster displayed in a clinic or workplace or advertisement.

What is the project about? What are the questions being addressed?

The project is a pilot study of a large size clinical trial. The pilot study will implement a double blinded, randomised, placebo controlled trial. Approximately 30 people with psoriasis vulgaris will be recruited. Participants will be randomly assigned into two groups; one group receive integrative care with Chinese herbal medicine (CHM) and conventional topical medical therapy (calcipotriol), the other group will be the control group and receive a placebo (looks, and tastes identical to the CHM but has no therapeutic action) plus conventional therapy (calcipotriol). The study will compare psoriasis symptoms as well as quality of life measures between the two groups to evaluate any difference. The study will involve regular self-administration of calcipotriol in combination with either CHM or placebo (all provided to participants at no cost).

We aim to investigate if integrative therapy (CHM plus calcipotriol) is more effective than standard therapy (calcipotriol) plus placebo for psoriasis symptoms, improves quality of life and reduces relapse rates after ceasing of treatment.

If I agree to participate, what will I be required to do?

If you agree to participate in the study, you will be required to attend the Dermatology Institute of Victoria clinic or RMIT clinical trial lab (location dependent on convenience) 5 times over 24 weeks for about 1 hour on each occasion, and have 7 phone interviews of around 10 minutes per call.

1st visit – Screening (15 minutes)

You will be screened by the research team for eligibility. During this screening you will be provided with all the details of the study and you will be given opportunity to ask questions. At this time you will be asked to sign this patient information form if you consent to participate. From this time you will be instructed to stop all psoriasis related medication and supplements. You can discuss any medication queries with the researchers of your physician prior to signing the consent. You will then have an appointment booked in for your baseline assessment 2 weeks from the screening date.
2nd visit – Baseline assessment (30 minutes to 1 hour)

At this visit you will be assessed using a number of questionnaires, some will be related directly to your psoriasis symptoms and others will be related to your life quality and emotions. You will also undertake a blood test which will measure a number of biological functions related to psoriasis, that will be used to measure biological changes for improvement and safety. Please Note: We will be storing the collected blood samples so that they can be used for further research into psoriasis. If you do not want your blood samples stored for future research please advise the research team. You can still take part in this research if you decline the storing of your samples and it will not affect your involvement in the study. You will then be randomised to either the treatment group (CHM plus calcipotriol) or control group (placebo plus calcipotriol). Neither yourself nor the researchers will know which group you have been assigned to as a code will determine what intervention pack you get. The appearance of the intervention packs will be identical and will contain 8 weeks of packaged CHM or placebo in granulated form and calcipotriol. The CHM or placebo will be mixed with water and drunk twice per day and the calcipotriol applied twice as per the provided instructions for application and dosage. You will also receive a study diary which will contain a number of questions regarding your psoriasis symptoms and medication used that will need to be filled out either daily or weekly.

Please note: at this time we would like to take digital photos of your lesion areas. This will be taken in a way they do not reveal your facial identity and will then be coded so as they are not identifiable and stored in your trial file. Please let the researchers know if you do not consent to this part for any reason. The photos may be used in future publications and presentations but at no time will they be identifiable.

1st Phone interview – 1st Follow up phone call assessment (10 minutes)

During the first follow up phone call you will have a number of verbal questions regarding your symptoms and medication usage to answer similar to the baseline assessment. An appointment will be made for the next follow up call.

2nd Phone interview – 2nd Follow up phone call assessment (10 minutes)

As per 1st phone interview (10 minutes)

3rd Visit – Mid treatment assessment (30 minutes to 1 hour)

As per baseline assessment

3rd Phone interview – 3rd Follow up phone call assessment (10 minutes)

As per 1st and 2nd phone interview (10 minutes)

4th Phone interview – 4th Follow up phone call assessment (10 minutes)

As per 1st, 2nd and 3rd phone interview (10 minutes)

4th Visit – End of treatment assessment (30 minutes to 1 hour)

As per baseline assessment. We will also collect any unused herbs or calcipotriol at this point. A 12 weeks symptom diary will be provided to you and an appointment made for 12 weeks after this assessment.

Fortnightly phone interviews during the 12 week follow up period (10 minutes each)

Assess your psoriasis symptoms and use of health care resources.

5th Visit – Final assessment (1 hour)
As per baseline assessment

**What are the possible risks or disadvantages?**

Risks associated with the trial are those usually found when taking calcipotriol and may include minor risks of skin irritation (including peeling or rash), skin discoloration and/or skin sensitivity to light.

Chinese Herbal medicine risks are typically minor and may consist of diarrhoea and/or nausea, these symptoms commonly subside once the medication is ceased. Your psoriasis symptoms may exacerbate during the treatment phase and if any symptoms persist please seek medical assistance from your GP. The blood tests can cause minor discomfort and pain with insertion of the needle and can leave bruising afterwards. All blood tests will be performed by trained staff and risks are no different to those for any other routine blood tests you have undertaken.

If you have any concerns about the responses to any of the questionnaire items or if you find participation in the project distressing, you should contact one of the investigators Dr Tony Zhang as soon as convenient. Dr Tony Zhang will discuss your concerns with you confidentially and suggest appropriate follow-up, if necessary. Similarly you may contact your GP and the RMIT Ethics committee for concerns if you would prefer them handled by someone outside the research team.

If you are allocated to the control group you will not receive any potential therapeutic effect of the CHM.

The trial will be conducted in accordance with International Conference on Harmonisation (ICH) Note for Guidance on Good Clinical Practice.

**What are the benefits associated with participation?**

All participants will receive treatment for their psoriasis symptoms at least topical calcipotriol, which is recommended by clinical guidelines. There is possible additional benefit to those who are allocated to the CHM group. The results of this research will add to current knowledge of psoriasis and made lead to the development of new treatments for people with psoriasis in the future.

**What will happen to the information I provide?**

By signing the consent form you consent to the research staff collecting and using personal information about you for this research project. Any information obtained in connection with this research project that can identify you will remain confidential.

All information collected will be de-identified using a unique study code to protect your privacy. A reference table linking the study code to your personal details will be stored separately in a secured filing cabinet.

Only study investigators will have access to your information.

Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified. Data about individual participants will not be published. Only aggregate data will be published.

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to request access to the information collected and stored by the research team about you. You also have the right to request that any information with which you disagree being corrected. Please contact the research team member named at the end of this document if you would like to access your information.
Any information that you provide can be disclosed only if (1) it is to protect you or others from harm, (2) a court order is produced, or (3) you provide the researchers with written permission.

Research data will be kept securely at RMIT University for a minimum 15 years after publication, before being destroyed.

What are my rights as a participant?

- The right to withdraw from participation at any time;
- The right to request that any recording cease;
- The right to have any unprocessed data withdrawn and destroyed, provided it can be reliably identified, and provided that so doing does not increase the risk for the participant;
- The right to have any questions answered at any time.

Whom should I contact if I have any questions?

Any study related questions should be directed to Mr Shefton Parker at . . . . . . . Outside of business hours you should contact your local health service if you require urgent health related information or assessment.

What other issues should I be aware of before deciding whether to participate?

Before participating you should assess the requirements of the research for face to face visits and phone assessments as well as the diary recording requirements in between. Time availability for the duration of the study requires 24 weeks in total. Participants need to ensure they can commit the time required to complete the study.

Yours sincerely

Investigators:

Prof Charlie Xue

Dr Tony Zhang

Dr Claire Zhang

Prof Chuanjian Lu

A/Prof. Greg Goodman

Mr Shefton Parker
If you have any concerns about your participation in this project, which you do not wish to discuss with the researchers, then you can contact the Ethics Officer, Research Integrity, Governance and Systems, RMIT University, GPO Box 2476V VIC 3001.

CONSENT

1. I have had the project explained to me, and I have read the information sheet.

2. I agree to participate in the research project as described.

3. I agree:

   to undertake the tests or procedures outlined above
   to be interviewed and/or complete a questionnaire
   for blood samples collected to be used in future related research

   that my image will be taken.

4. I acknowledge that:

   (a) I understand that my participation is voluntary and that I am free to withdraw from the project at any time and to withdraw any unprocessed data previously supplied (unless follow-up is needed for safety).

   (b) The project is for the purpose of research. It may not be of direct benefit to me.

   (c) The privacy of the personal information I provide will be safeguarded and only disclosed where I have consented to the disclosure or as required by law.

   (d) The security of the research data will be protected during and after completion of the study. The data collected during the study may be published and presented at relevant conferences. Any information which will identify me will not be used.

Participant’s Consent

Participant: __________________________ Date: ____________

(Signature)

Witness:

Witness: __________________________ Date: ____________

(Signature)
Appendix 8 - Case Record Form example

<table>
<thead>
<tr>
<th>Date:</th>
<th>Assessor:</th>
<th>Study ID</th>
</tr>
</thead>
</table>

**Week -2 Pre-assessment**

1. DOB
2. Sex [Male] [Female]
3. Country of Birth
4. Post code
5. Weight: Kg
6. Height: cm
7. Blood pressure
   3a) Systolic/diastolic
   3b) Aortic SP DP MAP PP HR AP ALx
8. BMI
9. Current Medications (name, dosage, frequency):
10. Recent illnesses (Condition and duration eg. Conjunctivitis 2 days, flu 1 week etc):

---

11. PASI Score
12. BSA
13. DLQI Score
14. Skindex 29
15. CM SD Type
   Previous use of Traditional [YES] [NO]
   a) Chinese Medicine: [If NO go to Question 13]
   b) If yes was it for psoriasis? [YES] [NO]
   c) What form was the treatment: [Acupuncture]
      [Chinese Herbal medicine]
      [Other] (please state)
16. a) What age was the onset of your psoriasis? ______ years
17. At what age was it medically diagnosed as psoriasis? ______ years
19. [NO]
20. Do you smoke? [No Never]
   [No Previous smoker -> In which year did you quit? ______]
   [Yes current smoker -> How many cigarettes per day? ______]
21. Do you drink Alcohol □ Yes □ No -> If NO, no need to answer questions 22 to 24.

22. Which of the following best describes how often you would have an alcoholic drink?
   □ a) Daily or most days □ b) 2 – 3 days per week □ c) Once per week □ d) 2 – 3 days a month □ e) Less often

<table>
<thead>
<tr>
<th>The following are all equal to approximately one “standard drink”:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low alcohol beer (3.5%)</td>
</tr>
<tr>
<td>1 can or 1.5 ‘pots’; (volume 375mls)</td>
</tr>
<tr>
<td>Regular beer (4.9%)</td>
</tr>
<tr>
<td>1 ’pot’ or % ‘stubby’; (volume 285mls)</td>
</tr>
<tr>
<td>Wine (12%)</td>
</tr>
<tr>
<td>one small glass; (volume 100mls)</td>
</tr>
<tr>
<td>Spirits / liqueurs</td>
</tr>
<tr>
<td>one shot/hip; (volume 30mls)</td>
</tr>
<tr>
<td>Mixed drinks</td>
</tr>
<tr>
<td>1 glass; (volume 30mls of spirits + mixer)</td>
</tr>
<tr>
<td>Alcoholic soda (5.5%)</td>
</tr>
<tr>
<td>% of a 330ml bottle; (volume 250mls)</td>
</tr>
</tbody>
</table>

23. On a day that you would have an alcoholic drink, how many standard drinks do you usually have?
   □ 5 or more standard drinks
   □ 3 – 4 standard drinks
   □ 1 – 2 standard drinks

24. Over the last 12 months or so, how often would you have had more than 4 standard drinks in a day?
   □ Daily or most days
   □ 2 – 3 days per week
   □ Once per week
   □ 2 – 3 days a month
   □ Less often

Please attach a copy of the blood test results coded with identifiers removed

Please take a photo of the participant’s major lesion area and attach protecting the identity of the participant and mark with their study code. (Note: Lighting conditions should be consistently reproducible for all future photos, note the camera type used and the settings applied):
Appendix 9 – Study medication instructions

Participant instructions for administration and application of trial medication

Sorbolene:

This is supplied to you at no cost after you have been screened. For the 2 weeks leading up to your baseline assessment all psoriasis related medication should be ceased. The sorbolene is the only topical that should be used during this time.

Application dosage and frequency is at your own discretion general guide is typically 1-2 fingertip units per lesions but may be more or less. If you run out of the product please contact the research team before using any other topical creams.

Other moisturisers are permitted to unaffected regions of the body such as daily facial moisturisers.

Calcipotriol:

Please read the enclosed consumer medicine information for full caution and dosage advice. If you have any questions please direct them to the research team or your GP.

Do not use more than 100g per week. Apply daily as needed.

Topical application to the affected areas is according to American Academy of Dermatology (AAD) guidelines. See table 1. (1% surface area coverage = 0.5 fingertip units). On your first consultation the researchers will assist you to determine your initial dosage. If you have questions about dosage please ask.
**Chinese herbal medicine granules**

The trial medication (sachet of granules) is identical for all participants. Instructions to take the medication are identical. Each sachet consists of 5.5gs of granulated product (1 dose). The sachet is to be added to 3/4 to 1 a cup of water (preferably warm not cold or boiling), stirred until the granules dissolve and consumed orally (by mouth).

2 sachets in total should be taken daily, 1 sachet in the morning after your meal and 1 sachet in the evening again after your meal. The taste may be somewhat unpleasant the first few occasions; however people typically get used to the flavour. Please feel free to follow with a glass of juice or other beverage to assist detract from any unpleasant after taste.

**If you have adverse event to any of the trial medication**

If you have any adverse events such as allergies, nausea or diarrhoea (may be some other) and you believe them to be related to the herbal granules or calcipotriol please cease the medications and notify the research team. Please contact your GP or hospital (and emergency as appropriate) if you feel you require treatment as a result of any adverse event or if the symptoms persist.

**Your initial calcipotriol recommended daily dose is: ____ Fingertip units (Research staff to complete)**
Appendix 10 - Home study diary

Psoriasis Home Study Diary Week

*Please complete the following measures daily before bed*

1) Did you take your herbal medicine today (AM and PM dose)? (Place an ✓ in relevant box)

<table>
<thead>
<tr>
<th>Day</th>
<th>Date</th>
<th>AM</th>
<th>PM</th>
<th>Neither AM nor PM</th>
<th>If “AM only”, “PM only” OR “neither” then why?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Example only: 3</td>
<td>23-12-14</td>
<td>✓</td>
<td></td>
<td>Forgot to take in the evening.</td>
</tr>
<tr>
<td>Day 1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

2) Did you apply your Calcipotriol today?

<table>
<thead>
<tr>
<th>Day</th>
<th>Date</th>
<th>Calcipotriol application? (Yes/No)</th>
<th>No. of applications</th>
<th>Total no. of fingertip units</th>
<th>Other medication? Yes/No (record below)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Example only: 3</td>
<td>23-12-14</td>
<td>Yes</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>Day 1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
Did you take any other medication this week, even if it was not related to your psoriasis? (please circle) YES  NO

If YES please detail below:

<table>
<thead>
<tr>
<th>Date</th>
<th>Medication name</th>
<th>Form</th>
<th>Amount (eg. number of pills or finger tip units or mls)</th>
<th>If a topical please put location.</th>
<th>Reason for taking?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example only, 23-12-14</td>
<td>Panadol, capsules</td>
<td>2</td>
<td>N/A</td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Eg. 23-12-14</td>
<td>Canesten, cream</td>
<td>3</td>
<td>Left toes and foot</td>
<td>Itchy foot rash</td>
<td></td>
</tr>
</tbody>
</table>

3) Did you notice any new or atypical health symptoms? If yes rate their severity **mild**, **moderate**, or **severe**

<table>
<thead>
<tr>
<th>Day</th>
<th>Date</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Dizziness</th>
<th>Diarrhoea</th>
<th>Other (please state type and severity below)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Example only: 23-12-14</td>
<td>Moderate</td>
<td>Mild</td>
<td>N/A</td>
<td>Mild</td>
<td>Moderate headache and mild abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
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<td>3</td>
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<td>5</td>
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<td>6</td>
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<td></td>
<td>7</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
### Appendix 11 – Serious adverse events form

#### SERIOUS ADVERSE EVENT REPORTING FORM

<table>
<thead>
<tr>
<th>Site ID</th>
<th>Randomisation Code</th>
<th>Enrolment date: 2011 MM DD</th>
</tr>
</thead>
</table>

**Serious Adverse Event** - If fatal, life-threatening, disability (significant, persistent or permanent), requires or prolongs hospitalisation, congenital anomaly or malignancy, or requires medical/surgical intervention to prevent permanent impairment or damage.

Site Investigator(s) ________________________________

Onset Date 2011 MM DD Resolution Date 2011 MM DD

#### EVENT SUMMARY

(Description of the Serious Adverse Event including Corrective Treatment)

---

#### RELEVANT HISTORY / CONCURRENT CONDITIONS

---

#### EVENT OUTCOME

(Tick all that apply)

- [ ] Complete recovery to baseline
- [ ] Alive with sequelae
- [ ] Death
- [ ] Adverse event persisting
- [ ] Resulted in extended hospitalisation
- [ ] Unknown
- [ ] Resulted in persistent or significant incapacity/disability

#### INVESTIGATORS OPINION OF RELATIONSHIP

To study treatment
- [ ] not related
- [ ] possibly related
- [ ] probably related

To protocol procedures
- [ ] not related
- [ ] possibly related
- [ ] probably related

Please explain opinion

---

Reported to local ethics committee [ ] Reported to Principal Investigator [ ]

Investigators Signature: ____________________________ Date 2011 MM DD

#### COORDINATING CENTRE TO COMPLETE THIS SECTION

Reported to RMIT HREC Committee [ ] Actions Required [ ] Yes [ ] No

If Yes Actions carried out [ ]
Appendix 12 - Study discontinuation form

Psoriasis Study Discontinuation/End of Study Form

STUDY ID: ______________ DATE: __/____/____ Signed: ______________

Did participant complete all study related treatment, visits and procedures? Yes
No

► If No please complete the form below.

Date of discontinuation from the study ______________
D M Y

Reason for discontinuation?

☐ Lack of efficacy
☐ Lost to follow-up
☐ Deviation from protocol
☐ Consent withdrawn
☐ Death (complete SAE form)
☐ Not tolerated
☐ The subject's condition changed and inclusion/exclusion criteria are no longer met.
☐ Other

______________________________________________________________

All data has been recorded and collected.
Appendix 13 – RMIT University human research ethics approval letter

Human Research Ethics Committee (HREC)
Research and Innovation office
NH&MRC Code: EC00237

Notice of Approval

Date: 2 May 2014
Project number: 54/13
Project title: A randomized, double blinded, placebo-controlled trial of Chinese Herbal medicine integrated with pharmacotherapy for psoriasis vulgaris
Risk classification: More than low risk
Chief investigator: Prof Charlie Xue
Approved: From: 2 May 2014 To: 31 December 2015

Terms of approval:
1. Responsibilities of investigator
   It is the responsibility of the above investigator to ensure that all other investigators and staff on a project are aware of the terms of approval and to ensure that the project is conducted as approved by HREC. Approval is only valid whilst investigator holds a position at RMIT University.

2. Amendments
   Approval must be sought from HREC to amend any aspect of a project including approved documents. To apply for an amendment use the request for amendment form, which is available on the HREC website and submitted to the HREC secretary. Amendments must not be implemented without first gaining approval from HREC.

3. Adverse events
   You should notify HREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.

4. Plain Language Statement (PLS)
   The PLS and any other material used to recruit and inform participants of the project must include the RMIT university logo. The PLS must contain a complaints clause including the above project number.

5. Annual reports
   Continued approval of this project is dependent on the submission of an annual report.

6. Final report
   A final report must be provided at the conclusion of the project. HREC must be notified if the project is discontinued before the expected date of completion.

7. Monitoring
   Projects may be subject to an audit or any other form of monitoring by HREC at any time.

8. Retention and storage of data
   The investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

9. Special conditions of approval
   Nil.

In any future correspondence please quote the project number and project title above.

A/Prof Barbara Polus
Chairperson
RMIT HREC
Appendix 14 - TGA Clinical Trial Notification letter

Prof Charlie Xue - Principal Investigator  
Royal Melbourne Institute of Technology  
GPO Box 2476V  
MELBOURNE VIC 3001

CTN Scheme (Drugs): Acknowledgement of New Trial

Your notification to conduct a clinical trial under the Clinical Trial Notification (CTN) Scheme, pursuant to Schedule 5A of Regulation 12 of the Therapeutics Goods Regulations, has been received by the Office of Scientific Evaluation (OSE).

Trial Number: 2014/0330  
Protocol Number: YXBCM01

<table>
<thead>
<tr>
<th>Drug Active Name</th>
<th>Trade Name</th>
<th>Code Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcipotriol</td>
<td>Daivonex</td>
<td>N/A</td>
<td>50mcg</td>
</tr>
<tr>
<td>Smilax Glabra</td>
<td>Smilax Glabra Rhizhome</td>
<td>N/A</td>
<td>.98g</td>
</tr>
<tr>
<td>Arnebia Euchroma</td>
<td>Arnebiae Radix</td>
<td>N/A</td>
<td>.98g</td>
</tr>
<tr>
<td>Prunus Mume</td>
<td>Prunus Mume Fruit</td>
<td>N/A</td>
<td>.98g</td>
</tr>
<tr>
<td>Glycyrrhiza Uralsensis</td>
<td>Glycyrrhiza Uralsensis Root &amp; rhizome</td>
<td>N/A</td>
<td>0.39g</td>
</tr>
<tr>
<td>Chloranthus Glaber</td>
<td>Sarcandra Glaber</td>
<td>N/A</td>
<td>0.18g</td>
</tr>
<tr>
<td>Curcuma Zedoaria</td>
<td>Curcuma Wenyujin Rhizome</td>
<td>N/A</td>
<td>0.59g</td>
</tr>
<tr>
<td>Paonia Veitchii</td>
<td>Paeonia Lactiflora Root</td>
<td>N/A</td>
<td>0.59g</td>
</tr>
</tbody>
</table>

It is noted that:

i. the approval of the goods for this trial was given in accordance with Item 3 of Schedule 5A of the Therapeutic Goods Regulations by the body or organisation conducting the trial at each additional site.

ii. the representative of the Ethics Committee for each additional site has certified that the Committee is constituted and operates in accordance with the NHMRC “National Statement on Ethical Conduct in Human Research” has considered this clinical trial, and has provided advice to the body or organisation conducting the trial.