Chinese Herbal Medicine and Acupuncture for Acne Vulgaris: Efficacy, Patient Preferences and Health-Related Quality of Life

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; any editorial work, paid or unpaid, carried out by a third party is acknowledged; and ethics procedures and guidelines have been followed.

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Suzi Mansu ________________________

Date: 26 July 2019
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Publications

Thesis-related:


Conference papers


Additional papers:

Abbreviations

AA     auricular acupressure
AAD    American Academy of Dermatology
Acne-QoL Acne-Specific Quality of Life Questionnaire
Acne-QOLI Acne Quality of Life Index
ACORN Acne Core Outcome Research Network
AD     atopic dermatitis
ADI    Acne Disability Index
AE     adverse event
ANOVA  analysis of variance
ANZCTR Australian and New Zealand Clinical Trial Register
aP     adipocyte lipid-binding protein
AP     auricular pressure
APSEA  Assessment of the Psychological and Social Effects of Acne
AQOL   Acne Quality of Life Scale
BDI    Beck’s Depression Index
b.i.d.  twice daily
BIDQ   Body Image Disturbance Questionnaire
BMI    body mass index
BP     benzoyl peroxide
C      control
CADI   Cardiff Acne Disability Index
CAM    complementary and alternative medicine
CASS   Comprehensive Acne Severity Scale
CAT    catalase
CDER   Centre for Drug Evaluation and Research
CDI    Child Depression Inventory
CDLQI  Children’s Dermatology Life Quality Index
CES-D  Center for Epidemiologic Studies Depression Scale
CHEAN  College Human Ethics Advisory Network
CHM    Chinese herbal medicine
CI     confidence interval
CM     Chinese medicine
COC    combination oral contraceptive pills
COMET  Core Outcome Measures in Effectiveness Trials
CONSORT Consolidated Standard of Reporting Trials
COX    cyclooxygenase
CRF    case record form
CRP    C-reactive protein
CSPSCA Capa Social Phobia Scale for Children and Adolescents
CSV    comma-separated values
DHEA   dehydroepiandrosterone
DHT    dihydrotestosterone
<table>
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<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>DLQI</td>
<td>Dermatology Life Quality Index</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>EA</td>
<td>electro-acupuncture</td>
</tr>
<tr>
<td>EADV TF</td>
<td>European Academy of Dermatology and Venereology Task Forces</td>
</tr>
<tr>
<td>ECLA</td>
<td>Échelle de Cotation des Lesions d’Acne</td>
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<tr>
<td>EGSS</td>
<td>Evaluator’s Global Severity Score</td>
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<tr>
<td>EQ-5D</td>
<td>EuroQol 5-Dimension Questionnaire</td>
</tr>
<tr>
<td>ERK</td>
<td>extracellular signal-regulated kinase</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FDLQI</td>
<td>Family Dermatology Life Quality Index</td>
</tr>
<tr>
<td>FNE</td>
<td>Fear of Negative Evaluation Scale</td>
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<tr>
<td>FoxO1</td>
<td>forkhead box protein O1</td>
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<tr>
<td>GAGS</td>
<td>Global Acne Grading System</td>
</tr>
<tr>
<td>GEA</td>
<td>Global Acne Severity Scale</td>
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<tr>
<td>GHQ</td>
<td>General Health Questionnaire</td>
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<tr>
<td>GMP</td>
<td>good manufacturing practice</td>
</tr>
<tr>
<td>GnRH</td>
<td>gonadotropin-releasing hormone</td>
</tr>
<tr>
<td>GPx</td>
<td>gutathione peroxidase</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations, Assessment, Development and Evaluation</td>
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<td>HAD</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HP</td>
<td>haptoglobin</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>HREC</td>
<td>Human Research Ethics Committee</td>
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<tr>
<td>HRQoL</td>
<td>Health Related Quality of Life</td>
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<td>HSCL</td>
<td>Hopkins Symptom Check List</td>
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<td>HSD</td>
<td>hydroxysteroid dehydrogenase</td>
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<tr>
<td>I</td>
<td>intervention</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use</td>
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<tr>
<td>IGA</td>
<td>Investigator’s Global Assessment</td>
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<tr>
<td>IGF</td>
<td>insulin growth factor</td>
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<tr>
<td>IL</td>
<td>interleukin</td>
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<tr>
<td>iNOS</td>
<td>inducible nitric oxide synthase</td>
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<tr>
<td>IP</td>
<td>interferon-inducible protein</td>
</tr>
<tr>
<td>IRF</td>
<td>interferon regulatory factor</td>
</tr>
<tr>
<td>ISGA</td>
<td>Investigator's Static Global Assessment</td>
</tr>
<tr>
<td>ITT</td>
<td>intention-to-treat</td>
</tr>
<tr>
<td>KC</td>
<td>keratinocyte-derived chemokine</td>
</tr>
<tr>
<td>LPL</td>
<td>lipoprotein lipase</td>
</tr>
<tr>
<td>LPS</td>
<td>lipopolysaccharide</td>
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<tr>
<td>LSAS</td>
<td>Liebowitz Social Anxiety Scale</td>
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<tr>
<td>APK</td>
<td>mitogen-activated protein kinase</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>MBSRQ-AS</td>
<td>Multidimensional Body Self-Relations Questionnaire-Appearance Scales</td>
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<tr>
<td>MD</td>
<td>mean difference</td>
</tr>
<tr>
<td>MDD</td>
<td>major depressive disorder</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Heading</td>
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<td>MOCQ</td>
<td>Maudsley Obsessive Compulsive Questionnaire</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health (Malaysia)</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid</td>
</tr>
<tr>
<td>NF</td>
<td>nuclear factor</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NO</td>
<td>nitrous oxide</td>
</tr>
<tr>
<td>P. acnes</td>
<td>Propionibacterium acnes</td>
</tr>
<tr>
<td>PBV</td>
<td>pollen bee venom</td>
</tr>
<tr>
<td>PCOS</td>
<td>polycystic ovarian syndrome</td>
</tr>
<tr>
<td>PDT</td>
<td>photodynamic therapy</td>
</tr>
<tr>
<td>PedsQL-C</td>
<td>Pediatric Quality of Life Inventory-Child Version</td>
</tr>
<tr>
<td>PGE2</td>
<td>prostaglandin E2</td>
</tr>
<tr>
<td>PHQ</td>
<td>Patient Health Questionnaire</td>
</tr>
<tr>
<td>PI3K</td>
<td>phosphoinositide-3-kinase</td>
</tr>
<tr>
<td>PPAR</td>
<td>peroxisome proliferator-activated receptors</td>
</tr>
<tr>
<td>PPQFY</td>
<td>Pi Pa Qing Fei Yin</td>
</tr>
<tr>
<td>PVS</td>
<td>Peer Victimization Scale</td>
</tr>
<tr>
<td>q.d.</td>
<td>one time per day</td>
</tr>
<tr>
<td>q.i.d.</td>
<td>four times daily</td>
</tr>
<tr>
<td>qn</td>
<td>once nightly</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>QR</td>
<td>quick response</td>
</tr>
<tr>
<td>RADS</td>
<td>Reynolds Adolescent Depression Scale</td>
</tr>
<tr>
<td>RAGP</td>
<td>Royal Academy of General Practitioners</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
</tr>
<tr>
<td>RR</td>
<td>risk ratio</td>
</tr>
<tr>
<td>RSES</td>
<td>Rosenberg Self-Esteem Scale</td>
</tr>
<tr>
<td>SA</td>
<td>surround acupuncture</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
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<td>SDQ</td>
<td>Strengths and Difficulties Questionnaire</td>
</tr>
<tr>
<td>SF</td>
<td>short form</td>
</tr>
<tr>
<td>SOD</td>
<td>superoxide dismutase</td>
</tr>
<tr>
<td>SPIRIT</td>
<td>Standard Protocol Items: Recommendations for Interventional Trials</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for Social Sciences</td>
</tr>
<tr>
<td>SR</td>
<td>systematic review</td>
</tr>
<tr>
<td>STAIc</td>
<td>State-Trait Anxiety Inventories for Children</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>STRICTA</td>
<td>Standards for Reporting Interventions in Controlled Trials of Acupuncture</td>
</tr>
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<td>TAB</td>
<td>topical antibiotics</td>
</tr>
<tr>
<td>TCA Cross</td>
<td>trichloroacetic acid chemical reconstruction of skin scars</td>
</tr>
<tr>
<td>TER</td>
<td>therapeutic effective rate</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
<tr>
<td>THP</td>
<td>Tamm–Horsfall protein</td>
</tr>
<tr>
<td>t.i.d</td>
<td>three times daily</td>
</tr>
<tr>
<td>TLR</td>
<td>toll-like receptor</td>
</tr>
<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
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<tr>
<td>TR</td>
<td>topic retinoid</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>WHOQOL</td>
<td>World Health Organization Quality Of Life</td>
</tr>
<tr>
<td>YLD</td>
<td>years lived with disability</td>
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Summary

Background
Acne vulgaris (acne) is a common condition that affects adolescents and adults. Acne significantly affects people’s health-related quality of life (HRQoL), with reports of low self-esteem, body image concerns and depression. Acne can be initiated by *Propionibacterium acnes* (*P. acnes*) infection or androgen activity. Conventional medical treatment of acne includes antibiotics, retinoids, and benzoyl peroxides (BPs). These treatments are not free of adverse effects.

Chinese medicine (CM) usually attributes mild to moderate acne to heat in the Lung meridian or damp heat in the Stomach meridian, and severe acne to Blood stasis, toxic heat or binding of phlegm. CM is used in clinical practice for the treatment of acne; however, there is a lack of evidence on the clinical benefit and safety of Chinese herbal medicine (CHM) and acupuncture.

While both CM and western medicine (WM) health care paradigms can be used to treat acne, there are no correlations between CM diagnoses and WM disease states. This PhD describes mechanisms in both paradigms but does not seek to make correlations between the two.

Objectives
This project aims:

1. To understand the impact of acne on HRQoL and to obtain participant views on CM treatment options;
2. To employ the methods of the *Cochrane Handbook for Systematic Reviews of Interventions* to determine the current state of evidence of CHM and acupuncture for acne; and

3. To develop a randomised controlled trial protocol that evaluates the impact of CHM on HRQoL in people with acne vulgaris.

**Methods**

For Objective 1, a review of the current literature on the HRQoL of acne was undertaken with a focus on the psychological, emotional and social impacts of acne and the predictors of impairment. There were different general health, dermatology-specific and acne-specific instruments in the literature to assess the HRQoL of people with acne. The advantages and disadvantages of each were discussed.

An online survey was conducted to investigate the impact of acne on HRQoL and to obtain participants’ views on a proposed treatment protocol. Two validated surveys were used. Questions on patient preferences for CHM and acupuncture treatment duration and frequency were also included in this survey.

To address Objective 2, two systematic reviews (SRs) were conducted, guided by the methods of the *Cochrane Handbook for Systematic Reviews of Interventions*. The first SR evaluated the CHM formula *Pi Pa Qing Fei Yin* (PPQFY) and the second evaluated acupuncture and related modalities. Nine databases were searched for randomised controlled trials (RCTs) for these two interventions. Following study selection and data extraction, statistical analyses were conducted using RevMan 5.3. The strength and quality of the evidence were assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE).
Findings from the HRQoL review and the online survey, and from the two SRs (Objectives 1 and 2) informed the development of the trial protocol, which follows Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). A rigorous trial protocol of PPQFY compared to placebo was designed to address the issues in existing literature and improve the quality of new data generated from trials.

**Results**

The review of HRQoL showed that acne had a profound impact on patients’ HRQoL. Anxiety, depression, and social anxiety were reported to be associated with acne in the literature. Females, different ethnic groups such as Hispanic, Asian and Maori, and greater severity of acne tended to correlate with poorer HRQoL. However data on the impact of HRQoL on Australians was over ten years old. Despite the profound impact of acne on HRQoL reported in the literature, few CM studies on acne used HRQoL as an outcome measure. Studies that did use HRQoL had used dermatology-specific rather than acne-specific instruments.

An online survey was conducted using a convenience sampling method, including advertising in local high schools and through universities in Melbourne. Of the 28 respondents, most were female, had mild acne and were 15 to 24 years of age. For Acne-QoL, the lowest score was for the self-perception domain and the highest was for the acne symptoms domain. People with moderate acne were emotionally affected and worried about their acne. The most commonly used complementary and alternative medicine (CAM) by participants were alternative medical systems such as CM, chiropractic and osteopathy. Preferences for CM included topical herbs and oral pills/tablets and acupuncture; participants preferred four to eight weeks of CHM treatment and weekly acupuncture treatments.
Fifteen trials were included in the SR of PPQFY. PPQFY appeared to have greater benefit based on change in acne symptoms when compared with pharmacotherapies. None of the studies used placebo as a control. Twelve trials were included in the SR of acupuncture. There was no difference between acupuncture and related modalities when compared with pharmacotherapies. Few studies included in these SRs reported on HRQoL. Both reviews found methodological design issues such as lack of randomisation and blinding procedures, no sample size calculations and small sample sizes in the included trials.

The dearth of evidence for the effect of CM on HRQoL and limitations of clinical studies identified through SRs were addressed with the development of the trial protocol. A randomised, placebo controlled trial protocol informed by patient preferences was developed using PPQFY as an example. The proposed participants are 15 years or older with mild to moderate acne and a CM diagnosis of heat in the Lung. The intervention group will receive PPQFY capsules while the control group will receive identical placebo capsules. The primary outcome will be HRQoL using the Acne-QoL. Secondary outcomes include lesion count, severity grading, and adverse events (AEs).

Conclusions

This project examined the impact of acne on HRQoL, and determined CM treatment preferences of people with acne. The efficacy and safety of the CHM formula PPQFY and acupuncture for acne were systematically evaluated. Methodological issues identified in SRs were addressed in the trial protocol that evaluates the efficacy and safety of PPQFY for patients with mild to moderate acne. The implementation of the trial protocol may improve treatment adherence and improve the reliability and quality of future trials.
CHAPTER 1 : Introduction

1.1 Background

Acne vulgaris (acne) is a common dermatological condition of the pilosebaceous glands. It usually begins at adolescence and can affect adults up to 50 years old, while some have adult onset (1, 2). Acne affects over 9.4 per cent of the world population (3), with adolescents the most affected (4). Acne affects 79 to 90 per cent of people who live in countries with a high fat and carbohydrate diet (5). Acne lesions include comedones that range from small pustules and inflamed papules, to cysts that are located on the face, the upper torso and occasionally the neck (6). Inflammation can accompany comedones, being more prevalent in adolescents (2). Genetics, diet, androgen activity and stress have all been implicated in causing acne (7).

Studies have shown that acne can cause psychological, emotional and social issues affecting health-related quality of life (HRQoL). Low self-esteem, anxiety, depression, body image concerns and suicidal ideation have been reported in the literature (8-10).

Current conventional treatment therapies such as retinoids are effective for decreasing inflammation and lesion numbers, but have severe adverse effects (AEs) (11). Retinoids are teratogenic, and mood changes, depression and suicidal thoughts have been reported (11). Topical drugs such as topical retinoids and BP can cause skin irritation. The cost of medicines such as isotretinoin is less than one dollar per day (12). However, due to the severity of the side effects with these drugs, patients will need to weigh the benefits to their acne condition against the costs to their general health. Topical and oral antibiotics can become less effective with long-term use and increase the risk of antibiotic resistance (6). The use of topical antibiotics (TAB) with BP tends to decrease the risk of resistance, but leaves the skin dry and irritated.
Combination oral contraceptive pills (COC) are often prescribed to decrease the formation of androgens in women who also desire contraception, but women taking COC have a higher risk of thromboembolism (14).

People are increasingly looking for alternatives to conventional medicines when treatments do not meet their expectations or when AEs from conventional medicines are no longer tolerable (15-17). Chinese medicine (CM) treatment addresses the root cause of the disease (ben) and the presenting symptoms (biao), and may be appealing to some people. Chinese herbal medicine (CHM) and acupuncture have empirically been used for treatment of acne and have been shown to improve acne in systematic reviews (SR) (18).

1.2 Rationale for the project

The impact of acne on the HRQoL of people in Australia was last evaluated in 1997 (19). More recent data is needed to improve the understanding of HRQoL of people with acne. An online survey was conducted to obtain data on the HRQoL of people with acne in Australia. People with acne are looking to complementary therapies like Chinese medicine as treatments for acne, yet little is known of their knowledge and beliefs about CAM, and preferences relating to Chinese medicine treatments. These were assessed as part of the online survey described above.

Knowing patients preferences and values is one part of evidence-based medicine, another part is knowing the best available evidence. Few SR of CHM and acupuncture for acne have been published in English. Most of the clinical research on CM treatment of acne has been conducted in China and very few high-quality methodological trials have been published. There are limitations to these studies, such as no reporting of the type of acne-grading method and lack of the use of appropriate controls such as placebo as a control (20), and few studies have
examined the burden of acne on HRQoL. The quality of the evidence provided in previous systematic reviews is limited by the number of databases in their searches and the inclusion criteria of randomised controlled trials (RCTs) (18, 21). SRs of the two main treatment techniques of CM practice, CHM and acupuncture, were conducted in this study to inform the selection of the intervention for the trial protocol. The experimental findings on CHM were reviewed to gain an understanding of the pathophysiological effect of CHM. Systematic reviews of CHM and acupuncture highlighted methodological shortcomings. As a case example of how challenges in Chinese medicine research could be overcome, a trial protocol for the formula PPQFY was developed. The trial protocol was informed by participants preferences for CM treatments.

1.3 Objectives and research questions

1.3.1 Objectives

This project aims to evaluate the clinical evidence on CM and acupuncture treatment for acne, the HRQoL of patients with acne in Australia, and patient preferences in CM treatment for acne.

Objective 1: To understand the impact of acne on HRQoL and to obtain participant views on CM treatment options

Objective 2: To use the methods of the *Cochrane Handbook for Systematic Reviews of Interventions* to review the efficacy and safety of CHM and acupuncture for acne; and

Objective 3: To develop a randomised controlled trial protocol that evaluates the impact of CHM on HRQoL in people with acne vulgaris.

1.3.2 Research questions

1. What impact does acne have on acne patients’ HRQoL?
2. What views do people with acne have of CM treatment approaches?
3. What is the current clinical trial evidence of CHM treatment for acne?
4. What is the current clinical trial evidence of acupuncture treatment for acne?
5. Are acupuncture and CHM safe for treating acne?
6. What is the most appropriate trial design for evaluating the effectiveness of CHM to improve HRQoL of participants?

1.4 Scope of thesis

This project addresses the research questions by evaluating the evidence on CHM treatments (such as oral and topical CHM) and treatment by acupuncture and related modalities (such as body acupuncture/acupressure, electro-acupuncture (EA), auricular acupuncture/acupressure, laser acupuncture and moxibustion). These CM interventions are commonly used in clinical practice in Australia. Other CM modalities not commonly used in Australia, such as acupuncture point injection where saline or herbal medicine products are injected into acupuncture points, were not evaluated.

1.5 Organisation of thesis

Chapter 1 introduces acne and the project. It provides the background and research objectives and research questions to be answered.

Chapters 2 and 3 provide an overview of acne from both Western and Chinese medicine perspectives. Chapter 2 describes the definition of acne, prevalence, pathophysiology and current pharmacological and non-pharmacological management, and summarises the impact of acne on HRQoL. This chapter highlights the complex pathophysiology and severity assessment of acne and the complexity of conventional treatment of acne. Chapter 3 summarises the CM
understanding of acne. It describes the aetiology, pathogenesis, syndrome differentiation and CHM and acupuncture treatment of acne. A summary of the clinical evidence is provided and this highlights the lack of quality evidence on CM for acne.

Chapter 4 provides a comprehensive review of the HRQoL of people with acne. This chapter reveals the severe psychological, emotional and social impacts that acne can have on people. It also describes the numerous ways HRQoL can be assessed using general health surveys and dermatology- and acne-specific HRQoL instruments, and the lack of consensus on the evaluation of HRQoL of people with acne. It also highlights the lack of HRQoL outcome measures used in CM trials.

Chapter 5 presents the findings of an online survey that included two validated instruments: the Acne-Specific Quality of Life Questionnaire (Acne-QoL) and the Complementary and Alternative Medicine Questionnaire for Young Adults (CAM Questionnaire). The online survey also determined acne patients’ preferences in CM treatment and these results are presented in this chapter.

Chapter 6 provides the methods for conducting the SR which are guided by the *Cochrane Handbook for Systematic Reviews of Interventions*. The inclusion criteria, database search and data analysis methods are presented in this chapter.

Chapters 7 and 8 present the findings of two SRs. Chapter 7 systematically reviews the included RCTs of the CHM formula *Pi Pa Qing Fei Yin* (PPQFY). Chapter 8 presents the second SR, on acupuncture and related therapies including body acupuncture, EA, auricular acupuncture, auricular acupressure (AA) and moxibustion for acne.
Chapter 9 uses the clinical evidence from the burden on HRQoL and participant treatment preferences for CM described in Chapter 5 and findings from the SRs in Chapters 7 and 8, to design a trial protocol. This chapter proposes a randomised, double-blind, placebo-controlled, trial using the CHM formula PPQFY as a case example to improve the reliability and quality of CM trials for the management of acne. It follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline.

Chapter 10 summarises the project and discusses the findings of the research. It also provides a discussion of the study’s limitations and summarises the implications for research and clinical practice.

Appendices 1 to 18 present the supplementary data discussed in the above chapters.
CHAPTER 2 : Acne vulgaris

Overview

This chapter introduces acne vulgaris (acne), its identifying features and the pathogenesis, diagnosis and treatment. It also describes the prevalence of acne and the impacts on people’s health-related quality of life (HRQoL).

2.1 Introduction

Acne is a chronic non-life threatening disease that begins around the time of puberty, with the highest prevalence in people 15 to 17 years of age (22, 23). The condition can continue to affect adults up to 50 years of age (24), with reports of adult onset acne (acne tarda) increasing (1). The course of the condition can wax and wane over time (1). It can severely reduce a person’s quality of life and can lead to anxiety and suicidal thoughts (25, 26). The exact mechanisms of disease are still being debated (see section 2.5.3 for a description of the pathophysiology of acne). The main treatment targets include decreasing hyperkeratinisation, inflammation, androgen activity and infection due to Propionibacterium acnes (P. acnes) (27).

2.2 Definition of acne vulgaris

Acne vulgaris is defined as a chronic inflammatory disease characterised by open and closed comedones (blackheads and whiteheads, respectively) and inflammatory nodules (cysts), papules and pustules. Inflammation of sebaceous glands, increased sebum production and follicular plugging of keratinocytes can cause papules, pustules, nodules or cysts, and non-inflamed lesions characterised by open or closed comedones (27, 28).
Scarring can occur when there is damage to the skin during the healing process of the acne lesions. Scars are classified into two types. Atrophic scarring is milder and is the result of a loss of collagen, whereas hypertrophic scarring is more severe as the result of a gain of collagen which can lead to keloid scars (29).

2.3 Prevalence of acne vulgaris

2.3.1 Global prevalence and regional differences

Acne vulgaris is estimated to affect 9.4 per cent of the world population (3). Large population studies from different countries have shown variation in acne prevalence. Prevalence determined by dermatologist examination was 8.1 per cent in China (17,345 people examined) (30), 3.9 per cent in Germany (of 90,880 people) (31) and 5.4 per cent in Egypt (of 8,008 people) (32). In household surveys, self-reported acne prevalence was found to be lower in people from northwest Tanzania (0.1 per cent) (33) and Ethiopia (0.35 per cent) (34). There is no Australia-wide population data on the prevalence of acne. In Victoria, a study of school-aged children with acne was conducted in 1997 (22). This study found 36.1 per cent of 4- to 18-year-old children in Victorian schools had acne. No acne was reported in indigenous household surveys of people from Kitavan, Papua New Guinea, and Aché, Paraguay (5). The authors speculated that diets low in processed Westernised foods and where food was foraged or grown by the indigenous populations contributed to this finding (5).

2.3.2 Age differences

Studies have shown the prevalence of acne to be higher in adolescents and young adults (2, 4, 30). Up to 85 per cent of 12- to 24-year-olds reported being affected by acne (1), but it may persist in 64 per cent of adults in their 20s and in 43 per cent in their 30s (4). Prevalence increases with adolescent age, with 15- to 17-year-olds reporting higher occurrence of acne
(22, 23), and relapse of acne is often reported (2). In an online survey of adolescents and young adults aged 15 to 24 from seven countries in Europe (Belgium, Czech and Slovak Republics, France, Italy, Poland and Spain), 57.8 per cent self-reported the presence of acne and prevalence was highest among the 15- to 17-year-olds (35).

2.3.3 Gender differences

Reporting of gender differences in the literature varies considerably. In a study of global prevalence of skin diseases, 9.8 per cent of males and 9.0 per cent of females reported having acne (27). Some studies found more females than males reported acne (36, 37), while others showed no difference between genders (38, 39). Prevalence was higher in females than males in adolescents between 10 to 12 years old (22). The opposite was seen in older adolescents, with higher prevalence in males between 16 to 18 years of age (22), although this finding was not confirmed by Shen et al. (30). Prevalence increased in males as they reached pubertal age but was higher again in females in the young adult age group aged 19 to 25 years (30). Other studies reported higher prevalence in males (40-42). Prevalence of acne in adult women has been reported as 47.3 per cent (43) and 55.0 per cent (2). In a study by Perkins et al. (2), 50.8 per cent of women had had acne since onset in adolescence and 24.8 per cent reported substantial periods of relapsed acne. One study showed 76 per cent of women presenting with acne as adults compared to 24 per cent of men (44). About 18 per cent of women had true adult onset of acne and 37 per cent of women had hyperandrogenicity (44). Most teenage boys will have acne that disappears by 20 to 25 years of age, but women can have persistent acne up to 40 years of age (45).
2.3.4 Geographical differences

Acne affects 79 to 95 per cent of people living in Western societies and is more prevalent in developed countries where there is a high fat and carbohydrate diet (5). Acne does not seem to affect people from Kitavan, Papua New Guinea, and Aché, Paraguay, whose diets consist of wild, foraged foods and locally cultivated foods (5). Acne is more common in Caucasian people compared to African-American and Hispanic American people (2, 46, 47).

Table 2.1 Prevalence of acne across the globe

<table>
<thead>
<tr>
<th>Country</th>
<th>% of adolescent population</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>93.3 (16–18 years old)</td>
<td>(22)</td>
</tr>
<tr>
<td>Iran</td>
<td>93.3</td>
<td>(40)</td>
</tr>
<tr>
<td>USA</td>
<td>85*</td>
<td>(48)</td>
</tr>
<tr>
<td>Lithuania</td>
<td>82.9</td>
<td>(49)</td>
</tr>
<tr>
<td>Malaysia</td>
<td>67.5</td>
<td>(41)</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>56.2</td>
<td>(50)</td>
</tr>
<tr>
<td>Serbia</td>
<td>51.8</td>
<td>(42)</td>
</tr>
<tr>
<td>China</td>
<td>39.2*</td>
<td>(51)</td>
</tr>
<tr>
<td>Kenya</td>
<td>38.3</td>
<td>(52)</td>
</tr>
<tr>
<td>Germany</td>
<td>24.8*</td>
<td>(53)</td>
</tr>
</tbody>
</table>

*prevalence includes adolescents and young adults

A number of epidemiology studies across the world found the prevalence of acne varied from 39.2 per cent to 93.3 per cent (22, 40-42, 48, 50, 51, 54) (summarised in Table 2.1). The prevalence was highest in Australia (22), with 93.3 per cent (248 cases) of adolescents between 16 and 18 years old having acne. Prevalence of acne in Iranian adolescents was also 93.3 per cent (40). This was followed by the United States of America (USA) with 85 per cent of the total adolescents and young adults population aged between 12 to 24 years reporting acne (48).
Across Europe, 82.9 per cent of 1,277 Lithuanian schoolchildren had some form of acne (49) and in a study of 440 Serbian students 51.8 per cent self-reported acne, with prevalence significantly higher in one city (Uzice, 73.6 per cent) than another (Belgrade, 39.6 per cent) (42). The authors were unable to determine the reason for this difference. Germany was lower with 24.8 per cent of adolescents and young adults aged 16 to 20 years from 48,665 employees of German companies diagnosed with acne (53). In Asia, 67.5 per cent of 409 Malaysian adolescents between 13 to 18 years old assessed were affected with acne (41) and 56.2 per cent of 717 Saudi Arabian university students had acne (50). The prevalence in mainland Chinese adolescents and young adults was lower at 39.2 per cent of 83,008 people from a meta analysis of 25 epidemiology studies (51).

There is variation in the socioeconomic status of sufferers of acne. In the USA, those with lower socioeconomic status had higher reports of acne, whereas acne sufferers in Saudi Arabia reported higher socioeconomic status (55).

### 2.3.5 Severity and prevalence

Acne is a chronic disease which can last for 10 or more years (56). Severity is commonly assessed as mild, moderate or severe, although there are several different ways to classify severity (refer to section 2.7.1 for details). For example, mild and moderate acne is usually comedonal acne with fewer lesions and severe acne is higher number of comedones or lesions are cystic or nodular. A number of cross-sectional and observational studies of primary and high school students found greater severity of acne in later adolescence (22, 23, 37). Early onset of acne is a predictor of the severity of acne, as is increasing pubertal age (22, 40, 57). Other predictors of severity include genetics, where having a mother with acne influenced the severity of acne (40), and a higher body mass index (BMI) (39, 58).
Mild to moderate types of acne with comedonal and inflammatory lesions are seen in adolescents and is the most common type of acne (2, 22, 30, 38). Older adolescents have been diagnosed with greater severity of acne (22). In a study of 2,895 female adult acne across three cities from three countries Los Angeles, United States of America (USA), London, England and Rome, Italy, there were 57.8 per cent of women with mild acne and 35.6 per cent with moderate or severe acne had inflammatory acne (2). Clinical acne was seen in women of African-American and Hispanic origin, rather than Asian or Caucasian origin (59). Patients’ perception of their acne was often worse than assessors’ assessment of their lesions (22, 37, 60).

2.4 Impact of acne vulgaris

2.4.1 Economic impact and burden of disease of acne vulgaris

The global economic impact and burden of disease of acne vulgaris are high. Skin conditions are ranked fourth overall in years lost due to disability worldwide (3), with 33.7 million years lived with disability (YLD) collectively for 13 common skin conditions. Acne was only second to eczema in YLD (61). Acne is the most common condition seen by dermatologists, with 18.1 million visits from 1996 to 2005 and 4.6 million visits to paediatricians for acne in that same period in the USA alone (62). It is also the most frequent dermatological condition seen in general practice in the USA (63). In another study on the use of oral and topical retinoids in mild to moderate acne between 1990 to 1999, 54.2 million medical visits were reported (64).

It is estimated that a total of 12.6 per cent of money spent globally on topical and systemic treatments for skin conditions was directly related to acne (63). More recent reports suggest 36 per cent of all prescriptions in the USA are related to acne (1) and up to US$3 billion is spent
on acne worldwide (4). A United Kingdom (UK) report on the use of antibiotics found 80 per cent of the 1.2 million topical medicine prescriptions for acne were for topical antibiotics, dispensed at a cost of £15 million (65). It was also reported that over US$3 billion per year is lost in the direct and indirect costs of treatment and loss of productivity due to acne (66).

2.4.2 Health-related quality of life

The acne burden of disease is high, with anxiety, depression, body image concerns, poor self-esteem and suicide ideation and attempts reported in a number of studies (8, 26, 59, 67). More than 75 per cent of the 215 female respondents of a cross-sectional web-based survey of 15 to 40 years old from the USA “agreed” or “strongly agreed” that acne made them feel less confident, frustrated, embarrassed and more self-conscious around other people (59). In another cross-sectional survey in Norway of 3,775 older adolescents aged 18 to 19 years, suicidal ideation was reported by both girls and boys who suffered substantial acne (self-reporting of lesions described as “a lot or very much”). The rate of suicidal ideation was twice as high in girls with substantial acne (25.5 per cent versus 11.9 per cent) and three times as high in boys (22.6 per cent versus 6.3 per cent) compared to those with less severe acne (9). These adolescents also reported low attachment to friends, not thriving at school, never having romantic relationships and never having sexual intercourse (9).

The perception that acne and acne facial scars are negatively viewed by society (68) and negative attitudes and negative impacts of acne can last for a long time (37). Greater acne severity does not necessarily translate to worse HRQoL. Some patients with mild acne may have lower HRQoL compared to those with moderate or severe acne (69, 70).
Having acne can prohibit participation in social activities and impair performance at school or work, or even reduce employment opportunities (25, 59, 71, 72). In a workforce study, unemployment was higher in those with acne (73). A Turkish study which assessed the HRQoL of those affected by acne and the impact on their families found that lower HRQoL scores correlated with higher risk of depression and anxiety (74). Family members were also negatively affected. Family members who attended their kin’s appointments were asked to fill out the Family Dermatology Life Quality Index (FDLQI), which assesses social, physical and psychological wellbeing (75). Acne had a negative impact on family members and the impact lessened as their kin’s condition improved (74).

2.5 Pathophysiology of acne vulgaris

The mechanisms for the initial development of comedones are not well understood. A number of factors contribute to acne lesions. These include bacterial infection of \textit{P. acnes}, inflammatory mediators on the skin, alteration of the keratinisation of the skin and increased sebum production with increased androgen activity (27). Mites (\textit{Demodex folliculorum}) (76, 77) have also been implicated in contributing to this process. Acne was initially reported to be associated with the bacteria \textit{P. acnes} (78). However, acne in children younger than 10 years old is not associated with \textit{P. acnes}. Increased sebum production and follicular plugging are seen in this age group (63).

Acne is an inflammatory condition of the pilosebaceous glands of the skin. Comedones and inflammatory nodules are characteristic lesions in acne vulgaris that result from multifactorial pathogeneses. Infection from \textit{P. acnes} and mites (27, 76, 77) stimulates innate and acquired immune responses and triggers inflammation (79). The initiation of inflammation may be due to androgens such as testosterone and \(\alpha\)-dihydrotestosterone (DHT), with subsequent increase
in sebum, enlargement of sebaceous glands and hyperkeratinisation (7, 80). At the onset of puberty, gonadotropin-releasing hormone (GnRH) release causes dehydroepiandrosterone (DHEA) to be converted to DHT. Native enzymes in the pilosebaceous gland receptors forkhead box protein O1 (FoxO1) activate insulin growth factor-1 (IGF-1) to produce keratinocytes and sebum (60), causing comedone production and oily skin. *P. acnes* infections trigger inflammatory responses and lead to tissue damage. This triggers the release of interleukin-1α (IL-1α), a pro-inflammatory cytokine, from ductal keratinocytes, rupturing the skin and causing comedones (63, 78, 79). In patients with acne, expression of toll-like receptor (TLR)-2 by keratinocytes and macrophages and of TLR-4 by keratinocytes is increased, indicating that innate immunity is active against these microbes (78, 79).

Hyperkeratinisation is caused by altered sebum and lipid content in sebocytes and keratinocytes (81). Peroxisome proliferator-activated receptors (PPAR) increase human sebum production (82) and an innate immune response to pathogens such as *P. acnes* activates adaptive immune responses from T and B-cells (79). *P. acnes* stimulates keratinocytes, which produce cytokines, causing ductal rupture (79). They activate TLR-2 and TLR-4 cytokines. Interleukin-6 (IL-6) cytokine production caused by lipoxygenase is associated with sebaceous glands and also increases concomitant PPAR-α and –γ (81). Pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), IL-1, IL-8 and IL-12 are produced with *P. acnes* infections (79).

Androgens are stimulated at puberty (usually 12 to 14 years of age), increasing sebum production and the likelihood of acne (83). Sebum production can be stimulated by androgens and IGF-1. During puberty, the rise of androgens DHT and IGF-1 inhibits FoxO1 regulation (a receptor that transcribes levels of DHT) and causes excess production of keratinocytes and sebum. Increase in sebum creates an ideal environment providing nutrients for *P. acnes*. An
increase in bacterial growth and free fatty acids intensifies inflammatory mediators and the production of extracellular products such as lipases, proteases, hyaluronidases and chemotactic factors. These inflammatory mediators plug pilosebaceous glands and cause epithelium overgrowth at the follicular surface to form comedones. The severity of acne is dependent on the transient IGF-1 levels (60).

Genetics (76), diet (84-86) and neuroendocrine regulatory mechanisms (60) can also contribute to the occurrence and the severity of acne. Genetics (76) and androgen imbalances can influence sebaceous gland lipid synthesis (7). Stress may influence acne lesion development. The level of substance P, which induces neurogenic inflammation in sebaceous glands, was higher in people with acne compared to healthy controls (87).

2.6 Risk factors and comorbidities

2.6.1 Risk factors

The most common risk factors associated with acne include genetics, diet, cigarette smoking, alcohol, high BMI and psychological stress. There is an 80 per cent familial risk of persistent acne in first-degree relatives (88), with reports suggesting 50 to 78 per cent of sufferers of acne have first-degree relatives who also had acne (22, 37, 38, 40, 89). In an online survey, participants who reported a history of maternal or paternal acne were associated with increased probability of having acne (35).

An acne lesion may involve cellular inflammation causing hyperkeratinisation of follicular ducts (7), with exacerbation due to single or multiple factors such as *P. acnes*, menstruation, occupation, sweating, diet and stress. This can lead to cellular inflammation and increase the number of acne lesions. An online survey of 215 female participants aged 18 to 45 found
participants’ acne could be exacerbated around menstrual cycles, or induced by stress, sweating, cosmetics and humid weather (59).

There are conflicting reports on the implication of diet in acne. A systematic review by Magin et al. (90) found no effect of diet on the worsening of acne, but a later review suggested the correlation between diet and acne needed to be revisited (91). Magin et al. (90) looked at diet, hygiene and sunlight exposure myths associated with acne. They found there were very few high-quality studies and were unable to provide any recommendations on diet, hygiene or face-washing. Bowe et al. (91) also reviewed studies on diet, including prospective controlled trials, retrospective cohort studies, case-control studies and large case series. They found that high glycaemic load diets may exacerbate acne, while the association between dairy and acne is weak. They also found a lack of RCTs and suggested further research in this area. Cordain and colleagues (5) found adolescents and young adult Kitavan Islanders of Papua New Guinea and Ache hunter gatherers of Paraguay had no incidences of acne, hypothesised to be related to a diet consisting of wild, foraged and locally cultivated foods. They also suggested high glycaemic load can lead to hyperinsulinaemia and subsequent endocrine cascade causing high IGF-1 that can mediate androgen activity as a pathogenesis pathway to acne. One small randomised controlled study of 43 participants evaluating the effect of low glycaemic index (GI) food supported this theory. The study compared a low GI diet to a carbohydrate dense diet in 43 adolescent boys and young adult males 15 to 25 years old. The study found a greater decrease in total lesion count after 12 weeks in the low GI compared to the carbohydrate dense group. Insulin sensitivity was improved, and weight loss was also noted in low GI group (86).

Chocolate and other high-sugar foods were associated with acne in studies from Korea and France (92, 93). Higher milk consumption increased risk of acne in another study in Italy (39).
In two studies on milk consumption by 6,094 girls and 4,273 boys (84, 85), total milk intake was associated with acne in girls (84) and skim milk intake with acne in boys (85). An online survey of 6,063 young people in Europe found the consumption of chocolate was associated with an increased probability of having acne (35). In a small Australian RCT, 23 participants who consumed a low-glycaemic, low-fat diet successfully decreased acne lesions and severity (86). In Korea, 36.2 per cent of 693 children aged 7 to 12 years had acne, and acne was associated with obesity (BMI greater than 25 kg/m²) at age 18 (92). Another study from Italy found a lower BMI reduced the risk of acne (39).

Cigarette smoke contains arachidonic acid and polycyclic aromatic hydrocarbons which induce phospholipase A2-dependent inflammatory pathways that may lead to acne (63). Cigarette smoking and alcohol consumption were found to be associated with acne in a study in Korean students (92). A German study found acne prevalence was significantly higher in active smokers (54) while two other studies, one in Italy and one in France, found no such association with smoking (39). Smoking more than 10 cigarettes per day was highly associated with no acne (93).

Psychological stress is associated with inducing or worsening acne. One study investigating a correlation between stress and acne surveyed 144 female medical students in their sixth year and found a high correlation between acne severity and stress (94). Acne severity was graded and stress levels determined using the Perceived Stress Scale (PSS) questionnaire. They found higher acne severity in people with higher PSS scores. In a cross-sectional study conducted in 3,778 adolescents aged 18 to 19 years old in Norway, the study found that mental distress increased when the severity of acne increased (9).
2.6.2 Comorbidities

Acne vulgaris can present in isolation or may be associated with conditions such as polycystic ovaries and polycystic ovarian syndrome (PCOS). PCOS is a common endocrine condition that presents with oligoanovulation and hyperandrogenism. Hyperandrogenism is a result of increased insulin levels in the body stimulating ovarian steroidogenesis and increasing the sensitivity of pituitary gonadotropes and GnRH (95).

Severe acne is associated with sinopulmonary, gastrointestinal and psychological conditions. Psychological comorbidities included anxiety, depression, migraines, attention deficit disorder/attention deficit hyperactivity disorder and insomnia (96). In a study by Silverberg and Silverberg (96), sinus infection, sore throats from causes other than streptococcal infection, asthma and respiratory allergies such as hayfever were found to be associated with severe acne. Acne was also found to be associated with reflux/heartburn, abdominal pain, nausea/vomiting and digestive allergies (excluding diarrhoea and constipation) (96).

2.7 Diagnosis of acne vulgaris

Diagnosis of acne is based on visual observation (13) and it can be classified as acne vulgaris, conglobata varioliformis, tropical, acne excoriee des jeunes filles (acne that has been exacerbated by picking, pressing or squeezing) and unspecified acne (97). Other classifications include infantile acne due to maternal androgens stimulating sebaceous activity, mechanical acne due to repeated picking or rubbing, tumours such as ovarian tumours that increase androgen secretion, polycystic ovaries that increase circulating androgens and drug-induced acne (83). Acneiform drug eruptions can be stimulated by corticosteroids, anabolic steroids, isoniazid, lithium carbonate and phenytoin, chemical irritants such as oils and cosmetics, and environmental exposure to dioxins or halogenate phenolic compounds (97). Differentiation of
Acne vulgaris excludes rosacea and endocrine-related syndromes such as PCOS. Clinical classifications of acne lesion types are recommended. These include comedonal acne, mild–moderate papulopustular acne, severe papulopustular acne or moderate nodular acne, and severe nodular or conglobate acne (28). Diagnosis and differentiation of acne in CM is discussed in Chapter 3.

2.8 Assessment of acne vulgaris

2.8.1 Severity classification

Acne is graded numerically or by severity, which guides treatment. There is no consensus on the grading system, with 25 acne-severity grading systems being identified in the literature (98). Some tools have been developed for research and others for the clinical setting. The tools developed for research can be complicated and time-consuming, and therefore may not be appropriate during a short clinical interview (99). There has been a suggestion that lesion count is superior to grading as it is more objective (100).

The earliest clinical grading system was proposed by Pillsbury in 1956 (101) and estimated the number and type of lesions and overall involvement (area). Others have used variations of this system, including a four-point grading system (102), a six-point grading system (103) and a five-point reference that also includes a comparison with photographs (104, 105). Attempts have been made to provide a universal scale combining both lesion count and severity grading that is suitable for research. The Global Acne Grading System (GAGS) (106) is an ordinal scale used for lesion count and severity for the face, chest and back. The Investigator’s Global Assessment (IGA), also known as the Investigator’s Static Global Assessment (ISGA) and the Evaluator’s Global Severity Score (EGSS), is commonly used (98) and is another ordinal overall grading scale that assesses severity grade based on the dominant lesions and extent of
inflammation. The IGA was used in up to 33 per cent of clinical trials published up to 2011 (98) and is the preferred scale used in guidelines for drug development by the Center for Drug Evaluation and Research (107). Tan et al. (108) modified the IGA to develop the Comprehensive Acne Severity Scale (CASS), which includes photographic grading.

Two photographic grading scales have also been developed. The Leeds (104) and Leeds Revised Acne Grading systems (109) are comprised of 15 facial grades, 3 for comedones and 8 for chest and back. It also includes photographic standards. The Echelle de Cotation des Lesions d’Acne (Acne Lesion Score Scale, ECLA) developed by Dreno and colleagues (110) for clinical practice takes two minutes to complete. A scale from 0 (absent) to 5 (very severe) is used. The Global Acne Severity Scale (GEA Scale) was also developed by Dreno and colleagues for European patients in 2011 (111). A scale from 1 to 5 is used to categorise the severity of juvenile facial acne. A summary of these grading systems can be found in Table 2.2.

2.8.2 Qualify of life assessment

Various tools are available to assess the QoL of patients with acne. These include general wellbeing instruments such as the Short Form-36 (SF-36) (112) and Patient Health Questionnaire-4 (PHQ-4) (113); dermatology QoL instruments such as the Dermatology Life Quality Index (DLQI) (114), Skindex-16 (115) and Skindex-29 (100, 116, 117); and disease-specific instruments such as the Acne Quality of Life Index (Acne-QOLI) (118), Acne-Specific Quality of Life Questionnaire (Acne-QoL) (119-121), Acne Disability Index (ADI) (70), Cardiff Acne Disability Index (CADI) (122) and Acne Quality of Life Scale (AQOL) (123).
Table 2.2 Grading systems used in acne vulgaris

<table>
<thead>
<tr>
<th>Scale</th>
<th>Measures</th>
<th>Body area</th>
<th>Score system</th>
<th>Severity criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASS (108)</td>
<td>Lesion count and photographic severity grading</td>
<td>Face and body</td>
<td>0 = No lesions to barely noticeable ones. Very few scattered comedones and papules, 1 = Hardly visible from 2.5 m away. A few scattered comedones, few small papules, and very few pustules, 2 = Easily recognisable; less than half of the affected area is involved. Many comedones, papules and pustules, 3 = More than half of the affected area is involved. Numerous comedones, papules and pustules, 4 = Entire area is involved. Covered with comedones, numerous papules and pustules, and a few nodules and cysts, 5 = Highly inflammatory acne covering the affected area, with nodules and cysts present</td>
<td>0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe</td>
</tr>
<tr>
<td>ECLA (110)</td>
<td>Lesion count</td>
<td>Face</td>
<td>0 = Absent; no comedones, papules, pustules, nodules or cysts, 1 = Rare; &lt;5 comedones, &lt; 5 papules and pustules, 1 nodule or cyst, 2 = Mild; 5–9 comedones, 5–9 papules and pustules, 2 nodules or cysts, 3 = Moderate; 10–19 comedones, 10–19 papules and pustules, 3 nodules or cysts, 4 = Severe; 20–40 comedones, 20–40 papules and pustules, 4 nodules or cysts, 5 = Very severe; &gt;40 comedones, &gt;40 papules and pustules, ±5 nodules or cysts</td>
<td></td>
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<tr>
<td>Scale</td>
<td>Measures</td>
<td>Body area</td>
<td>Score system</td>
<td>Severity criteria</td>
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<tr>
<td>GAGS (106)</td>
<td>Lesion count, severity</td>
<td>Face, chest and back</td>
<td>0 = no lesions, 1 = comedones, 2 = papules, 3 = pustules, 4 = nodules</td>
<td>1–18 = mild, 19–30 = moderate, 31–38 = severe, 39+ = very severe</td>
</tr>
<tr>
<td>GEA Scale (111)</td>
<td>Photographic evaluation of severity of juvenile facial acne</td>
<td>Face</td>
<td>0 = Residual pigmentation and erythema may be seen, 1 = Few scattered open or closed comedones and very few papules, 2 = Easily recognisable: less than half of the face is involved. A few open or closed comedones and a few papules and pustules, 3 = More than half of the face is involved. Many papules and pustules, many papules and pustules, open or closed comedones. One nodule may be present, 4 = Entire face is involved, covered with many papules and pustules, open or closed comedones and rare nodules, 5 = Highly inflammatory acne covering the face with the presence of nodules</td>
<td>0 = clear, no lesions, 1 = almost clear, almost no lesions, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe</td>
</tr>
<tr>
<td>IGA (ISGA) or (EGSS) (107)</td>
<td>Lesion count, severity</td>
<td>All affected areas</td>
<td>0 = Clear skin with no inflammatory or non-inflammatory lesions, 1 = Almost clear, rare non-inflammatory lesions with no more than one small inflammatory lesion</td>
<td>0 = not severe, 1 = not severe, 2 = mild severity, 3 = moderate severity</td>
</tr>
<tr>
<td>Scale</td>
<td>Measures</td>
<td>Body area</td>
<td>Score system</td>
<td>Severity criteria</td>
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<td></td>
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<td></td>
<td>2 = Some non-inflammatory lesions with no more than a few inflammatory lesions</td>
<td>4 = severe</td>
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<td></td>
<td></td>
<td></td>
<td>(papules/pustules only), no nodules</td>
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<td></td>
<td></td>
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<td>3 = Up to many non-inflammatory lesions and some inflammatory lesions,</td>
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<td></td>
<td></td>
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<td>but no more than one small nodular lesion</td>
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<td></td>
<td></td>
<td></td>
<td>4 = With many non-inflammatory and inflammatory lesions, but no more than a few nodular lesions</td>
<td></td>
</tr>
<tr>
<td>Leeds (109)</td>
<td>Photographic evaluation of severity</td>
<td>Face, chest and back</td>
<td>Facial grades 1–8</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Chest grades 1–8</td>
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<td></td>
<td>Back grades 1–8</td>
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<td></td>
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<td></td>
<td>Face: 1–8 with increasing severity</td>
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<td></td>
<td></td>
<td></td>
<td>Chest: 1–8 with increasing severity</td>
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<td></td>
<td></td>
<td></td>
<td>Back: 1–8 with increasing severity</td>
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<td></td>
<td></td>
<td></td>
<td>Combined score for severity</td>
<td></td>
</tr>
<tr>
<td>Lehmann et al. (124)</td>
<td>Lesion count, severity</td>
<td>Face and body</td>
<td>Mild: comedones &lt;20, inflammatory lesions &lt;15, total lesions &lt;30</td>
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<td></td>
<td></td>
<td></td>
<td>Moderate: comedones 20–100, inflammatory lesions 15–50, total lesions 30–125</td>
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<td></td>
<td>Severe: &gt; 5 cysts or &gt; 50 inflammatory lesions or &gt; 125 total lesions</td>
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</table>

Abbreviations: CASS Comprehensive acne severity scale, CDER Center for Drug Evaluation and Research, ECLA Echelle de Cotation des Lesions d’Acne Scale, EGSS Evaluator Global Severity Score, GAGS Global Acne Grading System, GEA Global Acne Severity Scale, IGA Investigator’s Global Assessment, ISGA Investigator’s Static Global Assessment.
Both the Acne-QOLI (118) and the Acne-QoL (119-121) tools have been validated. The Acne-QoL is a 21-item tool that examines four domains: self-perception, role-emotional, role-social and acne symptoms. The Acne-QOLI is a 24-item instrument with validated content but the tool itself is yet to be validated. There is no published consensus guideline on outcome measures for acne, but there are efforts to gain consensus (99).

2.9 Treatment and management of acne vulgaris

Treatment guidelines published by the American Academy of Dermatology (28), the Royal Australian College of General Practitioners (125), the Malaysian Ministry of Health with the Dermatological Society of Malaysia and Academy of Medicine Malaysia (126) and the European Academy of Dermatology and Venereology (127, 128) all published similar management strategies for acne across their guidelines. There were four recommended approaches to treatment including decreasing hyperkeratinisation, microbial colonisation of *P. acnes* and sebum production, and inhibiting inflammation (28). Treatment of mild acne includes education about skin hygiene and debunking myths (13, 125). Topical and oral retinoids are prescribed for moderate to severe acne and topical BP is combined with TAB to decrease antibiotic resistance with long-term use (129).

Current conventional treatment therapies are effective but can have adverse effects (AEs). Retinoids are teratogenic and oral use is associated with mood changes, depression and suicidal thoughts (11). Topical retinoids and BP can leave the skin dry and cause skin irritation (13). The effectiveness of topical and oral antibiotics can decrease over time and increase the risk of antibiotic resistance (129).
2.9.1 Pharmacological agents

Topical treatment is generally recommended for eight to twelve weeks (28). Numerous clinical practice guidelines for acne vulgaris have been published for adults and children. The most recent publication was by the American Academy of Dermatology (AAD) in 2016, the *Guidelines of the Care of the Management of Acne Vulgaris* (28). In Australia, the *Acne Best Practice* was published in 2010 by the Royal Australian College of General Practitioners (RACGP) (125). In Europe, the *European Evidence-based (S3) Guidelines for the Treatment of Acne* was published in 2012 (127) with an update in 2016 (130) and in the UK the National Institute for Health and Care Excellence published clinical knowledge summaries for acne vulgaris in 2014 (131) with an update expected in 2021. There is one clinical guideline for paediatric acne, *Evidence-based Recommendations for the Diagnosis and Treatment of Pediatric Acne* in 2013 by the American Acne and Rosacea Society (13). The Malaysian Ministry of Health in conjunction with the Dermatological Society of Malaysia and the Academy of Medicine Malaysia published the *Clinical Practice Guidelines Management of Acne* in 2012 (126).

Zaenglein and colleagues (28) gave a simple and clear treatment algorithm for the treatment of acne (summarised in Table 2.3). This includes first-line treatment for mild, moderate and severe acne and alternative treatments. For mild acne, topical application of BP or topical retinoid (TR) alone, or combinations of BP with TAB, BP with TR or BP with TR and TAB are recommended. For moderate acne, oral antibiotics (OAB) plus topical combination therapy are recommended if topical treatment alone is ineffective. In severe acne, OAB with topical combination therapy are recommended. If this is ineffective, oral isotretinoin is recommended.
Table 2.3 American Academy of Dermatology Guideline recommended treatments for acne vulgaris

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>• BP or TR</td>
<td>• BP &amp; TAB or TR &amp; BP &amp; TAB &amp; TAB</td>
<td>• OAB plus topical combinations</td>
</tr>
<tr>
<td>• BP &amp; TAB</td>
<td>• OAB plus TR &amp; BP</td>
<td>• TR &amp; BP or TR &amp; BP &amp; TAB</td>
</tr>
<tr>
<td>• BP &amp; TR</td>
<td>• OAB plus TR &amp; BP &amp; TAB</td>
<td>• Oral isotretinoin</td>
</tr>
<tr>
<td>• BP &amp; TR &amp; TAB</td>
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</table>

Abbreviations: BP benzoyl peroxide, TAB topical antibiotics, TR topical retinoid, OAB oral antibiotics (summarised from Zaenglein et al. 2016 (28))

OAB should always be used with topical therapy, with a break-in treatment of two to four weeks where topical treatment only is used, to reduce the chance of antibiotic resistance. Isotretinoin is recommended for treatment for up to six months. For moderate acne, a break in treatment can cause relapse so the full course is recommended.

The AAD Guideline recommended treatments for children and adults are similar, with the exception that oral tetracycline derivatives (tetracycline, doxycycline and minocycline) are not recommended for children younger than 8 years old (28). Most of the topical therapies are also not recommended for children under 10 to 12 years of age and some, such as tetracycline, are not recommended for children under 8 years of age. Topical and oral retinoids are recommended in adolescent and younger children if the acne is severe and there is risk of scarring (13). Although Eichenfield et al. (13) do not indicate an age limit, they suggest careful monitoring of potential side effects and toxicities, extensive counselling and avoidance during pregnancy.
Combination oral contraceptive pills (COC) are recommended for females with no history of cardiovascular disease. Treatment is long term and treatment response is usually seen after the third cycle. Second-line treatment of acne vulgaris includes COC for females of any age with inflammatory lesions (13, 14) to suppress ovarian androgen activity and prevent sebum plugging in sebaceous glands. COC should not be used in adolescents within two years of first starting menses and in young girls less than 14 years old. COC are not recommended for males due to adverse effects such as gynecomastia. Eichenfield et al. (13) recommend COC within one year of the onset of menstruation. They do not indicate an age limit. Recent studies on prescribing practices for acne have shown a decrease in prescribing COC for acne (132).

Spironolactone, an aldosterone receptor antagonist that has potent antiandrogen activity, is not approved by the US Food and Drug Administration (FDA) for the treatment of acne. Nevertheless, it is still recommended by both the AAD (28) and the American Acne and Rosacea Society (13) based on expert opinion rather than published data.

Although acne vulgaris is not strictly considered an infection, OAB are prescribed to decrease *P. acnes* in sebaceous glands producing inflammation and sebaceous plugging (125, 133-135). *P. acnes* can create biofilms which are a physical barrier for antibiotics to penetrate, which may impact on their effectiveness (Suh and Kwon 2015; Tan and Bhate 2015). Despite the risk of antibiotic resistance, systemic antibiotic prescriptions for acne by general practitioners have increased (132, 136).
TRs such as adapalene gel normalise desquamation of follicular epithelium, preventing new comedonal activity. Oral retinoids such as isotretinoin and tretinoin are used long term (up to one year in eight treatment week intervals with a break of two to four weeks) in severe refractory or scarring acne, but have AEs including hip growth plate injuries, neutropenia, depression and suicidal ideation (125, 137) and are teratogenic (137, 138). The number of isotretinoin courses prescribed for patients with acne by dermatologists and non-dermatologists decreased from 2004 to 2014 (132).

Studies on acne prescribing trends by general practitioners have found increasing prescriptions for systemic tetracyclines and isotretinoin from 2005 to 2015, with 75 per cent of tetracyclines prescribed for an average of 2.8 and 3.3 months (136). Prescriptions for spironolactone, COC and OAB by dermatologists and non-dermatologists all increased between 2004 and 2013 (132).

The European Evidence-Based (S3) Guidelines for the Treatment of Acne 2012 (127) provide comprehensive guidance on improving management of adult patients with acne, including diagnosis, reduction of scarring that can occur with cystic or nodular/conglobate acne, promotion of adherence to treatment and reducing antibiotic resistance. The American Acne and Rosacea Society (13) has provided consensus treatment recommendations based on a literature review of current evidence on the various types of acne found in children. The guideline also includes recommendations on methods of rating severity and clarification of categorisation of paediatric acne. Treatment algorithms are included to aid practitioners in diagnosis and treatment.
The most recent Australian treatment guidelines for acne were published in 2010. The Royal Australian College of General Practitioners (RACGP) (125) provided treatment recommendations for mild, moderate, moderate-to-severe and severe acne for both children and adults. There is a strong emphasis on patient education and countering myths patients might encounter. First- and second-line treatments described in the Australian guideline are similar to those described in the guideline of the AAD. A recent review of treatment in Australia suggested that expert consensus was the basis for treatment guidelines (139). They supported early treatment intervention with systemic therapy when topical therapy was unsuccessful. The British Association of Dermatologists and the Royal College of General Practitioners both published guidelines for acne in 2012 (140). Topical and oral therapies recommended are similar to those of other published guidelines. No guidelines were provided for severity grading. They do, however, emphasise the need to refer to specialists if there are diagnostic uncertainties, a failure to respond to recommended treatments after six months, nodular or moderately severe acne with deeply pigmented skin, or major psychological disturbances.

The Ministry of Health (MOH) of Malaysia published a clinical practice guideline for the management of acne in 2012 (141). The main recommendations are similar to those of other published recommendations for topical and oral treatments, with the exception that it does recommend single topical therapy such as TRs for mild to moderate acne as well as combined topical therapy. It also recommends other topical therapies not mentioned in other guidelines, such as sulfur-based topical combinations and azelaic acid. Salicylic acid used in chemical peels is also recommended by the MOH. These interventions only provided mild improvements in mild and
moderate acne, and the other guidelines do not recommend them as first-line treatments (13, 28, 125).

Four Cochrane reviews evaluated the efficacy and safety of COC, laser therapy, minocycline and spironolactone for acne (14, 142-144). Arowojolu et al. (14) found, in 31 RCT, that COC reduced total lesion counts, but no benefit was seen with spironolactone. Jordan et al. (144) found a lack of controlled studies of laser therapy for acne scars, and evidence was based on 14 case series. There was some evidence that laser improved scars, but most was visual observation of improvement without blinded assessments. Garner et al. (143) found that minocycline was effective for moderate and moderate-to-severe inflammatory acne with the same AE and antibiotic-resistance profiles as other tetracyclines. Brown et al. (142) evaluated spironolactone for acne and hirsutism and found no benefit for the management of acne, although spironolactone did decrease the degree of hirsutism.

2.9.2 Non-pharmacological approaches

2.9.2.1 Cultural and self-management practices

Skin hygiene improves acne by reducing *P. acnes* and sebum production (145). Gentle face-washing with cleansers that are not too drying, washing hair that is oily and not picking lesions so as to prevent scars are advice from the AAD (28). Facial makeup is often used by females and males to hide lesions and is not thought to worsen lesions (146). It has been shown to improve QoL for those on treatment for acne (147). Sunlight was previously thought to improve lesions due to the relationship with *P. acnes*; however, this is no longer thought to be the case as sunlight can cause environmental damage to the skin (90).
2.9.2.2 Diet

Treatment guidelines currently do not include any dietary changes, although there is limited evidence that low-glycaemic diets and skim milk may be associated with acne (28). It is suggested that, due to a significant association between strong IGF-1, high BMI and severe acne, diet may be a valuable dietary intervention (148). Low glycaemic index diets have been shown to improve acne in a pilot study, as high glycaemic load foods tend to increase insulin growth factors which increase sebum production, worsening acne (149, 150).

2.9.2.3 Laser light

Lasers and light devices are yet to be recommended and more studies are needed. The most promising evidence is for photodynamic therapy (PDT) with a photosensitiser such as aminolevulinic acid applied for 15 minutes to three hours. Consensus on incubation time and light sources is yet to be determined (28). The MOH recommends phototherapy and PDT as an alternative therapy for those who are unable to tolerate standard acne therapies and for those in whom standard therapies have failed (141).

2.9.2.4 Physical modalities

Surgery is not recommended in any of the treatment guidelines for treatment of acne vulgaris. Other physical therapies such as chemical peels with agents such as salicylic acid, trichloroacetic acid, chemical reconstruction of skin scars (TCA Cross) technique, dermabrasion/microdermabrasion and skin needling have been proposed (29), but the strength of evidence for these treatments is low (28). Comedone removal is only recommended for comedones
resistant to other therapies and intralesional corticosteroid injections are recommended for the treatment of individual acne nodules (28).

2.9.2.5 Complementary and alternative medicine

Many people use complementary and alternative medicine (CAM) for skin conditions (151). Due to antibacterial resistance, investigations of alternatives to antibacterial treatment have been conducted (152-154). In a study by Magin et al. (155) of patients recruited from dermatological practices in Australia, the majority of respondents with acne had used CAM products including witch hazel (*Hamamelis virginiana*), tea-tree oil (*Leptospermum spp.*), citrus washes, aloe vera (*Aloe vera*), zinc tablets, herbal remedies, tissue salt tablets, natural oils and evening primrose oil (*Oenothera biennis*). In another review of CAM products, basil oil (*Ocimum sanctum*, *Ocimum basilicum* and *Ocimum gratissimum*) was found to have antimicrobial effects and reduced lesion counts faster than 10 per cent BP lotion (156). Copaiba oil and green tea are reported to have anti-inflammatory effects. Green tea and resveratrol also have antimicrobial properties (152). The traditional Italian herbs *Vitis vinifera* leaves, *Asphodelus microcarpus* leaves and *Vicia sativa* aerial parts were found to inhibit *P. acnes* growth and affect the biofilm of the bacteria (153). A combination of the Ayurvedic herbs Guduchi (*Tinospora cordifolia*), Manjishtha (*Rubia cordifolia*), Sarva (*Hemidesmus indicus*), Nimba (*Azadirachta indica*), Khardira (*Acacia catechu*) and Kakmachi (*Solanum nigrum*) extracts had significant anti-inflammatory and antimicrobial activity (154).

A Cochrane review of CAM included 3,227 participants from 35 trials (157). Trials included in the review evaluated herbal medicine, acupuncture, wet cupping, diet, purified bee venom (PBV)
and tea-tree oil. There was low-quality evidence that low glycaemic load diet, tea-tree oil and PBV may reduce total skin lesions, but a lack of evidence to support herbal medicine and acupuncture for acne. Overall, the methodological quality of trials was low and weakened the evidence (157).

A systematic review of botanical and phytochemical treatments for acne vulgaris (20) included 23 clinical trials published in English, 3 of which were trials of Kampo/Chinese herbal formulations. Meta-analysis was not performed. The herbal preparations showed improvement for mild to moderate acne, although there were limitations to the studies such as a lack of acne-grading methods, lack of control or placebo groups, and no assessment of lesion count.

Two systematic reviews of acupuncture, one in English (157) and one in Chinese (18), have been published. Cao et al. (157) evaluated acupoint-stimulation techniques including acupuncture, moxibustion, cupping, acupoint injection and acupoint catgut embedding compared with no treatment, placebo or conventional pharmaceutical medication. They also included combinations of acupoint-stimulation techniques plus other therapies as interventions, compared to the same or other therapies alone. The review included 43 trials with 3,453 participants. They described the methodological quality of the trials as generally poor. They found acupuncture plus herbal medicine was better than herbal medicine alone and acupuncture plus a herbal facial mask was better than a herbal facial mask alone. Cupping was significantly better than pharmaceuticals, with no serious adverse events (SAEs) reported (157). Li et al. (18) evaluated manual acupuncture and moxibustion compared to routine conventional medicine (isotretinoin and antibiotics) and multiple Chinese medicine therapies. They included 17 trials with 1,613 participants. They found acupuncture and moxibustion were better than acupuncture alone and better than routine Western medicine, although the quality of the evidence again was low (18).
Both reviews included studies that compared interventions to other herbal medicines or CM techniques where the effectiveness of these techniques are not established. Including these studies into these reviews can dilute the strength of the results. A review that includes studies that compared controls using placebo or medications with known efficacy will give rigour to the results. The above reviews included studies of techniques that are not common outside of China such as catgut embedding and blood cupping as “acupuncture” techniques. The above reviews also included acupuncture combined with herbal medicines and did not analyse herbal medicines alone.

2.10 Chapter summary

Acne vulgaris is a multifaceted chronic skin condition lasting up to ten years. It can affect patients’ QoL and impact on social and work life. The pathophysiological understanding of acne is evolving, with current mechanisms including inflammation and hyperkeratinisation. Treatment using topical and oral antibiotics, and topical and oral retinoids are recommended; these decrease inflammation and suppress sebum production that causes follicular plugging. Other therapy options include complementary and alternative medicines and dietary recommendations, although good evidence for these therapies is lacking.
CHAPTER 3 : Chinese medicine for acne vulgaris

3.1 Introduction to Chinese medicine

CM is a health care system that groups symptoms into a pattern of disease (syndrome differentiation) (158). The aim of CM is to balance *yin* and *yang*, which are opposing yet complementary forces in the body. Environmental, lifestyle, diet and exercise factors can contribute to an imbalance of *yin* and *yang* in the body. Pathogenic factors from external or internal sources such as wind, heat, summer-heat, dampness and fire can cause dermatological conditions in CM. Other aetiological factors include insects and parasites (159). These aetiological factors can affect a person’s *zang fu* (internal organs) or their meridians where *qi* (energy) circulates.

During a patient consultation, CM practitioners use their clinical skills to ask a series of questions about the patient’s main complaint, as well as other questions about their general health. Questions also relate to emotional, psychological and physical symptoms such as possibility of pain, sleep disturbances, emotional disturbances, food taste and preferences, chest or abdominal symptoms and other bodily functions. CM practitioners observe the patient, using their senses of sight, smell and listening.

Based on the answers given and the observations made, the practitioner uses their clinical reasoning to formulate a syndrome, taking into consideration the aetiology (cause) and the pathogenesis (how the disease develops). The practitioner will then differentiate it from other possible syndromes, arriving at a diagnosis that conforms to CM theory (160). After a diagnosis is made and a syndrome is differentiated, a treatment principle is formed. Practitioners treat the main
complaint, as well as addressing all presenting symptoms together. They also consider the environmental, dietary, emotional and lifestyle factors of the patient and provide advice according to CM principles. CM emphasises individualised treatment based on differentiation of the pathogenic or inherent differences in the patient (161).

3.2 Chinese medicine definition of acne vulgaris

In CM, acne vulgaris (acne) is called *cuo chuang* and *fen ci* (162). It is also known as *fei feng fen ci* (肺风粉刺) (Lung-wind powder prickles) or *fen ci* (粉刺) (powder prickles). These terms reflect the starch-coloured fluid contained within the comedones that is attributed to the Lungs (肺 fei) (159). Other terms include *cuo chuang* (痤疮) and *an chuang* (暗疮) and in lay terms it is called *jiu ci* (酒刺) and *qing chun ci* (青春刺). The name *jiu ci* (酒刺) is translated as “wine prickles” related to acne rosacea and *qing chun ci* (青春刺) translates as “teenage prickles” reflecting the condition affecting adolescents.

3.3 Aetiology and pathophysiology in Chinese medicine

Acne is a disorder of the sebaceous glands that are distributed on the face, chest and back (6). In CM, sebaceous glands are associated with the Lungs and Spleen (159). The Lungs protect the surface of the body (in CM, this is known as *wei*) to prevent invasion of pathogenic factors. Along with the Stomach, the Spleen transforms and transports food to produce nutrients (*ying* in CM) (158). Figure 3.1 summarises the aetiology and pathogeneses in a flow chart.

In CM there are a few factors that can cause acne. Underlying heat in the Blood is the main aetiological factor responsible for acne (159). Adolescents are considered more active or warmer
in nature and constitutionally tend towards *yang* (159, 163). The abundant *yang*, due to constitutional *yang* type or Kidney *yin* deficiency, can lead to heat. Heat in CM describes the nature of the condition rather than a symptom of inflammation. Heat warms the *yin* and Blood levels. The flow of *qi* and Blood slows in the meridians and collaterals and they become congested, leading to Blood stagnation. Blood stagnation that stays in the body generates heat in the Blood, transforming into Blood-heat. Blood and heat push outwards to the surface, causing red eruptions. Blood-heat can further consume *yin* and Blood and causes *qi* and Blood stagnation that can cause nodular eruptions.

Damp is both an external and internal pathogenic factor that can develop due to environmental factors or poor diet. Poor diet such as a diet high in greasy, sweet or spicy foods or fish and shellfish can weaken the transforming and transporting function of the Spleen, leading to damp accumulation. Dampness manifests in the body with skin symptoms such as acne, vesicles (fluid filled blisters) and greasy, oily skin (159). Dampness that remains in the body over time can transform into damp-heat. Damp-heat can accumulate in the Lungs and Stomach. It can transfer to the Stomach and Large Intestine (*Yangming* meridians), which reflects on the jaw and around the nose (159). Damp-heat can also accumulate in the skin and tissues, causing inflammation and swelling. Damp-heat can transform into fire that steams upwards to the surface of the skin, causing small red eruptions of papules or comedones (159, 164). Toxins in CM refer to paroxysmal and extreme pathogenic factors that attack the body or are associated with bacteria, viruses and fungi (159). An attack of damp toxins can block Blood circulation, resulting in damp toxins with Blood stasis (165). These previous syndromes are associated with mild-to-moderate comedonal acne.
Dampness can block the circulation of body fluids and lead to phlegm accumulation in the body. This can also lead to blockage of qi and thus Blood circulation over time. When these blockages manifest on the skin, it can lead to cysts and nodules. Cystic or nodular acne is associated with toxic heat and/or phlegm and Blood stagnation.

General poor health can allow external pathogenic wind and heat to enter the body, as can washing in cold water. Both activities can block the pores. Existing heat in the Blood combined with these factors leads to inflamed comedones. If existing qi and Blood stagnation is aggravated by emotional disturbances, qi stagnation can further lead to heat in the body which consumes Blood and body fluids and cause Blood stasis. If there is prolonged heat in the Lungs and Stomach, heat can transform damp into phlegm, which can cause cystic or nodular acne resulting in toxic heat or Blood stasis binding with phlegm (159). These last two syndromes are associated with moderate-to-severe acne.

Constitutional Kidney yin deficiency combined with emotional disturbances resulting in qi stagnation can cause a disharmony between Chong (冲, Thoroughfare vessel) and Ren (任, Conception vessel). The “sea of Blood” (Chong and Liver meridians) cannot be nourished and irregular menstruation and worsening of acne around menstruation can occur (164).
<table>
<thead>
<tr>
<th>Onset of adolescence</th>
<th>Emotions</th>
<th>External pathogenic attacks</th>
<th>Improper diet</th>
<th>Blood stagnation; Heat in the blood; Phlegm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendency towards yang</td>
<td>Qi stagnates</td>
<td>WH invasion or washing in cold water</td>
<td>Impair TT of SP</td>
<td>Accumulate in LU &amp; ST</td>
</tr>
<tr>
<td>Warms ying &amp; Blood</td>
<td>Congest meridians</td>
<td>Bind Blood heat</td>
<td>Generate fire / transform damp into phlegm</td>
<td>Heat toxins bind with phlegm or Blood stasis</td>
</tr>
<tr>
<td>Congest meridians</td>
<td>Qi and Blood stagnation</td>
<td>Heat in the Blood</td>
<td>Heat rises to upper body</td>
<td></td>
</tr>
<tr>
<td>Stagnation in Qi &amp; Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comedonal acne**

Abbreviations: LU Lung, ST Stomach, SP Spleen, TT transforming transporting, WH wind-heat

**Figure 3.1 Aetiology and pathogenesis of acne in CM**
3.4 Chinese medicine diagnosis and differentiation compared to Western Medicine

CM diagnosis first requires the practitioner to ask a series of questions on the main complaint and then use “10 traditional questions” to gather information on the patient’s reason for seeking treatment and their overall health (158). The practitioner will also perform physical examination using their senses such as observing for skin colour changes or other physical symptoms, olfaction for different smells that may come from the patient, and auscultation, listening for changes in voice, lung sounds or cough sounds. This overall narrative of signs and symptoms is then categorised into a number of syndromes depending on the various CM theories. Examples include five-element theory, Zang-fu (organ) theory and meridian theory. Similar skills are used during WM consultations to obtain clinical information from patients. However, a WM practitioner will not necessarily ask about gastrointestinal function such as appetite or bowel movements when a patient presents with a headache whereas a CM practitioner will. In clinical practice a consultation with a CM practitioner is often up to 30 minutes in a new consultation.

Depending on the symptoms and conditions presented, the practitioner would group these symptoms and diagnose and treat based on this differentiation. For example, a patient with a common cold may present with a runny nose, clear nasal discharge, headaches and body aches would be categorised with a “wind-cold” syndrome. Another patient, also presenting with a common cold, may describe symptoms of a sore throat, cough, thirst and fever; they would be diagnosed with a “wind-heat” syndrome. CHM and acupuncture treatment will be different based on the syndrome diagnosis. Diagnosis in WM would be common cold from viral or bacterial infection. Treatment may or may not differ depending on the patients most bothersome symptoms.
3.5 **Chinese medicine syndrome differentiation**

CM textbooks and treatment guidelines categorises acne lesions into lesion types and syndromes. Comedonal acne is categorised into three main syndromes (159, 164, 165): heat in the Lung, heat in the Stomach (sometimes combined as heat in the Lung and Stomach), and heat in the Blood. Cystic or nodular acne (and severe inflammatory cystic acne, acne conglobata) is categorised into two syndromes: Blood stasis and Blood stasis with phlegm binding. Cyclic acne is categorised as qi and Blood stagnation. There are some variations in syndromes, including Kidney yin deficiency (164) describing the natural yang exuberance of adolescents, and damp toxins with Blood stasis (165), which has a similar presentation to Blood stasis with phlegm (159). CM treatment guidelines also have some variations in the syndrome names and have additional syndromes that are not present in CM textbooks. Syndromes include wind-heat stagnating in the Lung meridian, heat stagnating in the Liver meridian and imbalance of Chong and Ren vessels, dampness-heat stagnating in the Stomach and Intestines, dampness-heat stagnating in the Spleen and Stomach, accumulation of dampness-heat, toxic heat and Blood stasis, and phlegm obstruction and Blood stasis. A summary of the syndromes and related symptoms seen in comedonal acne are found in Table 3.1.

The following is a summary of the syndromes described in the textbooks and treatment guidelines. Three English-language publications describe the syndromes and treatments described below. These are the books *Dermatology in Traditional Chinese Medicine* (159), *Manual of Dermatology in Chinese Medicine* (165) and *Acne and Alopecia* (164). Three published treatment CM guidelines for dermatological conditions were also consulted: *Treatment Guidelines for Acne Vulgaris in China* (2014 edition) 中国痤疮治疗指南 (162), *Guidelines for Diagnosis and Treatment of
3.5.1 Heat in the Lungs and wind-heat stagnating in the Lung meridian

Acne due to heat in the Lungs is the most common clinical presentation. In his book on CM dermatology, Xu (159) describes comedones due to heat in the Lungs as small (approximately two millimetres) red or pale red papules. Closed comedones and pustules tend to be located on the forehead and cheeks and around the nose. The patient may have oily skin and accompanying dry mouth and nose. The tongue body is red with a thin yellow coating and the pulse will be floating.

CM treatment guidelines consider that wind and heat are both present in acne and describe the syndrome of wind-heat stagnating in the Lung meridian. Lesions include open and closed comedones and red papules. Accompanying symptoms and signs include red face, bad breath, itching, pain, dry mouth and dry stools. The tongue is yellow with a thin coating and there is a slightly floating or taut or floating and rapid pulse (162, 166).

3.5.2 Heat in the Stomach

Comedones due to heat in the Stomach present in a similar manner to heat in the Lungs; however, the lesions are distributed around the mouth. Accompanying symptoms include bad breath, aversion to heat, thirst with a preference for cold drinks, constipation and dark-yellow urine. The
tongue body will be red with a thin yellow or greasy coating and the pulse will be slippery and rapid (159). CM treatment guidelines do not describe heat in the Stomach as a separate syndrome. However, some of the symptoms in the syndrome wind-heat stagnating in the Lungs such as bad breath and dry stools may be due to heat in the Stomach.

3.5.3 Heat in the Blood and yin deficiency generating internal heat

Emotional disturbances cause qi to stagnate and transform into heat. This can aggravate existing heat in the body, causing heat in the Blood. In this syndrome, comedones are concentrated around the nose and mouth and between the eyebrows. Heat may also cause telangiectasia and a red face. Comedones can worsen around women’s menstrual cycles. Accompanying symptoms are similar to those seen with heat in the Stomach and include dry stools and yellow urine. The tip of the tongue will be red and there will be a yellow coating; the pulse will be thready, slippery and rapid (159).

Yin deficiency generating internal heat presents with red papules, pustules or nodules on the face. Additional symptoms include dry mouth, irritability, dream-disturbed sleep, dry and hard stools and reddish urine. The tongue is red with a thin yellow coating and the pulse is rapid or thready and rapid (164).

3.5.4 Stagnation of qi and Blood and heat stagnating in Liver meridian

In this syndrome, red or dark papules can be present for several years. Accompanying symptoms will be associated with a disharmony of the Chong and Ren meridians. In women, it is associated with irregular menstruation, clots in the menstrual blood and abdominal pain. In men, a darker
complexion may result. The stagnation of qi and Blood and heat in the Blood syndromes in women tend to relate to cyclic acne, but not in all women. Comedones worsen around women’s menstrual cycles and resolve after their menstrual cycles (159, 164). The tongue body is dark or has dark red or brown spots and the pulse is deep, thready and choppy.

Heat stagnating in the Liver meridian presents with similar symptoms as the stagnation of qi and Blood. Inflammatory papules and pustules along with irritability, insomnia, dream-disturbed sleep, dry mouth, bitter taste and dry stools may be present. In women, breast distension, irregular menstruation, menorrhagia or hypomenorrhoea may also be present with acne worsening around the menstrual cycle. The tongue is red with a yellow coating and the pulse is taut and thready or taut and rapid (166).

3.5.5 Imbalance of Thoroughfare (Chong) and Conception (Ren) vessels

Imbalance of Thoroughfare (Chong) and Conception (Ren) vessels are also described in the CM treatment guidelines. In this syndrome, lesions also worsen or improve around menstruation. Lesions are located on the forehead and cheeks or between the eyes. Lesions are aggravated before menstruation and improve after. Additional symptoms include irregular menstruation, premenstrual irritability and breast distension. The tongue is pale red with a thin coating and there is a deep and taut or hesitant pulse (162). These syndromes may be classified as mild-to-moderate acne.
3.5.6 Dampness-heat stagnating in Stomach and Intestines; dampness-heat stagnating in the Spleen and Stomach; accumulation of dampness-heat

These syndromes described in the CM treatment guidelines include papules and pustules that are painful, pores that are prominently seen, and skin that is oily and may develop into nodules or cysts. Additionally, there may be occasional bad breath, lack of thirst, bitter taste, loss of appetite, loose or sticky stools or constipation, and dark-coloured urine. The tongue is red with a yellow greasy coating (162, 166, 167). These syndromes may be classified as mild-to-moderate acne.

3.5.7 Damp toxin with Blood stasis and toxic heat and Blood stasis

Damp toxins with Blood stasis result in deep, painful inflamed nodules and pus-filled cysts with erythema on the face, chest and back. These symptoms are similar to the signs and symptoms reported in the Blood stasis and binding of phlegm syndrome (below). The affected areas will be oily and rupture of lesions can result in scarring. Other accompanying symptoms include headache and feeling hot in the body. The tongue body will be purple with a yellow or white coating. The pulse will be slow or submerged and choppy (165).

The toxic heat and Blood stasis syndrome presents with similar lesions types and locations as the damp toxins with Blood stasis. It can also include hyperpigmentation with scarring. It is noted that this may occur during puberty. Additional signs and symptoms include dry mouth and thirst, irritability, feverish sensation, bad breath, dry stools and dark urine. The tongue is red with a yellow coating and the pulse is surging or taut and rapid (166). These types of acne may be classified as moderate to severe.
3.5.8 **Blood stasis and binding of phlegm**

These lesions are double the size of the lesions described in the previous syndromes. Instead of pustules and papules, the lesions are 3-5 mm cysts or nodules that are red to purplish and soft on palpation. They will exude pus and blood if ruptured. Scarring may result from rupture of these cysts. The tongue body will be pale red with a greasy tongue coating and the pulse will be soggy and slippery (159, 164). Nodular or cystic acne may be classified as moderate to severe.

Phlegm obstruction and Blood stasis is also described in the CM treatment guidelines. Lesions are similar to the Blood stasis and binding of phlegm, although the Blood stasis and binding of phlegm may linger for a long time. Additional symptoms include chest tightness, abdominal distension, fatigue, sticky mouth, loss of appetite and loose stools associated with phlegm obstruction. In women, irregular menstruation, dark purple clots and dysmenorrhoea may result from Blood stasis. The tongue may have purplish spots on the tip and sides with a yellow and greasy coating. The pulse may be taut and slippery or deep and hesitant (166).

---

**Table 3.1 Comedonal features and syndrome related symptoms of acne**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Comedonal features</th>
<th>Related symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat in the Lungs</td>
<td>Small (approximately two millimetres) red or pale red papules located around forehead and cheeks</td>
<td>Oily skin and accompanying dry mouth and nose.</td>
</tr>
<tr>
<td>Wind heat stagnating in Lung meridian</td>
<td>Open and closed comedones and red papules</td>
<td>Red face, bad breath, itching, pain, dry mouth and dry stools</td>
</tr>
</tbody>
</table>

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51
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Comedonal features</th>
<th>Related symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat in the Stomach</td>
<td>Comedones distributed around the mouth</td>
<td>Bad breath, aversion to heat, thirst with a preference for cold drinks, constipation and dark-yellow urine</td>
</tr>
<tr>
<td>Heat in the Blood and <em>yin</em> deficiency generating internal heat</td>
<td>Comedones are concentrated around the nose and mouth and between the eyebrows</td>
<td>Telangiectasia and a red face. Comedones can worsen around women’s menstrual cycles, dry stools and yellow urine</td>
</tr>
<tr>
<td>Stagnation of <em>qi</em> and Blood</td>
<td>Red or dark papules can be present for several years</td>
<td>In women, irregular menstruation, clots in the menstrual blood and abdominal pain. In men, a darker complexion</td>
</tr>
<tr>
<td>Heat stagnating in Liver meridian</td>
<td>Inflammatory papules and pustules worsening around the menstrual cycle</td>
<td>Irritability, insomnia, dream-disturbed sleep, dry mouth, bitter taste and dry stools; in women, breast distension, irregular menstruation, menorrhagia or hypomenorrhoea may also be present with acne</td>
</tr>
<tr>
<td>Imbalance of Thoroughfare <em>(Chong)</em> and Conception <em>(Ren)</em> vessels</td>
<td>Lesions aggravated before and improve after menstruation, located on forehead and cheeks or between the eyes</td>
<td>Irregular menstruation, premenstrual irritability and breast distension</td>
</tr>
<tr>
<td>Dampness-heat stagnating in Stomach and Intestines, dampness-heat stagnating in the Spleen and</td>
<td>Papules and pustules that are painful, pores that are prominently</td>
<td>Bad breath, lack of thirst, bitter taste, loss of appetite, loose or</td>
</tr>
</tbody>
</table>

<p>| 52 |</p>
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Comedonal features</th>
<th>Related symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach accumulation of dampness-heat</td>
<td>seen, and skin that is oily and may develop into nodules or cysts</td>
<td>sticky stools or constipation, and dark-coloured urine</td>
</tr>
<tr>
<td>Damp toxin with Blood stasis</td>
<td>Painful inflamed nodules and pus-filled cysts with erythema on the face, chest and back, oily and rupture of lesions can result in scarring</td>
<td>Include headache and feeling hot in the body</td>
</tr>
<tr>
<td>Toxic heat and Blood stasis</td>
<td>Hyperpigmentation with scarring</td>
<td>Dry mouth and thirst, irritability, feverish sensation, bad breath, dry stools and dark urine</td>
</tr>
<tr>
<td>Blood stasis and binding of phlegm</td>
<td>Lesions are 3-5 mm cysts or nodules that are red to purplish and soft on palpation, exude pus and blood if ruptured</td>
<td>Chest tightness, abdominal distension, fatigue, sticky mouth, loss of appetite and loose stools, in women, irregular menstruation, dark purple clots and dysmenorrhoea</td>
</tr>
</tbody>
</table>

### 3.5.9 Chinese medicine syndromes in clinical trials

The syndromes described in the CM textbooks and treatment guidelines provide guidance for clinical practice. Clinical studies provide further guidance for selection of treatment and are particularly useful when results are presented according to CM syndromes. CM syndromes in clinical studies have been described in an *Evidence-based Clinical Chinese Medicine* monograph on acne vulgaris (168). The syndromes used as inclusion criteria for the clinical studies were similar to the syndromes outlined in the CM textbooks and treatment guidelines. The most
common syndrome encountered was heat in the Lungs or wind-heat stagnating in the Lung meridian. Damp-heat syndromes such as damp-heat toxins, damp heat in the Stomach and Spleen or Intestines, and damp-heat and Blood stasis were reported to be used. Phlegm syndromes included phlegm and dampness, and phlegm and Blood stasis. Heat in the Liver meridian, Liver qi stagnation, imbalance of Chong and Ren vessels were also used.

3.6 Chinese medicine treatment
There are several different forms of treatment in CM: CHM, acupuncture of body acupuncture points and acupuncture-related manual therapies. CHM is a common type of treatment used in CM for acne. For dermatological conditions, it is common for both oral and topical herbs to be prescribed together. Topical herbs are applied directly to the lesions on the afflicted skin, and oral herbs are used to address the internal or aetiological factors. Topical herbs have a long history in CM and are used in various forms from poultices to washes and powders. Oral herbs are traditionally in the form of decoctions and pills or boluses. In clinical practice, CHM may be combined with acupuncture treatment for acne.

The common types of acupuncture and acupuncture-related techniques include body acupuncture (insertion of fine needles into specific loci on the body), auricular acupuncture (insertion of fine needles into specific loci in the ear), acupressure (applying blunt pressure to specific loci in the body), moxibustion (heat from burning of artemisia argyi Levl. Et Vant. directed at specific acupuncture points), warming needles (where a small piece of moxa is placed on top of a needle and allowed to burn down), cupping (suction of skin and muscles from glasses or other type of
cups formed from a vacuum), cutaneous acupuncture (seven-star and plum-blossom needling) and EA (a mild electrical current applied to acupuncture needles to provide constant stimulation) (169).

Body acupuncture is the most common form of acupuncture technique used in treatment of acne. Additional acupuncture techniques may also be combined with body acupuncture. The Chinese term for acupuncture is zhen jiu (针灸), which literally means ‘acupuncture and moxibustion’. This shows the similarity between the two interventions, which are often combined in clinical practice. For acne, cupping, cutaneous needling, auricular acupuncture and EA are often combined with body acupuncture (157, 159, 165). All these acupuncture interventions have been evaluated in clinical trials of acne. There have been two systematic reviews on acupuncture for acne and one Cochrane review on complementary medicines for acne (157). A summary is found in Chapter 8: Systematic review of acupuncture for acne vulgaris.

3.6.1 Oral Chinese herbal medicine for acne vulgaris

The aim of CM treatment is to reduce the number of lesions by addressing the syndrome differentiation. This may include reducing heat in the Lungs or Stomach, reducing dampness-heat in the body and preventing dampness-heat from transforming into Blood stasis and phlegm (158), clearing heat toxins, resolving the phlegm and dissipating Blood stagnation by increasing Blood circulation (159, 164, 165).

CM treatments are tailored to each syndrome and lesion type. A summary of the acne lesion types, syndromes and oral and topical formulas is found in Tables 3.2 and 3.3. For the Chinese formula names and species names of oral herbs, refer to Appendix 1, and for topical herbs, refer to
Appendix 2. Ingredients and formulas are sourced from CM dermatology textbooks (159, 164, 165) and CM treatment guidelines (162, 166, 167). There are also recommendations for women to regulate their menstruation to prevent aggravation of symptoms around menstruation with acupuncture or CHM (159). For both men and women, it is recommended to regulate gastrointestinal functions by eating regularly and avoiding aggravating foods such as greasy and spicy foods. This prevents accumulation of dampness-heat internally which can turn into phlegm and worsen acne (159).

Individual oral CHM formulas are prescribed for each syndrome. Herbs included in these formulas act to clear Lung heat, regulate Blood circulation, clear heat toxicity or clear dampness-heat or phlegm. A summary of the acne lesion types, syndromes and oral formulas is found in Table 3.2. For comedonal or inflammatory acne, *Pi Pa Qing Fei Yin* (PPQFY) (枇杷清肺饮) is the key formula that is commonly prescribed for comedonal acne which acts to clear heat in the Lungs (159) and wind-heat in Lung meridians (162, 166). It is also recommended for this syndrome by the China Association of Chinese Medicine in their *Guidelines for Diagnosis and Treatment of Common Disease of Dermatology in Traditional Chinese Medicine* (166). The formula consists of herbs that clear heat in the Lungs and dampness-heat in the upper and middle energisers, tonify the *qi* and harmonise the herbs. The ingredients in the formula have been shown to decrease inflammation (170) and sebum (171).

*Liang Xue Qing Fei Yin* (凉血清肺饮) (159, 165) is another formula that addresses heat in the Lung and *qi* and Blood stagnation. It has similar ingredients to PPQFY. It differs in that it contains herbs that invigorate Blood circulation and cool the Blood. For heat in the Stomach, *Tiao Wei
*Cheng Qi Tang* (调胃承气汤) is used to purge the Stomach heat by purging the intestines.

For *yin* deficiency that generates internal heat, *Xiao Cuo Tang* (消痤汤) contains herbs that tonify essence (*jing* 精), clear deficient and pathogenic heat, and invigorate Blood circulation. *Tao Hong Si Wu Tang* (桃红四物汤) and *Liang Xue Wu Hua Tang* (凉血无华汤) are prescribed for heat in the Blood and have ingredients that invigorate Blood circulation, clear heat from the Blood, tonify Blood and clear pathogenic heat. *Tao Hong Si Wu Tang* is combined with modified *Wu Wei Xiao Du Yin* 五味消毒饮 for toxic heat and stasis syndrome. Finally, for heat toxins *Cuo Chuang Jian Ji Tang* (Chinese characters not identified) is prescribed. It contains ingredients that clear pathogenic heat, clear damp-heat and invigorate Blood circulation, and an ingredient (*Jie geng*, *Platycodon grandiflorum* (Jacq.) A. DC.) that will raise the herbs upwards to the afflicted area and resolve phlegm.

Modified *Chai Hu Shu Gan Wan* (柴胡疏肝丸加减) can be prescribed for *qi* and Blood stagnation and has similar ingredients to *Xiao Yao San* (逍遥散) and *Dan Zhi Xiao Yao San* 丹栀逍遥散加减. *Xiao Yao San* and *Dan Zhi Xiao Yao San* are prescribed for heat stagnating in the Liver meridian and imbalance of *Chong* and *Ren* vessels, respectively. Herb ingredients aim to regulate menstruation and clear heat in the Liver. *Liang Xue Qing Fei Yin* (凉血清肺饮) is also used in cyclic comedonal acne as it contains herbs that invigorate Blood circulation and cool the Blood, as well as herbs that clear heat in the Lung. Another suggested formula is modified *Chai Hu Shu Gan Wan* combined with ingredients...
from *Xiao Cuo Tang* (消痤汤) (164). The formula presented is heavily modified. It contains four ingredients from the two formulas plus herbs that tonify the Kidney *yin*, clear heat toxicity and invigorate Blood circulation.

Formulas that address cystic or conglobate acne have ingredients that clear dampness-heat, invigorate Blood stasis, clear heat in the Blood and resolve dampness-heat toxins and phlegm. For damp toxin with Blood stasis, *Chu Shi Jie Du Tang* (除湿解毒汤) (165) is prescribed. The formula ingredients clear dampness-heat and resolve toxicity. *Hai Zao Yu Hu Tang* (海藻玉壶汤) (159) is prescribed in cases of Blood stasis and binding of phlegm. The ingredients resolve phlegm, clear damp, regulate the middle energizer *qi* and clear external pathogens. Ingredients are also added to resolve hardness (*Xia ku cao, Prunella vulgaris* L.) and heal wounds (*Mu li, Ostrea gigas* Thunb.). *Tao Hong Si Wu Tang* is combined with modified *Hai Zao Yu Hu Tang* (海藻玉壶汤) to address phlegm obstruction and Blood stasis (162, 167).

### Table 3.2 Oral herb formulas for acne vulgaris

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Oral formula</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comedonal acne</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Heat in Lungs | *Pi Pa Qing Fei Yin* (159, 165)  
*Liang Xue Qing Fei Yin* (159, 165) |
| Wind-heat in Lung meridian | *Pi Pa Qing Fei Yin* (162, 167) |
| Heat in Stomach | *Tiao Wei Cheng Qi Tang* (159, 165) |
| Damp-heat stagnating in Stomach and Intestines; Pattern/syndrome of | Modified *Yin Chen Hao Tang* (162, 167); modified *Qin Lian Ping Wei San* (162) |
dampness-heat in Spleen and Stomach;
Accumulation of damp-heat

*Yin* deficiency generating internal heat  *Xiao Cuo Tang* (164)

Blood Heat  *Tao Hong Si Wu Tang* (159, 164, 165)

Heat toxins  *Cuo Chuang Jian Ji Tang* (165)

Toxic heat and stasis syndrome  Modified *Wu Wei Xiao Du Yin* plus *Tao Hong Si Wu Tang* (167)

**Comedonal cyclic acne**

Stagnation of *Qi* and Blood  *Liang Xue Qing Fei Yin* (159, 165)

Heat stagnating in Liver meridian  Modified *Dan Zhi Xiao Yao San* (167)

Imbalance of Thoroughfare (*Chong*) and Conception (*Ren*) vessels  Modified *Xiao Yao San* (162); modified *Er Xian Tang* plus *Zhi Bai Di Huang Wan* (162)

**Acne conglobate, cystic and nodular acne**

Damp toxin with Blood stasis  *Chu Shi Jie Du Tang* (165)

Blood stasis and binding of phlegm  *Liang Xue Qing Fei Yin* (159)

Phlegm obstruction and stasis  Modified *Hai Zao Yu Hu Tang* plus *Tao Hong Si Wu Tang* (162, 166); modified *Xian Fang Huo Ming Yin* (167); modified *Tao Hong Si Wu Tang* plus *Er Chen Tang* (162)

* May contain herbs that are restricted in Australia (172).

§ Refer to Appendix 1 for oral formula names in Chinese and herbal species.

### 3.6.2 Topical Chinese herbal medicine for acne vulgaris

Topical herbal medicines are also prescribed based on syndrome differentiation. A summary of the acne lesion types, syndromes and topical treatments can be found in Table 3.3. Ingredients and
formulas have been sourced from CM dermatology textbooks (159, 165). Many of the ingredients such as *liu huang* (sulphur), *zhang nao* (camphor) and lime water are ingredients that clear dampness and open orifices (159). Some of the ingredients listed in these topical formulations are on the scheduled list in Australia (172) or on the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) lists (173) and are restricted herbs in Australia.

**Table 3.3 Topical herb formulas for acne vulgaris**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Topical formula</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comedonal acne</strong></td>
<td></td>
</tr>
<tr>
<td>Lung Heat</td>
<td><em>Dian Dao San</em> (165)</td>
</tr>
<tr>
<td>Stomach Heat</td>
<td><em>San Huang Xi Ji</em> (159)</td>
</tr>
<tr>
<td>Yin deficiency generating internal heat</td>
<td>As per Lung heat</td>
</tr>
<tr>
<td>Blood Heat</td>
<td><em>Cuo Chuang Xi Ji</em> (159)</td>
</tr>
<tr>
<td>Heat toxins</td>
<td>As per Blood heat</td>
</tr>
<tr>
<td>Damp toxin with Blood stasis</td>
<td><em>Qu Ban Gao</em> (165)</td>
</tr>
<tr>
<td></td>
<td><em>Hei Bu Yao Gao</em> (159)</td>
</tr>
<tr>
<td>Blood stasis and binding of phlegm</td>
<td><em>Du Jiao Lian Gao</em> (159)</td>
</tr>
<tr>
<td></td>
<td><em>Si Huang Gao</em> (159)</td>
</tr>
<tr>
<td><strong>Cyclic acne</strong></td>
<td></td>
</tr>
<tr>
<td>Stagnation of Qi and Blood</td>
<td>As per comedonal acne Lung Heat</td>
</tr>
</tbody>
</table>

* May contain herbs that are restricted in Australia (172).

* May contain herbs that are on the CITES list.

§ Refer to Appendix 2 for topical formula names in Chinese and herbal species.

Topical preparations include powdered preparations (*san*, 散), cleansers or washes (*xi ji*, 洗剂) and ointments, plasters or masks (*gao*, 膏). Powdered herbs are placed directly on lesions.
Cleansers or washes are prepared with raw powdered herbs combined with distilled water and applied as a wash for two minutes or left on for up to 15 minutes and rinsed off. Ointments, plasters or masks are usually left on for up to 30 minutes (166) or overnight if necessary. Ointments are made with beeswax (*huang (feng) la – Apis cerana* Fabricius), honey (*feng mi – Apis cerana* Fabricius) or cold-pressed sesame oil (*xiang you – Sesamum indicum* L.).

For comedonal inflammatory acne, *Dian Dao San* (颠倒散) (165) is prescribed for Lung heat. This formula contains powdered herbs that are purgative and dry dampness. It is also used for cyclic comedonal acne due to stagnation of *qi* and Blood as the presentation of comedones is similar. *San Huang Xi Ji* (三黄洗剂) (159), prescribed for Stomach heat, contains powdered herbs that clear dampness-heat. *Cuo Chuang Xi Ji* (痤疮洗剂) (159) is prescribed for both heat in the Blood and heat toxins. It contains powdered herbs that clear heat toxicity. For cystic or conglobate acne due to damp toxins with Blood stasis, *Qu Ban Gao* (去斑膏) (165) is prescribed. It contains herbs that resolve toxicity, invigorate Blood circulation and clear heat in the Blood. *Hei Bu Yao Gao* (黑布药膏) (159) is also prescribed for this syndrome with herbs that open orifices, extinguish wind and resolve toxicity. *Du Jiao Lian Gao* (Giant Typhonium paste – Chinese characters not identified) (159) is an ointment prescribed for Blood stasis and binding of phlegm. Ingredients in this formula act to resolve phlegm, clear heat toxicity, resolve abscesses, clear external pathogens and invigorate Blood circulation. Another ointment used for this syndrome is *Si Huang Gao* (四黄膏) (159). It contains herbs that clear dampness-heat, invigorate Blood circulation and purge toxicity.

Many of the formulas and herbs described in the textbooks and clinical guidelines have also been evaluated in clinical studies. The *Evidence-based Clinical Chinese Medicine* monograph on acne
vulgaris (168) found PPQFY was evaluated in 11 studies. All of the studies used herb ingredients that differed from the standard formula ingredients of *Pi pa ye* (*Eriobotrya japonica* Thunb. Lindl.), *Sang bai pi* (*Morus alba* L.), *Huang lian* (*Coptis chinensis* Franch. or *Coptis teeta* Wall. or *Coptis deltoidea* C.Y. Cheng & Hsiao), *Huang bai* (*Phellodendron amurense* Rupr. or *Phellodendron chinense* Schneid.), *Ren shen* (*Panax ginseng* C.A. Mey.) and *Gan cao* (*Glycyrrhiza glabra* L. P. or *Glycyrrhiza uralensis* Fisch. or *Glycyrrhiza inflata* BAT.). *Run Zao Zhi Yang Jiao Nang*, a commercially available CHM product, was also evaluated in 11 studies.

The review found 171 individual oral herbs and 73 topical herbs included in the studies. The most frequently evaluated oral CHM was *Huang qin* (*Scutellaria baicalensis* Georgi) (80 instances), followed by *Gan cao* (*Glycyrrhiza glabra* L. P. or *Glycyrrhiza uralensis* Fisch. or *Glycyrrhiza inflata* BAT.) (64 instances), *Sheng di* (*Rehmannia glutinosa* (Gaertn.) Libosch.) (52 instances) and *Dan shen* (*Salvia miltiorrhiza* Bge.) (52 instances). These herbs are recommended in CM textbooks; see Appendices 1 and 2.

### 3.7 Acupuncture for acne vulgaris

#### 3.7.1 Acupuncture from textbooks

Acupuncture treatment can include body acupuncture (insertion of fine needles on different loci of the body) and auricular acupuncture or acupressure with ear pellets (stimulation of auricular points from traditional pellets made from *Wang bu liu xing* (*Vaccaria segetalis* (Neck.) Garcke) or stainless-steel ball bearings two millimetres in diameter). Acupuncture treatment can be based on syndrome differentiation or affected meridians. Treatment frequency varies from once daily to alternate days or weekly. Treatment duration is usually from seven to ten treatments. A summary
of the acupuncture treatments based on syndrome differentiation and meridian-based treatments is found in Table 3.4.

**Table 3.4 Acupuncture and manual therapies for acne from textbooks**

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Syndromes</th>
<th>Acupuncture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comedonal, inflammatory</td>
<td>Lung heat</td>
<td>GV14 Dazhui and BL20 Pishu needle (159)</td>
</tr>
<tr>
<td></td>
<td>Stomach heat</td>
<td>ST36 Zusanli, LI4 Hegu (159)</td>
</tr>
<tr>
<td></td>
<td>Blood heat</td>
<td>No details given</td>
</tr>
<tr>
<td></td>
<td>Heat toxins</td>
<td>No details given</td>
</tr>
<tr>
<td>Cystic or conglobata</td>
<td>Damp toxin with Blood stasis</td>
<td>GV14 Dazhui, GV4 Mingmen, GV8 Jinsuo, GV9 Zhiyang, GV11 Shendao, GV12 Shenzhu (165)</td>
</tr>
<tr>
<td></td>
<td>Blood stasis and binding of phlegm</td>
<td>No details given</td>
</tr>
<tr>
<td>Cyclic comedonal</td>
<td>Stagnation of qi and Blood</td>
<td>SP6 Sanyinjiao and BL23 Shenshu (159)</td>
</tr>
<tr>
<td>Meridian-based points</td>
<td>Large Intestine and Stomach heat meridian</td>
<td>LI11 Quchi, LI4 Hegu, SP6 Sanyinjiao, BL2 Zanzhu, LI20 Yingxiang (165)</td>
</tr>
<tr>
<td>Auricular acupuncture</td>
<td>For all types of acne</td>
<td>CO14 Lung Fei 肺, CO18 Endocrine Neifenmi 内分泌, Testicle (code cannot be confirmed) and LO5 6i Cheek Mianjia 面颊(165); Main points: Lung and Kidney. Add Heart for pustules; add Large Intestine for constipation; add Spleen for greasy skin; add Liver and Endocrine for painful periods. Empirical points: CO14 Lung Fei, TF4 Ear Shenmen 神门, AH6a Sympathetic 交感, CO18 Endocrine and AT4 Subcortex 皮质下(165)</td>
</tr>
</tbody>
</table>
Table 1

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Syndromes</th>
<th>Acupuncture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical remedies</td>
<td>For all types of acne</td>
<td>BL15 Xinshu, BL13 Feishu, BL18 Ganshu, BL20 Pishu, BL23 Shenshu (159, 165)</td>
</tr>
</tbody>
</table>

Body acupuncture points are stimulated by filiform needles. Common body acupuncture points include points that clear pathogenic factors (GV14 Dazhui), tonify the zang fu (BL15 Xinshu, BL13 Feishu, BL18 Ganshu, BL20 Pishu, BL23 Shenshu), clear heat (LI11 Quchi, LI4 Hegu) and regulate menstruation (SP6 Sanyinjiao and BL23 Shenshu) or local points on the affected areas such as face points (BL2 Zanzhu, LI20 Yingxiang) (159).

Auricular points are also similarly selected; for example, CO14 Lung (Fei 肺) for the affected zang organ, CO18 Endocrine (Neifenmi 内分泌) and Testicles (code unable to be confirmed) for regulating menstruation or hormones and LO5 6i Cheek (Mianjia 面颊) for the localised affected area (159, 165). In CM treatment guidelines, acupuncture points to clear heat and expel wind include GV14 Dazhui, LU5 Chize, LI11 Quchi, BL2 Cuanzhu, BL13 Feishu, ST2 Sibai, EX-HN5 Taiyang, GV20 Baihui, LI4 Hegu, ST2 Sibai, ST6 Jiache expel wind and affect the face (162). Auricular points include points that stimulate the affected areas such as Cheek (Mianjia 面颊) and AT1 Forehead (E’qu 额区) or points that affect endocrine or autonomic nervous system areas such as CO18 Endocrine (Neifenmi 内分泌), AT4 Subcortex (Pizhixia 皮质下), AH6a Sympathetic (Jiaogan 交感) and AT2,3,4i Central rim (Yuanzhong 缘中). Points are also chosen based on zang fu affected such as CO14 Lung (Fei 肺), CO15 Heart (Xin 心) and CO4 Stomach (Wei 胃) (162). Other acupuncture-related manual techniques seen in clinical trials of acne include EA on both
auricular and body acupuncture points (174, 175), surround needling around acne lesions (176, 177) and moxibustion (18). A summary of the acupuncture points based on syndrome differentiation and meridian-based treatments from the CM textbooks is found in Table 3.4.

3.7.2 Acupuncture from treatment guidelines

CM treatment guidelines suggest red and blue light therapy on acne lesions or acupuncture points for treatment of acne (162) as a related manual therapy. Acupuncture treatment guidelines suggest the use of local facial acupuncture points and acupuncture points based on syndrome differentiation. Acupuncture points for acne from treatment guidelines are found in Table 3.5.

3.8 Other CM treatment factors for acne

Dietary advice almost always forms part of CM treatment. Traditionally in CM, a diet of greasy (for example, high fat, dairy) and fried (oily, which contributes to heat) and spicy foods (for example, chilli which also contributes to heat) is discouraged as it is may induce or worsen existing acne though this has not been evaluated in studies. Stress can impair the free flow of Liver Qi. If Liver Qi is impaired, it may generate heat which can aggravate acne symptoms. Therefore advice to reduce stress such as traditional exercises, qi gong, tai chi which includes mindfulness meditation may be encouraged.
Table 3.5 Acupuncture points for acne from CM treatment guidelines

<table>
<thead>
<tr>
<th>Function/location</th>
<th>Acupuncture points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial acupuncture points</td>
<td>SI18 Quanliao, CV24 Chengjiang, EX-HN3 Yintang, EX-HN5 Taiyang, GB14 Yangbai, LI20 Yingxiang, ST2 Sibai, ST6 Jiache</td>
</tr>
<tr>
<td>Remove dampness or damp-heat or phlegm</td>
<td>CV10 Xiawan, CV12 Zhongwan, SP3 Taibai, ST25 Tianshu, LU9 Taiyuan, ST36 Zusanli, GV14 Dazhui, EX-B2 Huatuojiaji</td>
</tr>
<tr>
<td>Clear heat or wind-heat</td>
<td>LI 11 Quchi, LI4 Hegu, SP10 Xuehai, ST44 Neiguan, HT8 Shaofu</td>
</tr>
<tr>
<td>Tonify zang-fu, Qi, Blood or yin</td>
<td>BL13 Feishu, BL19 Danshu, BL20 Pishu, BL23 Shenshu, CV4 Guanyuan, CV6 Qihai, SP6 Sanyinjiao, KI3 Taixi</td>
</tr>
<tr>
<td>Calm mind or regulate Qi</td>
<td>LR3 Taichong, PC6 Neiguan</td>
</tr>
</tbody>
</table>

3.9 Current evidence of Chinese herbal medicine, acupuncture and related manual therapies treatment for acne vulgaris

3.9.1 Chinese herbal medicine systematic reviews

Most CM trials on acne vulgaris have been conducted in China and published in Chinese. There are very few trials in English on Chinese herbal medicine (CHM) or acupuncture for acne vulgaris (178-182). There have been some preclinical trials indicating Keigai-rengyo-to having effects on Propionibacterium acnes (P. acnes) by acting on infiltrated neutrophils (183, 184).

No published SRs of CHM have been identified in a search of English language biomedical databases. A large project by the China-Australia International Research Centre for Chinese Medicine at RMIT University is currently evaluating the evidence for Chinese medicine for a range
of health conditions. An evidence-based monograph on Chinese medicine for acne vulgaris was developed during the time of this PhD project, and has subsequently been published (168).

The review of oral CHM included 221 RCTs. More than half the studies combined CHM with guideline recommended pharmacotherapies and few compared CHM with placebo or no treatment. *Pi Pa Qing Fei Yin* (PPQFY) was the most frequently tested traditional formula, evaluated in 11 studies. All of the PPQFY studies made modifications by adding or removing herbs from the standard formula ingredients. Eighty of the studies used *Huang qin* (*黄芩, Scutellaria baicalensis* Georgi.) as an ingredient in their formulations.

There were 38 studies that used syndrome differentiation in their inclusion criteria, with 21 studies using one syndrome, seven studies using two syndromes and the remainder using three or more syndrome. Syndromes included wind-heat in the Lungs, dampness-heat in the either Stomach and Intestines or in Stomach and Spleen, phlegm obstruction and blood stasis which are common syndromes reported in textbooks (159, 164, 165).

Only three studies measured health related quality of life (HRQoL), the Dermatology Life Quality Index (DLQI), the Cardiff Acne Disability Index (CADI) and Skindex-29. The CADI is an acne specific HRQoL whereas the DLQI and Skindex-29 are general dermatology HRQoL measures. There were more AEs reported in the control group (1,961 cases) compared to the intervention group (1,344 cases).
There were few meta-analyses conducted in the reported review. Results showed CHM to be superior to guideline-recommended treatments in reducing acne grading when using both the 1994 guideline (greater than 30% chance of change in symptoms) and 2002 guideline (greater than 50% chance of change in symptoms). Many comparisons of lesion count and acne grading showed no difference between CHM and pharmacotherapy at the end of treatment though analysis of change from baseline to end of treatment did achieve statistically significant improvements from baseline. Therefore there may be evidence to show CHM may be as effective as guideline recommended treatments for acne.

3.9.2 Acupuncture systematic reviews

There have been two systematic reviews of randomised controlled trials on acupuncture for acne, one in Chinese (2009) and one in English (2013) (18, 185). Cao et al (2013) included 43 trials in their review with 3,453 participants aged between 17 to 43 years old. Interventions reviewed included acupuncture (electroacupuncture, auricular acupuncture and ear point pressure), cupping, point injection, catgut embedding, moxibustion and herbal stimulation of acupuncture points or combined with CHM. The review concluded that the included studies reported “cure rate” as a major outcome (reduction of lesion count), some gave recurrence rate and one gave quality of life (QoL) scores. None of the trials reported sample size calculations and have a high risk of bias. This included selection bias where there was inadequate allocation concealment in all but one trial and performance bias where blinding was not possible for researchers and patients due to the comparison of acupoint stimulation to pharmaceutical medications. Six trials reported dropout rates but did not use intention to treat analysis.
The review found that the “cure rate” for acupuncture plus CHM was better than CHM alone but there was no significant difference when acupuncture was compared to conventional treatment (pharmaceutical medicines) (185). The authors also reported the efficacy of cupping therapy, point injection, catgut embedding and moxibustion. Point injection and catgut embedding are not techniques commonly seen outside of China. Cupping therapy was significantly better than pharmaceutical medications (tetracycline, ketoconazole) and if combined with CHM was superior to CHM or acupuncture alone. Point injection on its own or combined with pharmaceutical medications was significantly better than pharmaceuticals alone but no benefit was seen when it was combined with CHM. Catgut embedding was better than pharmaceuticals and if combined with Chinese herbal medicine was better than Chinese herbal medicine on its own. Finally, moxibustion combined with acupuncture was better than on its own. The authors concluded that there is some evidence for acupuncture being effective for acne vulgaris however more rigorous studies are required. A Cochrane review was also conducted by the same authors which provided similar results to the systematic review (157).

The systematic review on acupuncture for acne published in Chinese (18) also reported overall poor design in the included 17 trials (involving 1,613 cases) and thus limited the ability to make conclusions. Nevertheless, all included trials reported cure rate as their main outcome. The authors conducted a meta-analysis for acupuncture and moxibustion compared to routine western medicine. The analysis showed the cure rate was higher in the acupuncture and moxibustion group compared with routine treatment and the combination of acupuncture and moxibustion was better than acupuncture or moxibustion on its own.
3.9.3 Limitations of Chinese medicine systematic reviews

No systematic reviews published in English on CHM for acne have been identified. With the publication of the Evidence-based Clinical Chinese Medicine monograph on acne vulgaris in 2019 (168), there is evidence to suggest that oral CHM may be at least as effective as conventional treatments. While this is important, there is still a gap in the evidence for specific CHM formulas for acne. Publication of these types of SRs will ensure the evidence is accessible to practitioners, and transferable to clinical practice.

The two systematic reviews and the Cochrane reviews used Chinese medicine as controls as part of their inclusion criteria. They also included acupuncture techniques not commonly used outside of China such as wet cupping, cat gut embedding and point injection. Li et al (18) only searched the Chinese databases and was published in Chinese. The systematic review by Cao et al (185) published in 2013 was also published later in the Cochrane review by the same authors (157). Both reviews did state that it was difficult to draw reliable conclusions on the effects of acupuncture for acne when comparing one unknown intervention with another. To address this issue, there needs to be a review that looked at more commonly used body or auricular acupuncture compared to conventional medicine treatments that have established efficacy and are recommended in clinical practice guidelines.

3.10 Chapter summary

CM treatment is based on syndrome differentiation. For the treatment of acne, oral and topical CHM and acupuncture techniques are aimed at decreasing lesion numbers, preventing recurrence and addressing associated hormonal (menstrual) or gastrointestinal (dietary) symptoms (159). The
syndromes identified in the CM treatment guidelines and CM textbooks include heat in the Lungs, heat in the Stomach, heat in the Blood, damp toxins with Blood stasis and Blood stasis with binding of phlegm. CM syndromes are also related to types of acne lesions such as comedonal and cystic types. Treatment is based on syndrome differentiation. Oral and topical CHM that clear heat, resolve phlegm and invigorate stasis are often combined to treat different acne lesions. The common acupuncture techniques recommended to treat acne include body acupuncture and auricular acupuncture.
CHAPTER 4 : Health-related quality of life of people with acne vulgaris

4.1 Introduction

In the Constitution of the World Health Organization (WHO), the definition of health is “A state of complete physical, mental and social well-being, not merely the absence of disease” (186). Many QoL instruments incorporate physical, mental and social dimensions to measure health and wellbeing. When QoL is measured in the context of a specific disease, this is referred to as health-related quality of life (HRQoL) (187). This excludes non-health aspects such as economic and political circumstances (188).

Acne can affect people’s psychological and emotional wellbeing and their social interactions (10, 37, 67). The impact of acne on HRQoL has been well documented in numerous studies and reviews. Major depression, anxiety, body image concerns and suicidal thoughts and attempts have been reported (9, 189). Most acne sufferers are adolescents and young adults (4), with adolescents being most represented. Adolescence is a time of change and desire for social acceptance. Adolescents with acne have higher social phobia due to their skin condition (190-192). Although rare, peer victimisation in adolescents can lead to psychological sequelae (193, 194). This chapter summarises the impact of acne on HRQoL, factors that may predict impaired HRQoL and types of instruments used to measure HRQoL in people with acne.
4.2 Impact of acne on health-related quality of life

4.2.1 Psychological impact

Anxiety, depression, body image concerns, suicidal ideation and suicidal attempts have been reported in several studies. Depression, anxiety and fear of persistent acne or scarring were present in adolescents with acne (71). A higher risk of major depressive disorder (MDD) was seen in people with acne (18.5 per cent) compared to the general population (12.0 per cent) in a retrospective cohort study in the UK. Risk of MDD was also significantly higher within five years of acne diagnosis, with the risk decreasing thereafter (189).

In a population-based study in Oslo, Norway, Halvorsen et al. (9) found that adolescents with acne had social, study and relationship issues. Using the Strengths and Difficulties Questionnaire (SDQ), they found late adolescents (aged 18 to 19 years) with acne had low attachment to friends, were not thriving at school and had never had a romantic relationship or sexual intercourse. Suicidal ideation, mental health problems and social impairment were noted in those with more severe acne (9). A population-based study in Taiwan found the prevalence of acne was common in 7- to 12-year-old children and a significant number of females aged 19 to 42 years. They found an association with major depression that was 1.5 times more common in women who had acne compared to men who had acne. They also found an increased risk of suicide in women with acne compared to men (26). A New Zealand survey of students aged 12 to 18 years found that adolescents who self-reported “problem acne” had a higher frequency of suicidal thoughts and attempts compared to those without. There was also an increased frequency of depressive symptoms and anxiety in adolescents with self-reported “problem acne” (25). In a study of the general population of people born in Dunedin, New Zealand, between April 1972 and March 1973, people with self-reported “problem acne” were found to have higher rates of anxiety (195).
Depression and anxiety were also reported in a US epidemiology survey of adolescents with severe acne and other comorbidities (96).

Duman et al. (74) assessed the QoL of people 14 to 35 years with acne compared to healthy volunteers. People with acne filled out the AQOL and the Hospital Anxiety and Depression Scale (HAD) (196) and age-matched healthy volunteers filled out the HAD only. Both groups filled out the questionnaires at the time of recruitment and two months later after treatment was administered to people with acne. In the follow-up evaluation, the researchers did not find an increased risk of anxiety and depression in people with acne (74). Jankovic et al. (197) translated the Children’s Dermatology Life Quality Index (CDLQI) and Cardiff Acne Disability Index (CADI) into Serbian to survey adolescents between 15 to 10 years of age. The CADI and CDLQI scores were low, indicating a higher HRQoL and only moderate impairment.

Marron et al. (198) also used the HAD to evaluate the HRQoL of people with acne before and after treatment. They found that anxiety and depression were higher in people with acne compared to the average population, and that mean scores on HAD decreased after isotretinoin treatment. Tanghetti et al. (59) used the Patient Health Questionnaire-4 (PHQ-4) and Acne-QoL to assess the HRQoL of 218 women aged between 25 to 45 years with acne. Results indicated mild-to-moderate depression and/or anxiety in the past two weeks. All four domains of the Acne-QoL (self-perception, role-emotional, role-social and acne symptom scores) were lower, indicating a worse HRQoL in adult women with acne (59).
In a study of 18-year-old males in compulsory military service in Brazil, males with lower levels of education were more dissatisfied with their acne (199). Using the Body Image Disturbance Questionnaire (BIDQ) and Skindex-16 to investigate body image concerns and QoL, one study found that, as severity of acne increased, the number of people reporting emotional, social and occupational impacts increased (8). People with severe acne also modified their behaviour as a result of their acne (8). Furthermore, almost half of the people with a clinical diagnosis of acne who had no current acne lesions or mild acne also reported experiencing emotional and social/occupational impacts. Psychological distress and attentional bias towards acne lesions were found in a study of people who had acne (200). People with acne tended to be fixated on their acne lesions and showed a gap in perceived attractiveness compared to controls. In a study looking at perfectionism, acne and appearance concerns, there was a greater tendency to be concerned with their acne and their appearance and to have a higher level of socially prescribed perfectionism (201). Acne patients had higher scores in relation to obsessive compulsive symptoms such as rumination, checking and slowness compared to controls (202).

Clinical improvement positively affected HRQoL. Whether oral isotretinoin, topical adapalene, cosmetic interventions or other treatments were used, improvement of the symptoms improved the HRQoL of people with acne (198, 203-206). Adherence to treatment was also important for clinical improvement and improvement of HRQoL (207). Reducing emotional symptoms with cognitive behavioural therapy, patient education and pharmacotherapy was also recommended to help improve HRQoL (208). One study comparing the use of an acne educational website that had automated counselling to use of a website without counselling found the website with automated counselling improved CDLQI scores and general skincare behaviour (209).
4.2.2 Emotional impact

Lower self-perception, self-esteem, self-consciousness and self-confidence, and feeling sad, angry and frustrated are all emotional issues related to acne reported in studies (118, 210). Self-esteem was lower as acne severity increased (211). One review showed that the presence of acne also correlated with poor self-attitude in boys and poor self-worth in girls (212). In a qualitative study of adolescents and adults with acne presenting to general and specialist dermatology practices in New South Wales, Australia, people with acne were interviewed on the psychological effects of acne (71). The study found that people with acne immediately had reduced self-esteem and poor self-image, and were self-conscious and embarrassed when acne appeared. This was exacerbated by taunting, stigmatisation and perception of being scrutinised (71). Fear of acne not ceasing or being persistent was also found in a study of children (67) and female adults (59).

Tasoula et al. (213) used the CDLQI to evaluate the HRQoL of adolescents between 11 to 19 years old. They found that adolescents with moderate-to-severe acne experienced greater psychosocial and emotional impairment. Decreased self-esteem and embarrassment were seen in 39.8 per cent adolescents with mild facial acne, 64.6 per cent of adolescents with moderate facial acne and 89.3 per cent of children with severe acne. They also found body image concerns increased proportionally to acne severity. Feelings of unworthiness and teasing due to acne were seen in 31.4 per cent of adolescents and 21.4 per cent had modified the way they dressed due to their acne (213). In a study of adolescents aged 12 to 17 years who sought treatment for their acne in a dermatology clinic, there were no differences found between people with acne and healthy controls in Rosenberg Self-Esteem Scale (RSES) scores on self-esteem or Capa Social Phobia Scale for Children and Adolescents (CSPSCA) social anxiety scores (192).
4.2.3 Social impact

Social interaction, employment (73), intimate relationships (72) and family relationships (74) are affected in people with acne. People with acne may be socially phobic and tend to remove themselves from social activities (71, 211). Social stigma and perception of scrutiny and being judged due to acne can isolate people in social situations (211). Social anxiety, depression and anxiety levels in people with acne and vitiligo were significantly higher than healthy controls in a study using the Liebowitz Social Anxiety Scale (LSAS), HAD and Dermatology Life Quality Index (DLQI) (191) regardless of clinical acne severity (192). More than half the participants in a Singaporean study of tertiary students felt embarrassed or self-conscious about their skin “sometimes” or “all the time”; feelings of embarrassment increased with worsening acne (214). They also felt their acne interfered with their social or leisure activities, but not their social or family relationships.

In a study of adolescents aged between 12 to 17 years of age who had had acne for six months or more, Bahali et al. (193) found no difference between study and control groups (of adolescents who did not have acne or other appearance-related skin diseases) in the Peer Victimization Scale (PVS), Child Depression Inventory (CDI), State-Trait Anxiety Inventories for Children (STAIc), RSES and Pediatric Quality of Life Inventory Child Versions (PedsQL-C) for depression, peer victimisation, trait anxiety and self-esteem. However, they did find HRQoL was worse with those who reported peer victimisation (193). Tasoula et al. (213) found that facial acne affected adolescents’ school work and personal activities in over one-fifth (21.4 per cent) of adolescents in their study. Nearly one-fifth of adolescents were affected in their hobbies (19.4 per cent) and
personal and social lives (19.2 per cent), which also affected their ability to build relationships with others (213).

Decreased employment was noted in 18- to 30-year-old people with acne compared to controls (73) and increased stress at work was found in a study of adult females with acne (215). School and work were affected in women aged 25 to 45 years. One-third of the 218 study participants reported either missing out on school or poor concentration at work due to their acne (59). One study that used the Family Dermatology Life Quality Index (FDLQI) on 110 family members of people with acne showed that the disease progression affected family members. When acne improved, the FDLQI scores of family members also improved (74). Appendix 3 summarises studies evaluating the psychological, emotional and social impacts in people with acne and the instruments used.

4.2.4 Comparison of health-related quality of life in people with acne and other medical conditions

A number of studies compared acne HRQoL with that of other dermatological or medical conditions. The impact of acne on HRQoL was comparable to that of psoriasis (116, 216-218), diabetes and asthma (216, 217). Acne had a greater impact on psychosocial health compared to psoriasis (218).

In a Danish population study of self-reported skin conditions, people with acne reported a worse score on the emotions domain of the SkinIndex-29 compared to those with a rash (psoriasis, atopic dermatitis and hidradenitis suppurativa) (219). A review comparing atopic dermatitis (AD) and
acne showed adolescents with AD had issues with self-identity whereas self-esteem, self-confidence and self-identity were affected in adolescents with acne (220). Another review by Nguyen et al. (190) comparing the psychosocial impact of acne with those of vitiligo and psoriasis found that more adolescents with acne had social phobia compared to those with vitiligo and psoriasis (190). This was thought to be due to acne occurring around adolescence, which is a time of identity formation and susceptibility to peer opinions.

4.3 **Factors predictive of impaired health-related quality of life**

There are conflicting reports of factors that impact on the HRQoL of people with acne. Some reports supported age of onset, while others did not. Some studies supported acne severity as a factor in worse HRQoL, but others found more severe acne did not necessarily correlate with worsening HRQoL. Hispanic, Asian and Pacific Islander/Maori people with acne reported greater impact on HRQoL compared to Caucasian and African-American people.

The peak acne occurrence is most often reported by adolescents between the ages of 15 to 17 years. There have also been reports of adult onset acne and an emerging subgroup of female adult onset of acne. Studies have shown acne has an impact on HRQoL in both adolescents and adults. Recurrence of acne is common; therefore acne has been redefined as a chronic inflammatory disease of the pilosebaceous glands (56). Persistent acne and acne breakouts or recurrence can play a role in HRQoL (59). Most studies have found mild impairment of HRQoL was more commonly reported (193, 205, 212, 221) but moderate and severe impairment has also been reported in people with acne (8, 9, 59, 192). Acne severity and gender have also been reported to be associated with worse HRQoL in people with acne (9, 211).
There is a correlation between greater acne severity and worse HRQoL scores (190, 211, 222). However, some studies have not found this correlation with severity (23, 223). One study of school-aged children in rural and urban Egypt found that DLQI and CADI scores were influenced by gender, residence, severity, scarring and previous treatment. Cosmetic concerns were greater in female students living in urban areas who suffered scarring (37). Another study in Erbil, Iraq, found HRQoL in females was more affected than in males and severity of acne was linked with the level of impairment of HRQoL (224). In a study of Victorian adolescents, those with self-reported moderate acne were more likely to report depression and anxiety, and were in the later stage of pubertal development (19). CADI was also used in a study investigating HRQoL in adolescents in Tunisia. Fifty participants (61 per cent) had acne and more than half of these (51 per cent) had altered HRQoL (225). A study in Greece of adolescents aged between 11 to 19 years using the CDLQI found an impact on HRQoL associated with the severity of symptoms and treatment (213). Self-reported severity was also correlated with worse DLQI scores in a study comparing acne and vitiligo to healthy controls (191). Another study of school-aged children found severe acne was correlated with worse HRQoL on the CDLQI, DLQI and RSES (67). A recent interview-based study conducted in the UK, Italy and Germany in adolescents and adults who were having treatment for acne highlighted that moderate-to-severe acne impacted on HRQoL (226). The type of treatment was also important (226).

Among adults who attended outpatient clinics in Mangalore, India, the location of acne on the face, the type of lesions and the severity were all influencing factors for worse HRQoL on the DLQI and CADI (227). Chernyshov et al. (228) found that 75 participants who had sought help
from a dermatologist had worse HRQoL on the DLQI and CADI and had more severe acne than participants who had not sought help from a dermatologist. In a study of Malaysian school-aged adolescents, males were found to have more severe acne and a higher CADI score, indicating lower HRQoL (41). However, a study in Hong Kong of late adolescents also found no correlation with severity and HRQoL (23). Girls had significantly worse HRQoL than boys.

One study compared HRQoL in people with acne with HRQoL in healthy volunteers (74). Using the AQOL in people with acne and the HAD in healthy volunteers, no relationship was found between lower HRQoL scores and age, age at disease onset or acne severity (74). Another study using CADI and the Global Acne Grading Scale (GAGS) to evaluate the HRQoL of senior high school students in Nigeria found HRQoL was mildly affected in people with mild-to-moderate acne proportionate to the severity of disease (229). Using the Assessment of the Psychological and Social Effects of Acne (APSEA) score to evaluate HRQoL, one study found emotional and social factors influenced HRQoL but not duration of the condition (230).

Lasek and Chren found older people with acne and people whose acne did not improve after three months of treatment reported greater effects on HRQoL than younger adults (116). Acne severity alone did not correlate with QoL in one study of university females with acne using the CADI. It was suggested that other factors such as acne sequelae or social, emotional or other reasons may contribute to worse HRQoL (223).

There have been studies that evaluated acne in different racial groups. In a population study in the USA, Gorelick et al. (231) found that the impact of acne was greater among Hispanic and
Asian/other participants than among Caucasian and African-American participants. An acne population study in New Zealand (NZ) found problem acne to be worse in Pacific Islander/Maori participants compared to NZ European participants (25, 232).

4.4 Quality of life scales used in acne vulgaris research studies

4.4.1 General health-related quality of life scales

Many different general HRQoL scales have been used to evaluate the impact of acne on HRQoL. A recent position paper by the European Academy of Dermatology and Venereology Task Forces (EADV TF) on QoL and patient-oriented outcomes for acne, rosacea and hidradenitis suppurativa (228) identified 24 different instruments used in the evaluation of HRQoL in people with acne. A summary of the general HRQoL instruments used can be found in Table 4.1.

General wellbeing scales are used to assess the physical, mental and social dimensions to measure health and wellbeing. These include the Medical Outcome Study 36-item Short Form Health Survey (SF-36) (112) and its shorter version SF-12, EuroQoL 5-Dimension questionnaire (EQ-5D) (233), PHQ-4 (113), SDQ (234), General Health Questionnaire (GHQ-28 or GHQ-12) (235, 236) and Hopkins Symptom Checklist (HSCL-90) (237). Some also include economic, political and/or environmental dimensions, such as the WHO Quality of Life (WHOQOL)-26 (238).

Instruments that directly assess emotional or psychological dimensions have been used in studies. The Center for Epidemiologic Studies Depression Scale (CES-D) (239), PHQ-4 (113) and Reynolds Adolescent Depression Scale (RADS) (240) have been used to evaluate the level of anxiety and/or depression. For social phobia the Fear of Negative Evaluation Scale (FNE) (241)
has been used, and the Liebowitz Social Anxiety Scale (LSAS) (242) and CSPSCA (221) have been used to measure social anxiety. When assessing body image concerns, the BIDQ (243) and Multidimensional Body Self-Relations Questionnaire-Appearance Scales (MBSRQ-AS) (244) have been used. The RSES (245) was used to assess self-esteem in three studies. For assessing obsessive compulsive behaviour, the Maudsley Obsessive Compulsive Questionnaire (MOCQ) (246) was used and one study used the Mood States (247) to assess anger. All the above general health scales have been validated in the general population, some relevant to children and adolescents, and some to the general population.

### Table 4.1 General health-related quality of life scales used in acne

<table>
<thead>
<tr>
<th>QoL outcome measure</th>
<th>Structure and assessment items</th>
<th>Validation in population</th>
<th>Used in acne (references)</th>
</tr>
</thead>
</table>
| Body Image Disturbance Questionnaire (BIDQ) (243) | • 7 items (concerns on appearance, mental preoccupation, emotional distress, social occupational impairment, impairment to social life, work/school interference, avoidance)  
  • Scale: 1 = not at all preoccupied/no distress to 5 = extremely preoccupied/extreme and disabling (lower is better)  
  • Open ended questions on Social, school/occupation and avoidance | Adults                   | (8)                       |
| Capa Social Phobia Scale for Children and Adolescents (CSPSCA) (221) | • 25 items  
  • 1-5 scale (lower is better)  
  • >76 points = significant social phobia | Children and adolescents | (192)                     |
<table>
<thead>
<tr>
<th>QoL outcome measure</th>
<th>Structure and assessment items</th>
<th>Validation in population</th>
<th>Used in acne (references)</th>
</tr>
</thead>
</table>
| Center for Epidemiologic Studies Depression Scale (CES-D) (239) | • 20 items  
• 0-3 scale (lower is better)  
• Depressive symptoms in the past week | Adolescents and adults | (8)                       |
| Fear of Negative Evaluation Scale (FNE) (241)            | • 12 items  
• 1-5 scale (lower is better)  
• Themes – social evaluative anxiety, overly concerned with others’ opinions, hiding from negative feelings, avoidance | Adults                   | (8)                       |
| General Health Questionnaire (GHQ-12) (236)              | • 12 items  
• 0-3 scale (lower is better)  
• Cut off score varied in literature (5/6 to 7 = distress/MDD) | General population       | (248, 249)                |
| General Health Questionnaire (GHQ-28) (235)              | • 28 items  
• 4 subscales – somatic, anxiety/insomnia, social dysfunction, severe depression  
• 0-3 score (responses: 0 not at all, 1 no more than usual, 2 rather more than usual, 3 much more than usual)  
• Total score 0-84, threshold 23/24 for presence of distress | General population       | (201, 217)                |
| Hospital Anxiety and Depression Scale (HAD or HADS) (196) | • 14 items  
• 0-7 normal, 8-10 borderline abnormal, 11-21 abnormal (lower is better)  
• 2 subscales – anxiety, depression – and total score | General population       | (74, 198, 202, 248)       |
<table>
<thead>
<tr>
<th>QoL outcome measure</th>
<th>Structure and assessment items</th>
<th>Validation in population</th>
<th>Used in acne (references)</th>
</tr>
</thead>
</table>
| Liebowitz Social Anxiety Scale (LSAS) (242) | 24 items – 11 social interactions, 13 performance situations  
• Score range 48-192 (lower is better)  
• Clinician administered | Adolescents and adults | (191) |
| Maudsley Obsessive Compulsive Questionnaire (MOCQ) (246) | 40 questions  
• 4 subscales – checking, cleaning, slowness, doubting  
• Higher scores = increased severity | Adolescents and adults | (202) |
| Mood States (247) | 6 items (angry, grouchy, annoyed, resentful, bitter and furious)  
• Score 1 (not at all) to 5 (extremely)  
• Sum of item ratings divided by 6 to get mean Trait Anger score  
• Score >3 (moderately, quite a bit, extremely) positive Trait Anger  
• Score <2 (not at all, a little) negative Trait Anger | Validation information not clear | (210) |
| Multidimensional Body Self-Relations Questionnaire-Appearance Scales (MBSRQ-AS) (244) | 16 items  
• 2 subscales: body area satisfaction scale, appearance satisfaction  
• Higher score, greater satisfaction with appearance | Validation information not clear | (8, 25, 201) |
| Patient Health Questionnaire-4 (PHQ-4) (113) | 4 items  
• 4-point scale – 0 (not at all) to 3 (nearly every day) | | (231) |
<table>
<thead>
<tr>
<th>QoL outcome measure</th>
<th>Structure and assessment items</th>
<th>Validation in population</th>
<th>Used in acne (references)</th>
</tr>
</thead>
</table>
|                      | • Score 0-12; 0-2 normal, 3-5 mild, 6-8 moderate, 9-12 severe  
• 2 domains – depression, anxiety |                          |                          |
| Reynolds Adolescent Depression Scale (RADS) (240) | • 30 items  
• 4-point scale – almost never to most of the time  
• Total score 30-120 (lower is better)  
• Score 3 or 4 in 4 of the 6 areas or total score >77 = clinically relevant depression  
• Used in 13- to 18-year-olds | Children and adolescents | (25) |
| Rosenberg Self-Esteem Scale (RSES) (245) | • 10 items  
• 5-point Likert scale – strongly agree to strongly disagree  
• Max score 30 – <15 low self-esteem, >15 high self-esteem | Validation information not clear | (192, 211, 217) |
| Short Form-12 or 36 (SF-12 or 36) (112) | • 8 dimensions – physical function, physical role difficulty, bodily pain, general health perception, vitality, social function, emotional role, mental health  
• Score 0-100  
• Higher score, better HRQoL | General population | (198, 202, 217, 249) |
| Strengths and Difficulties Questionnaire (SDQ) (for 4- to 17-year-olds) (234) | • 25 items  
• Score 0-2, 0 (not true) to 2 (certainly true), items 7, 11, 14, 21, 25 are negatively scored | Children and adolescents | (9) |
<table>
<thead>
<tr>
<th>QoL outcome measure</th>
<th>Structure and assessment items</th>
<th>Validation in population</th>
<th>Used in acne (references)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Sum of score max 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 5 domains – emotional, conduct,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>hyperactivity, peer problems,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>prosocial scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>World Health Organization</td>
<td>26 items</td>
<td>Validated General population</td>
<td>(211)</td>
</tr>
<tr>
<td>Quality of Life (WHOQOL-BREF or WHOQOL-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(238)</td>
<td>• 5-point Likert scale 0-100 (higher is better)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Four domains – physical health,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>psychological, social relations,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>environment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 4.4.2 Dermatology-specific health-related quality of life scales

Dermatology-specific HRQoL instruments assess the HRQoL of people with skin conditions, including physical, mental and social wellbeing. Table 4.2 summarises the dermatology QoL questionnaires used in acne. Questions include symptoms that may affect the skin such as feeling “itchy”, “sore”, “painful” or “stinging”. They can also include questions about the effect of the skin condition on daily activities like shopping or gardening and questions on social activities like sport, work, hobbies, leisure or personal and intimate relationships. Dermatology-specific QoL instruments have been used in many studies of people with acne.
### Table 4.2 Dermatology QoL scales used in acne

<table>
<thead>
<tr>
<th>QoL outcome measure</th>
<th>Structure and assessment items</th>
<th>Validation in population</th>
<th>Used in acne (references)</th>
</tr>
</thead>
</table>
| **Dermatology Life Quality Index (DLQI)**   | • 10 questions  
• Each ranked 0-3 (not at all, a little, a lot, very much respectively)  
• 0-1 no effect, 2-5 small effect, 6-10 moderate effect, 11-20 large effect, 21-30 extreme effect  
• Higher score = greater impairment       | General population                                                                 | (37, 198, 203, 217, 222, 227) |
| (114)                                        |                                                                                                 |                          |                           |
| **Children’s Dermatology Life Quality Index (CDLQI)** | • 10 items  
• 4 scores – 0 not at all, 1 only a little, 2 quite a lot, 3 very much  
• Max 30 score  
• Higher score = greater impairment | Children                                                              | (197, 213, 251)          |
| (250)                                        |                                                                                                 |                          |                           |
| **Patient-generated Dermatology Quality of Life Scales (DQOLS)** | • 29 items  
• 5-point Likert scale  
• 4 psychosocial subscales (embarrassment, despair, irritableness, distress)  
• 4 activity subscales (everyday, summer, social, sexual) | General population     | Found in skin studies including acne |
|                                              |                                                                                                 |                          |                           |
| **Family Dermatology Life Quality Index (FDLQI)** | • 10 items  
• Each item score 0 to 3  
• Domains – emotional impact, burden of care, physical wellbeing, extra household expenditure, others’ perceptions  
• Higher score = greater impairment | Adults                                         | (74)                      |
<p>| (75)                                        |                                                                                                 |                          |                           |</p>
<table>
<thead>
<tr>
<th>QoL outcome measure</th>
<th>Structure and assessment items</th>
<th>Validation in population</th>
<th>Used in acne (references)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skindex (252)</td>
<td>• 61 items</td>
<td>General population</td>
<td>None identified</td>
</tr>
<tr>
<td></td>
<td>• 8 scales (cognitive effects, social effects, depression, fear, embarrassment, anger, physical discomfort, physical limitations)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Score 0–100 (higher score, greater impact)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skindex-16 (115)</td>
<td>• 16 items</td>
<td>General population</td>
<td>(8)</td>
</tr>
<tr>
<td></td>
<td>• Subscales emotions, physical or social function</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Higher score = greater impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skindex-29 (100)</td>
<td>• 29 items</td>
<td>General population</td>
<td>(249)</td>
</tr>
<tr>
<td></td>
<td>• 3 domains: symptoms, emotional, functional</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 0-100 score for each domain (0 no effect, 100 effect experienced all the time)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Higher score = greater impairment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Dermatology Life Quality Index (DLQI) was found to be the most commonly used instrument in acne studies (54 studies) (228). Other commonly used instruments include the CDLQI (specifically developed for children) (15 studies) and Skindex-29 (13 studies). The DLQI and Skindex have been validated in people with acne (253). In studies that compared QoL instruments, the DLQI showed greater response sensitivity compared to global instruments such as the SF-36 (228). The DLQI does not assess depressive or anxious feelings, whereas the Skindex-29 elicits a greater emotional and psychosocial burden than the DLQI (254).
4.4.3 Acne-specific health-related quality of life scales

Acne-specific HRQoL instruments have been developed to assess the HRQoL effects of acne. Table 4.3 summarises the acne-specific HRQoL questionnaires. Instruments focus on physical, mental and social wellbeing specific to acne and exclude questions about generic skin symptoms such as itching and pain. Often questions have been developed based on focus groups of people with acne (118, 255). Questions focus on emotions surrounding acne, self-consciousness, attractiveness or avoidance of social or physical activities. Some have been developed for facial acne only (for example, the Acne-QoL) and others for acne on the face and other common areas such as the neck, upper back and upper chest (for example, the CADI). Numerous instruments have been developed; however, there is no consensus on the most appropriate instruments to use in clinical or research settings.

The Acne-QoL is the most frequently used acne-specific instrument used in clinical trials of pharmaceutical interventions (23 studies) (228). It has been recommended for research purposes by the EADV TF and other reviewers (228, 253). It showed similar results to APSEA and DLQI instruments (256). The Acne-QoL (119-121) is a 19-item questionnaire separated into four domains assessing the self-perception, social, emotional and acne symptom impacts on people with facial acne. It asks questions based on “the past week”. It is a validated instrument for people aged between 13 to 36 years old, and is scored using a 7-point Likert scale from 0 (extremely or extensively) to 7 (not at all or none). The maximum score for the domains of self-perception, role-emotional and symptom scores is 30. The maximum score for the role-social domain is 24. The higher the score, the better the HRQoL.
Table 4.3 Acne-specific scales used in acne

<table>
<thead>
<tr>
<th>QoL outcome measure</th>
<th>Structure and assessment items</th>
<th>Validation population</th>
<th>Used in acne (references)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne Quality of Life Index (Acne-QOLI) (118)</td>
<td>• 21 items</td>
<td>Validated for facial acne adolescents</td>
<td>(118)</td>
</tr>
<tr>
<td></td>
<td>• 7-point Likert scale – 1 not at all, 4 some, 7 extremely</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Questions for the past week</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Higher score = higher impact</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Validated for facial acne</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>Acne Quality of Life Scale (AQOL) (123)</td>
<td>• 9 items</td>
<td>Validated for adults</td>
<td>(74, 192)</td>
</tr>
<tr>
<td></td>
<td>• 0 not at all, 1 mildly, 2 moderately, 3 very markedly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sum of scores given as a total; higher score = greater impact</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Psychosocial domain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne-Specific Quality of Life (Acne-QoL) (119-121)</td>
<td>• 19 items</td>
<td>Validated for 13–36 years old</td>
<td>(201, 231, 257)</td>
</tr>
<tr>
<td></td>
<td>• 0 (extremely or extensively) to 7 (not at all or none)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Range 0–24 for role-social, 0–30 for other domains</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Higher score = better HRQoL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 4 domains – self-perception, role-social, role-emotional, acne symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne-Specific Quality of Life Four Items (Acne-Q4) (255)</td>
<td>• 4-item condensed version of Acne-QoL.</td>
<td>Validated for General population</td>
<td>(206)</td>
</tr>
<tr>
<td></td>
<td>• Feeling upset, dissatisfied with appearance, concern about meeting new people,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• concern about scarring</td>
<td></td>
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</tr>
</tbody>
</table>
The shortened version of the Acne-QoL, the Acne-Q4 (255), is condensed to four questions about feeling upset, dissatisfied with appearance, concerns about meeting new people and concerns about scarring. It has been validated in people with acne and is relevant to all ages. Due to its brevity, it has been recommended for use in routine clinical practice (254). Testing showed it was a good predictor of the Acne-QoL total score (255).

The CADI was developed by Motley and Finlay (122). It is the second most frequently used instrument to measure HRQoL in people with acne in a recent review (41 studies) (228). It has five questions, two on emotions, one on social activities, one on avoidance of activities and one on acne symptoms. These are scored 0 (not at all or not a problem) to 3 (very much, severely, all

<table>
<thead>
<tr>
<th>QoL outcome measure</th>
<th>Structure and assessment items</th>
<th>Validation population</th>
<th>Used in acne (references)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne-Specific Impact Scale (ASIS) (256)</td>
<td>• 17 items</td>
<td>Validated Adolescents and adults</td>
<td>(258)</td>
</tr>
<tr>
<td></td>
<td>• Score (unable to be determined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 2 domains (items 1–9 for signs, items 10–17 on impact)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of the Psychological and Social Effects of acne (APSEA) (259)</td>
<td>• 15 items</td>
<td>Validated</td>
<td>(230)</td>
</tr>
<tr>
<td></td>
<td>• Score 0–138</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Higher score = worse HRQoL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiff Acne Disability Index (122)</td>
<td>• 5 items</td>
<td>Validated General population</td>
<td>(211, 224, 227, 229, 260)</td>
</tr>
<tr>
<td></td>
<td>• Scores 0–3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Emotions (2 questions), social, avoidance and acne symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Range 0–15; higher score = worse HRQoL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
the time). The higher the score, the worse the HRQoL. As it is such a brief instrument, it has been recommended for use in clinical practice (228, 253, 254).

Other less frequently used acne-specific instruments include the Acne-QOLI (118), AQOL (123), APSEA (259) and Acne-Specific Impact Scale (ASIS) (256). The Acne-QOLI is similar to the Acne-QOL, also validated for acne on the face in adolescents and adults. It uses a 7-point Likert scale of 1 (not at all) to 7 (extremely); in this case, higher scores indicate worse HRQoL. It also asks questions based on “the past week”, but does not separate questions into domains. It has also been recommended for clinical practice for a more comprehensive, in-depth view of HRQoL compared to the CADI or AQOL (254).

The AQOL was developed by Gupta et al. (123) and is a validated instrument for adults over 18 years. It has 9 items on psychosocial domains, and is scored between 0 (not at all) and 3 (very markedly). A higher score means a greater impact on HRQoL. It is also recommended to be used in clinical practice due to its brevity (254). The APSEA (259) has 15 items which are summed to provide a total score between 0 and 138. The first 6 questions of the APSEA relate to rumination and self-perception. Participants can choose responses ranging from “a great deal of time” to “only occasionally” for each question. The final 9 questions are on social activities such as shopping and going out with friends. Participants can indicate their response by placing a line on an unmarked visual analogue scale (0 to 10, with a blank space in between) or indicating “all the time”. The APSEA has good correlation with the BDI and is suggested to be used in people with acne with suspected psychiatric symptoms (254). The ASIS has 17 items divided into two domains. The first domain relates to signs and symptoms such as oiliness and pimples. The second measures the
impacts of acne such as feeling embarrassed, self-conscious or annoyed. The instrument is validated for facial acne only in adolescents and adults.

4.5 Health-related quality of life in Chinese medicine acne trials

HRQoL outcome is poorly studied in clinical studies of CHM and acupuncture for acne. Few studies used HRQoL as an outcome measure in CM trials of acne (168). In a Cochrane review of complementary medicine therapies for acne, only two studies reported on HRQoL (157). None of the reported trials used an acne-specific HRQoL instrument. The dermatology-specific HRQoL instruments Skindex-29 and DLQI were used. Recent trials from 2014 onwards have included Skindex and DLQI. Most trials coming out of China have not reported on HRQoL.

4.6 Discussion

Acne vulgaris can be distressing to people due to the highly visible nature of the skin lesions along with social stigmatisation (127). Scarring can result from acne and lead to longer term distress (68). Acne often affects adolescents, at a time when many physiological, social and emotional changes are occurring (207). Adolescents are trying to navigate through body image expectations, development of intimate and personal relationships, and other social and sexuality issues. They could be vulnerable to the psychological effects of skin conditions (261). They have less skills and experience in coping with the additional stress of a condition that can cause considerable embarrassment, depression and anxiety (190, 253). Acne HRQoL has also been associated with gender, severity and late onset or relapses of acne into adulthood. In studies that used physician assessment of acne severity, HRQoL scores did not correlate with severity; however, studies that used self-assessment of acne severity had a correlation with worse HRQoL scores (74). Females
with acne and having facial acne have also been more associated with worse HRQoL (116, 215). Other factors can be related to emotions such as anger and satisfaction with treatment (210).

Assessing the impact of acne on a patient’s HRQoL is important for acne management, and recommendations have been made to include HRQoL assessments as part of routine clinical visits (228, 253, 254). In the European clinical guidelines for acne, QoL instruments that are easy to use, readily accessible and have meaningful scores that guide treatment choice have been recommended. For example, worse HRQoL scores might influence the decision for a more aggressive therapy (127). The Malaysian MOH Guidelines for Acne Management also state QoL is an important factor in treatment adherence and subsequent treatment outcomes (126). Education of the general public and people with acne is lacking and may improve people’s understanding and lessen the impact on HRQoL (208, 214). Research can improve the understanding of the impact and burden acne has on people.

The EADV TF (228) recommends brief instruments that are age, culturally and linguistically appropriate for patients for clinical practice. For research, simultaneous use of general health, dermatology-specific and acne-specific instruments was suggested, depending on the research question being answered. The SF-36 is a general health instrument to measure HRQoL in people with acne, the DLQI, CDLQI and Skindex-29 are dermatology-specific questionnaires, and the CADI and Acne-QoL are acne-specific measures. Outcome measures for research should also be language and age appropriate. Some instruments require payment for use; therefore researchers and clinicians need to consider the financial cost of the instrument, and the limitations or biases this may introduce in research.
Studies have shown that acne duration and severity do not necessarily correlate with acne-related QoL changes (223); however, there have been more studies that have found a correlation with acne severity than not (19, 37, 67, 191, 213, 224, 225). The assessment of severity grading is considered an important factor in helping to understand if there is an impact on HRQoL according to acne severity, and for clinical assessment and treatment. There is no consensus on the best tool to assess severity. The AAD has suggested that grading systems need to be reproducible, easy to use and accepted by dermatologists (145). The MOH has recommended using the Comprehensive Acne Severity Scale (CASS), which is a modified version of the Investigator Global Assessment (IGA) of Acne Severity and uses photographs to ensure there is consistency between assessors. It is simple, reproducible and correlates with the Leeds technique. The Australian guideline – Acne Best Practice Management (125) – suggests the textual and photographic grading used by Warner and Plosker (262). The Acne Core Outcome Research Network (ACORN) as part of the Core Outcome Measures in Effectiveness Trials (COMET) initiative has included HRQoL as one of the core outcomes for clinical research (263).

Currently there is poor adoption of HRQoL outcomes in trials of CM. There have not been many reviews on CHM and acupuncture for acne. Few trials used HRQoL as an outcome measure in previous reviews such as DLQI and Skindex-29 (20, 185). The DLQI asks questions about itchiness and the effect of acne on social activities such as sport, which may not be as relevant to someone with acne. It is not sensitive to people with anxiety and depression associated with acne (253). Similarly, the Skindex-29 also asks questions about itching, burning or stinging which again are not specific to acne. The Skindex-29 is recommended as a complementary tool as there was no
correlation with the direct impact of the cutaneous signs on people with acne (253). Given this, a study tool needs to be sensitive to emotional, social and symptom changes in relevant cohorts. The use of an acne-specific HRQoL outcome tool would provide more meaningful data on the impact of CM on acne.

4.7 Chapter summary

Acne vulgaris has been shown to have a substantial impact on the HRQoL of people with acne including depression, anxiety, embarrassment and social isolation. There are more than 30 instruments used to evaluate HRQoL in people with acne ranging from general HRQoL scales to dermatology-specific HRQoL scales and acne-specific HRQoL scales. The use of HRQoL tools have been suggested in order to assess the impact and possible justification of treatment types for acne. HRQoL is a poorly assessed outcome measure in CM clinical trials for acne. Previous CM trials have used general health and generic dermatology instruments as outcome measures. Previous HRQoL used in CM acne studies have included the Skindex-29 and DLQI. There is a need to incorporate acne-specific HRQoL in order to assess the effect of CM interventions in relation to acne on HRQoL.
CHAPTER 5 : Acne quality of life and acceptance of Chinese medicine

5.1 Introduction

The previous chapter (Chapter 4) summarised the impact that acne can have on HRQoL. These included emotional, psychological and social impacts. Acne vulgaris (acne) can adversely affect people’s HRQoL, with a similar disability impact as psoriasis (216). Clinical severity does not always correlate with the burden of acne, as mild severity can still have a high impact on QoL (223). This has been shown in several studies where older adolescents’ perceptions of their acne were worse than clinicians’ assessments of lesions (22, 37, 60).

Acne has been associated with higher social phobia (190, 191, 195) and higher unemployment levels (73) than for healthy controls. The perception of acne and acne scars are negatively viewed (68). One study has shown that people with acne were scored less attractive compared to those without acne (200). Low self-esteem is also common in people with acne (71, 192, 212). In interviews conducted with people with acne, interviewees expressed they were worried, embarrassed and self-conscious about taunting or teasing, and thought they were judged by others as unclean, unattractive or less worthwhile than other people (71). This affected personal and family relationships (72).

Facial acne has been shown to negatively affect HRQoL in women (121) and can lead to depression and anxiety that impact on work and school (59). More than 75 per cent of the 218 female participants in one study reported that facial acne made them feel less confident, more self-
conscious around other people, frustrated and embarrassed (59). Acne can negatively impact on family members (74) and the negative impact of acne can last for a long time (37).

Australian data from 1997 showed 12 per cent of 2,491 school-aged children between 4 and 18 years old reported a high Acne Disability Index (ADI) score which correlated with clinical severity (22). The most recent Australian survey on how acne affects the QoL of adolescents was published in 2010 (248). Adolescents ($n = 209$) from high school year levels 8, 9 and 11 (aged 14 to 17 years old) were surveyed three times within a year on the relationship between acne and psychiatric and psychological comorbidities. The authors found no correlation between acne and psychological comorbidities in the sample population. Response to the third survey round was low (11 per cent, $n = 25$), limiting the reliability of the conclusions. There is no recent data on acne severity and QoL in Australian adolescents, young people or adults.

**5.1.1 Complementary and alternative medicine for management of acne**

Most adolescents self-manage their acne. The proportion of people seeking medical management has been reported to range from 2.4 per cent (264) to 17 per cent (265). In addition to medical management, the use of complementary and alternative medicine (CAM) for acne is common (151, 155). In a small study of patients’ acne practices in Australia, the common products included witch hazel (*Hamamelis virginiana*), tea-tree oil (*Leptospermum* spp.), citrus washes, aloe vera, zinc tablets, herbal remedies, tissue salt tablets, natural oils and evening primrose oil (*Oenothera biennis*) (155). A review of medicinal plants showed many had inhibitory effects on bacteria, viruses and fungi *in vitro* (266).
In addition to evidence from experimental studies, there is some evidence for herbal products from clinical studies. A systematic review of botanical and phytochemical treatments for acne reported herbal preparations improved mild-to-moderate acne (20). The authors found only a few SAE were reported, although the studies had methodological issues. AE such as sensitisation of skin from topical CAM, specifically Chinese herbal medicine (CHM) which is considered a form of CAM, have been reported but less than for BP (267).

5.1.2 Attitudes to treatment

Patients’ use of CAM including Chinese medicine (CM) is influenced by their perceptions and beliefs about CAM (268, 269). These include the perception that CAM is a more natural approach with less potential for adverse effects (267). For CM, beliefs are related to the perceived safety and efficacy of herbs (269-271), a belief that CM is better for symptomatic relief (269) and herbs being perceived as being more natural than chemical pharmaceuticals (270). The use of CAM (268) and CM (270) is also influenced by recommendations from family and friends, and cultural or educational knowledge of CM (271, 272).

People who have a more positive belief in CAM products are more likely to use such products (273, 274). Patients’ belief in complementary medicine influences whether they will participate in a trial (275) and how they participate in a trial (271). In considering trial designs, patient preferences and stakeholder engagement are suggested to be taken into consideration to improve participation (276). Tailoring a clinical trial according to stakeholders’ input can improve the feasibility of a study, recruitment and retention, and adherence with treatment or trial protocol (277, 278). Other factors for consideration include travel time and cost, and other health issues that
may prevent people from attending (277, 279). A recent survey of compliance with CHM in a community acupuncture clinic highlighted barriers such as cost, efficacy, quality of herbs, side effect of herbs, taste and product availability (280). A survey on the opinions of adolescents, young people and adults on their perceptions of and preferences for CM treatments has the potential to inform clinical trial design to maximise recruitment and adherence. Knowing patient preferences will help with designing trials that closely reflect patients’ expectations and the reality of clinical practice. This will provide direct evidence that can be translated into practice.

5.2 Aims and objectives

5.2.1 Aims

This study addresses three aims, to:

1. Determine how facial acne affects the HRQoL of adolescents, young people and adults in Australia
2. Determine the attitudes towards CAM in adolescents, young people and adults with facial acne
3. Assess the willingness to take CM and preferences for different forms of CM interventions.

5.2.2 Objectives

To meet these aims, the following objectives were developed:

1. Conduct an online survey using Qualtrics including three components:
   a. Use of a validated HRQoL for people with facial acne: Acne-Specific Quality of Life
   b. Use of a validated questionnaire to assess attitudes about CAM: Complementary and Alternative Questionnaire for Young Adults
   c. Determining preferences for different types of CHM and acupuncture techniques.
2. Analyse the results to inform the development of a clinical trial protocol.

5.3 Methods

5.3.1 Study design

The aims of this study were addressed through the use of an online survey. Qualtrics is a secure tool recommended by the RMIT Human Research Ethics Committee for distributing online surveys and therefore was chosen to implement the survey. Ethics approval was obtained from the College Human Ethics Advisory Network (CHEAN; SEHAPP 55-17; Appendices 8-12).

5.3.2 Inclusion and exclusion criteria

The survey was open to adolescents and young people (15 to 24 years old) and adults (≥ 25 years old) with facial acne. Differences exist between authoritative sources in the definition of adolescents and young people. The WHO defines the age of adolescents as between 10 and 19 years of age, and of young people as between 10 to 24 years of age (281). The UN defines adolescents as between 10 and 19 years of age, and youth and young people as between 15 and 24 years of age (282). For the purposes of this study, the definition of youth and young people from the UN has been adopted.

People with acne usually have lesions on their face, chest, upper back and neck (6). The face is more visible to the public and more of a concern to patients (121), and is more likely to affect the QoL. The outcome tool selected for assessment of HRQoL is specific to facial acne; hence one of the inclusion criteria was people with facial acne.
5.3.3 Survey sampling

The survey was aimed at youth and young people (15 to 24 years old) and adults (>25 years old) living in Australia. A convenience sampling approach was used. Convenience sampling, particularly online methods, have the potential to reach a larger audience to recruit larger sample sizes. These methods may reach participants in larger geographical locations and promote higher engagement with those identifying with a condition or intervention (283). As one of the aims of the study was to examine the impact of facial acne on QoL generally, it was not necessary to structure sampling to obtain equal numbers of gender and age groups.

5.3.4 Participant recruitment

Participants were not offered incentives nor were they reimbursed for their participation in the survey. For the pilot study, fifth year student representatives from the Disciplines of Chinese Medicine, Chiropractic and Osteopathy in the School of Health and Biomedical Sciences of RMIT University were contacted and asked to share the study information with their peers in August 2017. The response rate was low with only five pilot participants, so after two months, fourth year students were also invited to participate and disseminate the pilot survey. Participants were directed to the online website through a quick response (QR) code or an online link and asked to answer two additional questions on the time they took to complete the survey and any questions that were ambiguous to them (Appendix 4, Section 6). These two questions were removed from the final survey and were not included in the final analysis. No ambiguous questions were identified during the pilot period and no changes were made to the final survey questions.
The full survey was conducted between October 2017 and concluded in August 2018. Recruitment for the full survey used various strategies. Student representatives from years one to four in the programs of Chinese Medicine, Chiropractic and Osteopathy in the School of Health and Biomedical Sciences were contacted to share information about the survey with their classmates. Posters were placed around Melbourne-based university campuses and e-posters were placed in the RMIT student and staff online newsletters. A specific Facebook page was developed for the project. Other established websites were approached to disseminate the survey such as www.acne.org, an online forum support website for people with acne. Administrators of Facebook pages for RMIT, RMIT Student Association, RMIT social clubs and RMIT Big Science and Small Science were also approached to link to the survey Facebook page. Sixty-nine local schools were approached to advertise in their local school newsletters (see advertising details in Appendix 5). Recruitment was slower than anticipated and ethics approval was obtained for additional recruitment strategies including contacting dermatologists and other healthcare professionals such as acupuncturists and naturopaths to place the advertisements in their practices.

Advertising directed the potential participants to an online website that held the secure Qualtrics survey. If participants wanted to contact the researchers, telephone and email addresses were added to the participant information and consent statement at the start of the survey. Participants indicated consent to participate by selecting “agree to participate” in the survey and continuing on to the survey. If they selected “I do not agree to participate”, the survey would take them to a thank you note. Participants were able to close the browser to end participation in the survey at any point in time.
5.3.5 Instrument

The survey was separated into four sections (see Appendix 4):

- Acne-QoL (questions 1 to 19)
- CAM Questionnaire for Young Adults (questions 20 to 37)
- Preferences for CM and trial design (questions 38 to 43)
- Demographics and previous treatment sought for acne (questions 44 to 51).

The Acne-QoL instrument (119, 121, 205) is a validated questionnaire for facial acne. It has 19 questions on participants’ feelings about their acne, medication usage and social interactions. Questions include how unattractive, embarrassed, self-conscious or upset they feel about their acne. The questions are grouped into four domains: self-perception, role-social, role-emotional and acne symptoms. Scores are calculated by summing all items in each domain using an ordinal scale of 0 (“extremely” or “extensive”) to 6 (“not at all” or “none”). Each domain is weighted equally and the higher the score, the better the HRQoL result. Self-perception, role-emotional and acne symptoms are scored out of 30; role-social is scored out of 24 (refer to Appendix 4, Section 2). Permission from the original author was obtained for its use (Appendix 6).

The CAM questionnaire was included into this survey to gain an understanding of the types of CAM being used by people with acne. Questions in this component was directed at overall prior use of CAM and not specifically CAM used for their acne. It also used to gauge a negative or positive attitude to CAM. The CAM Questionnaire for Young Adults has been validated in young adults (268). Permission has been obtained for its use (Appendix 7). It contains 18 questions in all, 6 on prior use of CAM and 13 on beliefs about CAM. Questions relate to the effectiveness and
safety of CAM, social factors influencing choices, and CAM providers. It uses a five-point Likert scale ranging from 1 (“strongly disagree”) to 5 (“strongly agree”) (Appendix 4, Section 3). The CAM beliefs component (questions 25–37 of the survey) is categorised into three domains – positive beliefs about CAM (items 25–30, maximum score 30), environmental influences (items 31–34, maximum score 20) and psychological comfort (items 35–37, maximum score 15). Patterson and Arthur (2009) explained psychological comfort as the reasoning behind people’s attitudes to CAM. This can include physical, mental and spiritual aspects of health, and people’s use of CAM due to the fear of discomfort from medical interventions and belief that using CAM is not harmful. The maximum total score is 65. To determine respondents’ positive or negative attitude towards CAM and their likelihood of using CAM, the total score is dichotomised at the median. Participants were asked to answer questions on their beliefs about CAM treatments, their prior use of CAM and the frequency of their usage of CAM. Some preliminary work has been published on the validity of the CAM Questionnaire for Young Adults (268).

No existing surveys were identified that explore people’s preferences for CM treatments. The questions for this section have been developed specifically for this survey. Questions include preferences relating to the use of CHM and acupuncture therapies, and factors participants would consider appropriate for the design of a clinical trial (refer to Appendix 4, Section 4). The additional questions on CM were piloted with 10 people.

Additional questions on the demographics of participants included age, gender, ethnicity, self-assessment of acne severity, acne duration and previous acne treatments (refer to Appendix 4, Section 5). These questions were modelled on the Australian Bureau of Statistics Census 2016
demographics questions (284). Data was also collected on the length of time to complete the questionnaire.

As the survey was anonymous and no identifying information was collected, a participant consent and information form did not form part of the survey. Instead, a statement of participation and consent was presented to participants prior to beginning the survey (Appendix 4, Section 1). A question to “agree to participate” or “do not agree to participate” was asked prior to starting the survey. Agreement for participation was implied through completion of the survey. Participants could end participation or refuse to continue to participate or withdraw from the survey prior to completion by closing their browser. Participants were also given the investigators’ contact details to suggest follow-up if necessary. Should they plan to make a complaint or express concern about the survey, the RMIT Human Research Ethics Committee details were given.

5.3.6 Ethics
The research was conducted in the College of Science, Engineering and Health, RMIT University. Ethics was fully granted by the College Human Ethics Advisory Network (CHEAN) in August 2017 (SEHAPP 55-17) (Appendix 8). There were four further applications for amendments (Appendices 9, 10, 11 and 12) to include additional recruitment methods. The amendments included recruitment through Facebook and online media (Appendix 9), and two extensions of time to allow for additional numbers to respond to the survey to (first to 30 May 2018, then to 31 December 2018) (Appendices 10 and 11). The fourth amendment was to gain permission to approach health practitioners in the Melbourne metropolitan area to place the advertisements in their health practices (general practitioners, dermatology specialists, CM practitioners and natural health practitioners) to promote the survey (Appendix 12).
5.3.7 Data collection, storage and security

The online survey tool Qualtrics collated anonymous data and no identifying details of participants were gathered. Data was downloaded into CSV and SPSS formats for further analysis. The data was stored on a password-protected computer, secured by a password known only to the investigators. Data will be held on the RMIT secure internet server for a minimum of five years according to the RMIT research data storage policy.

5.3.8 Data analysis

SPSS (v.24 IBM Corporation) (285) was used to analyse the data. Descriptive statistics were used for the demographics of the respondents. Inferential statistics were used to analyse the variables of demographics, Acne-QoL, CAM Questionnaire for Young Adults and CM treatment preferences. Results with probability ($p$) values of less than or equal to 0.05 were considered significant.

Chi-square analysis was used to compare the characteristics of respondents (gender, age, ethnicity, duration of acne and self-perception of acne severity) in order to examine the differences in their responses to the Acne-QoL. Age was collapsed into two age groups as defined by the UN for youth and adults. As respondents were all aged 45 and under, the youth group included 15 to 24 years and the adult group included 25 to 45 years. Student’s t-test was used to determine the mean differences between domains in the Acne-QoL survey (self-perception, role-social, role-emotional and acne symptoms). For data that was not normally distributed, non-parametric tests were used. Chi-square analysis was also used to examine the differences in CAM use and attitudes to CAM by the characteristics of respondents. Student’s t-test or one-way analysis of variance (ANOVA)
was used to determine the mean difference of the three domains of positive beliefs, environmental influences and psychological comfort compared between the different groups.

The Acne-QoL authors give instructions for handling missing data. A minimum of three items must be answered within each domain to calculate domain scores, and a mean value within the domain was calculated and replaced the missing values. Domain scores were not calculated if the minimum number of questions was not answered for that domain. There was no missing data in this section of the survey.

5.4 Results

Local high schools in the metropolitan Melbourne area were contacted in two rounds to place the posters in their newsletters to advertise the survey. In the first round 29 schools were contacted and in the second round 40 schools were contacted. Only two schools contacted agreed to place the advertisement in their online newsletter. There is no data on the number of health practices that placed the advertisement in their practices.

A few recruitment issues arose during the survey process. The timing of the initial recruitment phase occurred around the end of the semester, when there were fewer students around to see the advertisements. Students at the end of the semester were also receiving requests from the University to complete other learning and teaching surveys, and there is anecdotal evidence that students can have “survey fatigue” and therefore may be less inclined to complete other surveys. Online forms of recruitment such as the University Facebook page and RMIT Social Groups’ pages were not successful as these pages limited the type of information they would allow. For
example, the RMIT Students’ Facebook page would only allow an advertisement if the project offered an incentive to students such as vouchers or discounts. Contact with other online sources such as www.acne.org did not yield a response. Another online recruitment issue was with the timing of the creation of the Facebook page. During the creation of the page, Facebook was receiving negative media publicity and the public was protesting by decreasing use of the social media website (286).

Contacting high schools did not yield many positive responses with only two of the 69 schools contacted agreeing to advertise in their school newsletters. Most schools responded that they received many requests to participate in research and would participate if the research aligned with their school’s mission. Finally, reaching out to health professionals such as dermatologists and other CAM providers did not yield many responses.

5.4.1 Demographic data
At termination of the survey, 36 responses had been obtained (Table 5.1). Of the 36 respondents, 8 (22.2 per cent) consented only and did not answer any further questions, with 28 continuing on to the survey questions. Of the 28 remaining respondents, 22 (61.1 per cent) completed all sections of the survey and 6 (16.7 per cent) partially completed the survey. The number of responses varied across different sections. Twenty-eight completed the Acne-QoL section (none missing), 27 completed the CAM use component of the CAM questionnaire (one missing), 25 completed the CAM beliefs component of the CAM questionnaire (3 missing), 22 completed the treatment preferences (6 missing) and 22 completed the demographics section (6 missing). Data were tested for normal distribution and no deviations were detected. More respondents were female (17/22)
Table 5.1 Demographics of the participants

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N = 36</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed survey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22</td>
<td>(61.1)</td>
</tr>
<tr>
<td>Consented only</td>
<td>8</td>
<td>(22.2)</td>
</tr>
<tr>
<td>Partially completed survey</td>
<td>6</td>
<td>(16.7)</td>
</tr>
<tr>
<td>Access to survey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QR code</td>
<td>19</td>
<td>(52.8)</td>
</tr>
<tr>
<td>Weblink</td>
<td>17</td>
<td>(47.2)</td>
</tr>
<tr>
<td>Gender*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>(77.3)</td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>(18.2)</td>
</tr>
<tr>
<td>Not specified (other)</td>
<td>1</td>
<td>(4.5)</td>
</tr>
<tr>
<td>Age (years)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–24</td>
<td>17</td>
<td>(77.3)</td>
</tr>
<tr>
<td>25–45</td>
<td>5</td>
<td>(22.7)</td>
</tr>
<tr>
<td>Ethnicity*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>11</td>
<td>(50.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>9</td>
<td>(40.9)</td>
</tr>
<tr>
<td>Other (both indicated Australian)</td>
<td>2</td>
<td>(9.1)</td>
</tr>
<tr>
<td>How long have you had acne?*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>3</td>
<td>(13.6)</td>
</tr>
<tr>
<td>1–4 years</td>
<td>9</td>
<td>(40.9)</td>
</tr>
<tr>
<td>5+ years</td>
<td>10</td>
<td>(45.5)</td>
</tr>
<tr>
<td>Do you think your acne is*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>13</td>
<td>(59.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7</td>
<td>(31.8)</td>
</tr>
</tbody>
</table>
than male (4/22). One respondent chose “other” in the question on gender. The youngest respondents were between 15 and 19 years old, and the oldest was between 36 and 40 years old. Of the 22 participants who responded to the question of their age, most were between 15 and 24 years old (young people group; 17 respondents, 77.3 per cent) and the remainder were 25 to 45 years old (adult group; 5 respondents, 22.7 per cent). There were no respondents older than 45 years. Respondents mostly identified themselves as Caucasian (11 respondents, 50.0 per cent), with 40.9 per cent (9 respondents) identifying as Asian. Of the two who responded “other” for ethnicity, one identified as Australian and the other stated “A”. Compared to the general population, the age group of the respondents of the survey is within the age range of adolescents and adults with acne. There are less reports of people with acne over the age of 45 and more at adolescent and young adults age.

There were slightly more respondents who had had their acne for five or more years (10 respondents, 45.5 per cent) compared to one to four years (9 respondents, 40.9 per cent) and three respondents who had had their acne for less than a year (13.6 per cent). Most respondents considered their acne to be mild in severity (13 respondents, 59.1 per cent), with seven who considered their acne to be moderate (31.8 per cent) and two who considered their acne to be severe (9.1 per cent). More than half of the respondents who responded to gender reported having mild acne (11/17 females, 64.7 per cent and 2/4 males, 50 per cent), seven reported moderate acne (5/17 female, 29.4 per cent, 2/4 males 50 per cent) and one “other” gender reported severe acne
(100 per cent) \((\chi^2 = 11.149, df = 4, p = 0.025)\) with no significant difference in severity across the different age groups and ethnic groups \((\chi^2 = 1.351, df = 2, p = 0.509 \text{ and } \chi^2 = 5.368, df = 4, p = 0.252 \text{ respectively})\).

Most had sought medical advice for their acne (14/22 respondents, 63.6 per cent). Just over two-thirds used prescribed topical medications such as antibiotics, adapalene, retinoids and BP (15/22 respondents, 68.2 per cent). Details of the medications are listed in Table 5.2. Nine respondents had previously used prescribed oral medications such as antibiotics and isotretinoin. Nine respondents had used both topical and oral medications, five had used topical medications only and no respondents had used oral medications only. Two respondents had used oral contraceptive pills to control their acne. One respondent selected a number of the medications listed and also selected “none of the above”. Since the respondent also checked many of the drugs, the “none of the above” response was not applicable and therefore not calculated as a response.

Of the over-the-counter medications, salicylic acid lotions and creams such as Clearasil® were the most used preparations (16 respondents, 72.7 per cent) (Table 5.3). As with the prescribed medications section, one respondent chose many over-the-counter medicines and also “none of the above”; therefore the “none of the above” response was not included in the calculations.
### Table 5.2 Previous prescribed medications used

<table>
<thead>
<tr>
<th>Previous prescribed medications used</th>
<th>(N=22)</th>
<th>(N=%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical antibiotics and benzoyl peroxide (such as Duac Once Daily Gel®)</td>
<td>14</td>
<td>(63.6)</td>
</tr>
<tr>
<td>Oral antibiotics</td>
<td>9</td>
<td>(40.9)</td>
</tr>
<tr>
<td>Topical antibiotics and benzoyl peroxide</td>
<td>6</td>
<td>(27.3)</td>
</tr>
<tr>
<td>Topical adapalene (such as Differin Topical Gel® or cream®)</td>
<td>5</td>
<td>(22.7)</td>
</tr>
<tr>
<td>Isotretinoin (such as Roaccutane®)</td>
<td>4</td>
<td>(18.2)</td>
</tr>
<tr>
<td>Topical retinoids (such as Stieva A Cream®, Re-Trieve Cream®)</td>
<td>4</td>
<td>(18.2)</td>
</tr>
<tr>
<td>Topical retinoids and benzoyl peroxide</td>
<td>4</td>
<td>(18.2)</td>
</tr>
<tr>
<td>Other (oral contraceptive pill, Chinese medicine, unspecified)</td>
<td>4</td>
<td>(18.2)</td>
</tr>
<tr>
<td>Benzoyl peroxide alone (such as Bentonite®)</td>
<td>2</td>
<td>(9.1)</td>
</tr>
<tr>
<td>None of the above</td>
<td>6</td>
<td>(27.3)</td>
</tr>
</tbody>
</table>

*Participants may have used more than one medication

### Table 5.3 Previous over-the-counter medications used

<table>
<thead>
<tr>
<th>Previous over-the-counter products used</th>
<th>(N=22)</th>
<th>(N=%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylic acid lotions and creams (such as Clearasil® with salicylic acid)</td>
<td>16</td>
<td>(72.7)</td>
</tr>
<tr>
<td>Benzoyl peroxide lotions and creams (such as Proactive® or Clearasil® with benzoyl peroxide)</td>
<td>15</td>
<td>(68.2)</td>
</tr>
<tr>
<td>Azelaic acid preparation (such as Dermatologica® or Ego Azclear®)</td>
<td>7</td>
<td>(31.8)</td>
</tr>
<tr>
<td>Glycolic acid preparations (such as Glycolix®)</td>
<td>4</td>
<td>(18.2)</td>
</tr>
<tr>
<td>None of the above</td>
<td>3</td>
<td>(13.6)</td>
</tr>
<tr>
<td>Other (unspecified)</td>
<td>1</td>
<td>(4.5)</td>
</tr>
</tbody>
</table>

*Participants may have used more than one over-the-counter product
5.4.2 Acne-Specific Quality of Life Questionnaire

A summary of the descriptive statistics for the four domains can be found in Table 5.4. There were 28 respondents for this section. The mean scores were lowest for the self-perception domain (14.8 ± 8.9) and highest for the acne symptoms domain (17.7 ± 6.6). However, each of the domains had different score ranges. When the mean score was calculated as a percentage of the total possible score, the highest was for role-social (15.1/24 = 62.9 per cent) rather than for the acne symptoms scores. Table 5.5 also summarises the comparative analysis of the different domains with gender, ethnicity, age, self-reported severity and duration of acne.

Table 5.4 Acne QoL summary of four domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Average, minimum and maximum (n)</th>
<th>Self-perception (range 0–30) (Q1,3,10,2,6) Mean ± SD$</th>
<th>Role-social (range 0–24) (Q12,11,14,13) Mean ± SD$</th>
<th>Role-emotional (range 0–30) (Q5,9,8,7,4) Mean ± SD$</th>
<th>Acne symptoms (range 0–30) (Q15,16,17,18,19) Mean ± SD$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (n=28)</td>
<td></td>
<td>14.8 ± 8.9</td>
<td>15.1 ± 7.3</td>
<td>15.4 ± 8.9</td>
<td>17.7 ± 6.6</td>
</tr>
<tr>
<td>Median (n=28)</td>
<td></td>
<td>12.0</td>
<td>16.0</td>
<td>14.5</td>
<td>18.5</td>
</tr>
<tr>
<td>Min (n=28)</td>
<td></td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Max (n=28)</td>
<td></td>
<td>30</td>
<td>24</td>
<td>30</td>
<td>29</td>
</tr>
</tbody>
</table>

5.4.2.1 Self-perception

There was no difference in the Acne-QoL scores for the self-perception domain when comparing gender, age, ethnicity and severity (Table 5.5). Those who had had their acne for less than one year (3 respondents, mean 23.0 ± 7.8) had a slightly higher self-perception score than those who had had acne for one to four years (9 respondents, 18.4 ± 7.9) and a higher score compared to those
who had had acne for more than five years (11.1 ± 7.8). This result was statistically significant ($p = 0.049$). In a post-hoc analysis, there was no significant difference between the less than one year group and the one to four year group ($p = 1.000$) or the five or more years group ($p = 0.099$). There was also no significant difference between the one to four year group and the five or more years group ($p = 0.168$).

### 5.4.2.2 Role-social

There was no difference in the Acne-QoL score for the role-social domain when comparing group differences in all the characteristics: gender, age, ethnicity, severity of acne and duration of acne.

### 5.4.2.3 Role-emotional

There was also no difference in the Acne-QoL score in the role-emotional domain when comparing gender, age, ethnicity and severity. Those with self-reported moderate acne (7 respondents, mean 10.3 ± 4.2) had a lower mean score than those with mild or severe acne, although this result was not statistically significant ($p = 0.064$). Those who had had their acne for five or more years (10 respondents, mean 11.0 ± 8.4) were more emotionally affected by their facial acne. In a post-hoc analysis, there was more emotional impact in people who had had acne for five or more years compared to the less than one year group ($p = 0.031$) and in the five or more years group compared to the one to four years group ($p = 0.050$). There was no statistical difference between the less than one year group and the one to four years group ($p = 0.979$).
5.4.2.4 Acne symptoms

There was no difference in how worried participants were about their acne symptoms when comparing age, ethnicity and duration of disease. There was a statistically significant result for the Acne-QoL acne symptom domain compared to gender ($p = 0.013$). A post-hoc analysis was not able to be performed as there was only one response to “other” gender. Based on the mean scores presented, the difference may be between males (4 respondents, $19.0 \pm 6.0$) and the “other” gender ($0.0$). It may also be between females (17 respondents, $18.9 \pm 5.5$) and the “other” gender. Respondents with self-reported severe acne were more worried about their acne symptoms (2 respondents, mean $4.5 \pm 6.36$). In a post-hoc analysis, the self-reported mild acne group was less worried than the moderate ($p = 0.000$) and severe groups ($p = 0.000$). The moderate group was less worried than the severe group ($p = 0.005$) and more worried than the mild group ($p = 0.000$) and the severe group was more worried than both the mild ($p = 0.000$) and moderate groups ($p = 0.005$).

Table 5.5 Acne QoL domain results by demographics

<table>
<thead>
<tr>
<th>Demographics (n)</th>
<th>Self-perception (range 0-30) Mean ± SD</th>
<th>Role-social (range 0-24) Mean ± SD</th>
<th>Role-emotional (range 0-30) Mean ± SD</th>
<th>Acne symptoms (range 0-30) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 4)</td>
<td>16.8 ± 9.6</td>
<td>17.5 ± 6.8</td>
<td>17.8 ± 10.2</td>
<td>19.0 ± 6.0</td>
</tr>
<tr>
<td>Female (n = 17)</td>
<td>14.7 ± 8.3</td>
<td>16.0 ± 6.5</td>
<td>15.4 ± 8.2</td>
<td>18.9 ± 5.5</td>
</tr>
<tr>
<td>Other (n = 1)</td>
<td>30.0</td>
<td>24.0</td>
<td>30.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>F=1.562, $p=0.235$</td>
<td>F=0.745, $p=0.488$</td>
<td>F=1.436, $p=0.263$</td>
<td>F=5.531, $p=0.013*$</td>
</tr>
</tbody>
</table>
## Demographics ($n$)

<table>
<thead>
<tr>
<th>Demographics (range 0-30)</th>
<th>Self-perception (Q1,3,10,2,6) Mean ± SD$^\dagger$</th>
<th>Role-social (Q12,11,14,13) Mean ± SD$^\dagger$</th>
<th>Role-emotional (Q5,9,8,7,4) Mean ± SD$^\dagger$</th>
<th>Acne symptoms (Q15,16,17,18,19) Mean ± SD$^\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–24 ($n = 17$)</td>
<td>15.6 ± 9.1</td>
<td>16.0 ± 7.0</td>
<td>16.9 ± 8.2</td>
<td>17.0 ± 6.9</td>
</tr>
<tr>
<td>25–45 ($n = 5$)</td>
<td>16.2 ± 8.6</td>
<td>18.8 ± 4.4</td>
<td>14.8 ± 11.4</td>
<td>21.8 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>$t=-0.134, p=0.895$</td>
<td>$t=-0.844, p=0.409$</td>
<td>$t=0.472, p=0.642$</td>
<td>$t=-1.453, p=0.162$</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian ($n = 11$)</td>
<td>13.7 ± 8.7</td>
<td>14.7 ± 7.3</td>
<td>13.4 ± 8.4</td>
<td>17.4 ± 5.1</td>
</tr>
<tr>
<td>Asian ($n = 9$)</td>
<td>17.7 ± 7.8</td>
<td>18.8 ± 4.8</td>
<td>18.8 ± 8.4</td>
<td>20.9 ± 5.8</td>
</tr>
<tr>
<td>Other ($n=2$)</td>
<td>18.0 ± 17.0</td>
<td>17.5 ± 9.2</td>
<td>23.0 ± 9.920</td>
<td>9.5 ± 13.424</td>
</tr>
<tr>
<td></td>
<td>$F=0.550, p=0.586$</td>
<td>$F=0.986, p=0.391$</td>
<td>$F=1.664, p=0.216$</td>
<td>$F=3.004, p=0.073$</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild ($n = 13$)</td>
<td>18.6 ± 7.9</td>
<td>18.7 ± 5.5</td>
<td>19.7 ± 8.0</td>
<td>22.5 ± 3.3</td>
</tr>
<tr>
<td>Moderate ($n = 7$)</td>
<td>10.4 ± 4.8</td>
<td>13.4 ± 5.9</td>
<td>10.3 ± 4.2</td>
<td>13.9 ± 1.6</td>
</tr>
<tr>
<td>Severe ($n = 2$)</td>
<td>15.5 ± 20.5</td>
<td>14.5 ± 13.4</td>
<td>17.0 ± 18.4</td>
<td>4.5 ± 6.4</td>
</tr>
<tr>
<td></td>
<td>$F=2.217, p=0.136$</td>
<td>$F=1.736, p=0.203$</td>
<td>$F=3.187, p=0.064$</td>
<td>$F=37.440, p=0.000^*$</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 1 year ($n = 3$)</td>
<td>23.0 ± 7.8</td>
<td>20.7 ± 4.2</td>
<td>24.7 ± 7.5</td>
<td>25.7 ± 4.9</td>
</tr>
<tr>
<td>1–4 years ($n = 9$)</td>
<td>18.4 ± 7.9</td>
<td>17.7 ± 6.2</td>
<td>19.8 ± 5.7</td>
<td>17.0 ± 7.1</td>
</tr>
<tr>
<td>5+ years ($n = 10$)</td>
<td>11.1 ± 7.8</td>
<td>14.5 ± 7.0</td>
<td>11.0 ± 8.4</td>
<td>16.8 ± 5.6</td>
</tr>
<tr>
<td></td>
<td>$F=3.557, p=0.049^*$</td>
<td>$F=1.270, p=0.304$</td>
<td>$F=5.658, p=0.012^*$</td>
<td>$F=2.589, p=0.101$</td>
</tr>
</tbody>
</table>

* Statistically significant results

$^\dagger$ Results presented of available responses
5.4.3 Complementary and Alternative Medicine (CAM) Questionnaire for Young Adults

There were 27 respondents who started the CAM Questionnaire for Young Adults section of the survey and 25 who completed this section. For the first question on CAM use: “Have you used complementary/alternative medicine (CAM)?”, participants were asked to “check all that apply”. Most respondents had used CAM for treating illness (14 respondents, 51.9 per cent). Twelve respondents (44.4 per cent) had never used CAM before, 11 (40.7 per cent) had used it to improve their health and one chose “other” but did not specify the purpose (3.7 per cent). Nine respondents (33.3 per cent) had used CAM to prevent illness. Nine had used CAM to prevent and treat illness and to improve their health, three had used it to treat illness only, two had used it to treat illness and to improve health, and one chose “other” but did not describe why they had used CAM. When asked to best describe their healthcare practices, six respondents (22.2 per cent) had only used CAM and not other treatments, and nine (33.3 per cent) had used CAM given by their medical doctors.

Fifteen participants responded to the questions on which natural health products or therapies they had used, all having used CAM previously. None of the respondents reported using colour or dance movement therapy, magnetic therapy, reflexology, shiatsu or therapeutic touch. Respondents were able to choose more than one CAM. Results presented are categorised according to the National Center for Complementary and Alternative Medicine (15). All respondents had used at least one of the alternative medical systems such as traditional CM, Ayurvedic medicine or naturopathy. Within this group, CM was the most used, with 13 respondents having used “traditional Chinese medicine”. Twelve had used CAM products, nine had used mind-body therapies, seven had used
manipulative and body-based therapies, two had used creative therapies and two had used others (aromatherapy and magnet therapy).

Five of these 15 participants (33.3 per cent) took natural health products daily, four (26.7 per cent) took them weekly and three (20 per cent) took them monthly. Another respondent (2.7 per cent) took natural health products less often than once a year. Seven (46.7 per cent) saw CAM providers weekly, two each (13.3 per cent) saw them monthly or less than once per year (13.3 per cent), and one respondent saw them once per year (6.7 per cent). Participants were not asked about the reason for their use of CAM.

There were 25 respondents to the CAM beliefs component of the survey. The total score of three domains ranged from 29 to 61 (maximum score 65) with a mean total score of 48.2 (± 7.4). The minimum, maximum and mean scores of the three domains are presented in Table 5.6.

For individual question responses, answers for “agree” and “strongly agree” were combined and answers for “disagree” and “strongly disagree” were combined. Respondents believed young adults would use CAM if they had more knowledge (question 31, 21 respondents), exposure to CAM (question 32, 21 respondents) and if their friends were using it (question 33, 21 respondents) (Table 5.7). Young adults agreed or strongly agreed that CAM providers gave good information on maintaining a healthy lifestyle (question 25, 19 respondents) and would use CAM if their coaches or teachers discussed CAM with them (question 34, 18 respondents). Over 60 per cent of respondents believed that CAM has fewer side effects when taking natural remedies (question 26, 17 respondents), that young adults who believe in physical, mental and spiritual health are more
likely to use CAM (question 35, 17 respondents), that CAM involves plant formulas and is more healthy than taking drugs given by medical doctors (question 27, 16 respondents) and that they fear the discomfort of treatments from medical doctors (question 36, 16 respondents).

Table 5.6 Summary of CAM beliefs by individual questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Strongly disagree N (%)</th>
<th>Disagree N (%)</th>
<th>Haven’t decided N (%)</th>
<th>Agree N (%)</th>
<th>Strongly agree N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q25 CAM providers give good information on maintaining a healthy lifestyle</td>
<td>0</td>
<td>0</td>
<td>7 (28.0)</td>
<td>13 (52.0)</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td>Q26 There are less side effects when taking natural remedies</td>
<td>1 (4.0)</td>
<td>1 (4.0)</td>
<td>6 (24.0)</td>
<td>14 (56.0)</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Q27 CAM involves natural plant formulas which are more healthy than taking drugs given by the medical doctor</td>
<td>2 (8.0)</td>
<td>2 (8.0)</td>
<td>5 (20.0)</td>
<td>12 (48.0)</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>Q28 Young adults would be more likely to use CAM if there were more CAM clinics</td>
<td>1 (4.0)</td>
<td>5 (20.0)</td>
<td>6 (24.0)</td>
<td>9 (36.0)</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>Q29 Young adults are more empowered when using CAM because CAM providers involve them in decisions about their health care treatments</td>
<td>2 (8.0)</td>
<td>4 (16.0)</td>
<td>10 (40.0)</td>
<td>6 (24.0)</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Q30 Young adults believe that CAM builds up the body’s own defenses and promotes self-healing</td>
<td>1 (4.0)</td>
<td>3 (12.0)</td>
<td>6 (24.0)</td>
<td>11 (44.0)</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>Q31 The more knowledge a young adult has about CAM, the more likely he/she is to use it</td>
<td>1 (4.0)</td>
<td>1 (4.0)</td>
<td>2 (8.0)</td>
<td>17 (68.0)</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>Question</td>
<td>Strongly disagree N (%)</td>
<td>Disagree N (%)</td>
<td>Haven’t decided N (%)</td>
<td>Agree N (%)</td>
<td>Strongly agree N (%)</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------------------------</td>
<td>----------------</td>
<td>-----------------------</td>
<td>-------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Q32 Parent(s) and family can influence a young adult’s CAM use by exposing them to it</td>
<td>1 (4.0)</td>
<td>0</td>
<td>3 (12.0)</td>
<td>11 (44.0)</td>
<td>10 (40.0)</td>
</tr>
<tr>
<td>Q33 Young adults are more likely to use CAM if their friends are using it</td>
<td>1 (4.0)</td>
<td>0</td>
<td>3 (12.0)</td>
<td>13 (52.0)</td>
<td>8 (32.0)</td>
</tr>
<tr>
<td>Q34 Young adults are more likely to use CAM if coaches and teachers discuss it with them</td>
<td>0</td>
<td>2 (8.0)</td>
<td>4 (16.0)</td>
<td>13 (52.0)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>Q35 Young adults who believe in the physical, mental and spiritual aspects of health are more likely to use CAM</td>
<td>1 (4.0)</td>
<td>2 (8.0)</td>
<td>5 (20.0)</td>
<td>10 (40.0)</td>
<td>7 (28.0)</td>
</tr>
<tr>
<td>Q36 Young adults who fear the discomfort of treatments from medical doctors are more likely to use CAM</td>
<td>1 (4.0)</td>
<td>0</td>
<td>8 (32.0)</td>
<td>11 (44.0)</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td>Q37 Young adults believe that taking CAM therapies is not harmful</td>
<td>2 (8.0)</td>
<td>3 (12.0)</td>
<td>8 (32.0)</td>
<td>10 (40.0)</td>
<td>2 (8.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CAM Complementary and alternative medicine, N number, Q question

Table 5.7 CAM beliefs domain scores by groups

<table>
<thead>
<tr>
<th>CAM beliefs</th>
<th>Positive beliefs Mean ± SD</th>
<th>Environmental influences Mean ± SD</th>
<th>Psychological comfort Mean ± SD</th>
<th>Total score Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 4)</td>
<td>19.0 ± 5.7</td>
<td>16.8 ± 1.7</td>
<td>11.3 ± 1.5</td>
<td>47.0 ± 7.5</td>
</tr>
<tr>
<td>Female (n = 17)</td>
<td>22.5 ± 2.7</td>
<td>16.7 ± 2.1</td>
<td>11.5 ± 1.6</td>
<td>50.7 ± 5.6</td>
</tr>
<tr>
<td>Other (n = 1)</td>
<td>20.0</td>
<td>6.0</td>
<td>3.0</td>
<td>29.0</td>
</tr>
<tr>
<td>CAM beliefs</td>
<td>Positive beliefs Mean ± SD</td>
<td>Environmental influences Mean ± SD</td>
<td>Psychological comfort Mean ± SD</td>
<td>Total score Mean ± SD</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------</td>
<td>-----------------------------------</td>
<td>-------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td></td>
<td>F=1.917, p=0.174</td>
<td>F=13.125, p=0.000*</td>
<td>F=13.743, p=0.000*</td>
<td>F=6.476, p=0.007*</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>21.7 ± 2.8</td>
<td>15.9 ± 2.1</td>
<td>11.3 ± 1.7</td>
<td>48.9 ± 5.9</td>
</tr>
<tr>
<td>Asian</td>
<td>21.8 ± 4.7</td>
<td>17.7 ± 1.6</td>
<td>11.6 ± 1.4</td>
<td>51.0 ± 6.6</td>
</tr>
<tr>
<td>Other</td>
<td>22.0 ± 2.8</td>
<td>11.0 ± 7.1</td>
<td>7.5 ± 6.4</td>
<td>40.5 ± 16.3</td>
</tr>
<tr>
<td></td>
<td>F=0.05, p=0.995</td>
<td>F=6.257, p=0.008*</td>
<td>F=3.066, p=0.070</td>
<td>F=1.788, p=0.194</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–24</td>
<td>21.6 ± 3.7</td>
<td>15.8 ± 3.3</td>
<td>10.8 ± 2.4</td>
<td>48.2 ± 7.9</td>
</tr>
<tr>
<td>25–45</td>
<td>22.4 ± 3.0</td>
<td>17.4 ± 1.1</td>
<td>11.8 ± 2.1</td>
<td>51.6 ± 4.7</td>
</tr>
<tr>
<td></td>
<td>t=-0.445, p=0.661</td>
<td>t=-1.040, p=0.311</td>
<td>t=-0.814, p=0.425</td>
<td>t=-0.893, p=0.382</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>22.6 ± 3.1</td>
<td>17.0 ± 2.0</td>
<td>11.3 ± 1.6</td>
<td>50.9 ± 6.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>20.4 ± 4.5</td>
<td>16.0 ± 2.2</td>
<td>11.9 ± 1.6</td>
<td>48.3 ± 6.6</td>
</tr>
<tr>
<td>Severe</td>
<td>21.0 ± 1.4</td>
<td>11.0 ± 7.8</td>
<td>6.5 ± 5.0</td>
<td>39.0 ± 14.1</td>
</tr>
<tr>
<td></td>
<td>F=0.926, p=0.413</td>
<td>F=3.727, p=0.043*</td>
<td>F=6.530, p=0.007*</td>
<td>F=2.691, p=0.094</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>22.3 ± 3.2</td>
<td>17.0 ± 2.00</td>
<td>10.0 ± 1.0</td>
<td>49.3 ± 5.9</td>
</tr>
<tr>
<td>1–4 years</td>
<td>22.8 ± 3.0</td>
<td>15.7 ± 4.2</td>
<td>11.0 ± 3.1</td>
<td>49.4 ± 9.5</td>
</tr>
<tr>
<td>5+ years</td>
<td>20.7 ± 4.1</td>
<td>16.4 ± 1.9</td>
<td>11.4 ± 1.8</td>
<td>48.5 ± 6.2</td>
</tr>
<tr>
<td></td>
<td>F=0.859, p=0.440</td>
<td>F=0.254, p=0.778</td>
<td>F=0.392, p=0.681</td>
<td>F=0.039, p=0.962</td>
</tr>
</tbody>
</table>

Abbreviations: CAM complementary and alternative medicine, n number, SD standard deviation

*Statistically significant
5.4.3.1 Positive beliefs domain

There was no difference in the CAM questionnaire positive beliefs domain when comparing group differences in all the characteristics: gender, age, ethnicity, severity of acne and duration of acne.

5.4.3.2 Environmental influences domain

There were no differences when comparing age and duration of acne for the domain of environmental influences. There was a statistically significant result in gender difference in the environmental influences domain ($p = 0.000$). Post-hoc analysis was not able to be performed due to only one respondent in the “other” gender category. Based on the data presented, the difference may be between males (4 respondents, 16.8 ± 1.7) and the “other” gender (1 respondent, 6.0). The difference may also be between females (17 respondents, 16.7 ± 2.1) and the “other” gender. Only a post-hoc analysis with additional respondents in the “other” gender category can truly show where the differences lie. Asians had a slightly higher score (9 respondents, mean score 17.7 ± 1.6) than Caucasians (11 respondents 15.9 ± 2.1) and “other” (11.0 ± 7.1) for environmental influences, indicating that their environment had an influence on their attitudes and possible use of CAM. In a post-hoc analysis, the differences were seen between the Asian and “other” group ($p = 0.007$).

Environmental influences was also scored higher by people who reported their acne as mild (13 respondents, 17.0 ± 2.0) than people with self-reported severe acne (2 respondents, 11.5 ± 7.8). In a post-hoc analysis, those with self-reported mild acne scored higher on environmental influences than those with self-reported severe acne ($p = 0.041$). There was no difference between the moderate and mild groups ($p = 1.000$) and no difference between the moderate and severe groups ($p = 0.145$).
5.4.3.3 Psychological comfort domain

There was no difference in scores in the psychological comfort domain when comparing age and duration of acne. Similar to the environmental influences domain \((p = 0.000)\), there were statistically significant gender differences in the psychological comfort domain \((p = 0.000)\). A post-hoc analysis was not able to be performed due to only one respondent in the “other” gender category. As with environmental influences, the differences may be between males (4 respondents, 11.3 ± 1.5) and the “other” gender (3.0) and also between females (17 respondents, 11.5 ± 1.6) and the “other” gender. The self-reported mild severity group (11.3 ± 1.6) scored higher in the psychological comfort domain compared to the self-reported severe group (6.5 ± 5.0). In a post-hoc analysis, the mild severity group scored higher in the psychological comfort domain compared to the severe group \((p = 0.010)\). The moderate group scored higher than the severe group \((p = 0.007)\) and there was no difference between the mild and moderate groups \((p = 1.000)\).

5.4.3.4 Attitudes to CAM

There were 25 valid responses to the questions on CAM attitudes. The median of the total score was 48 and results were dichotomised at this point. A score of 1 to 48 was defined as a negative attitude and being less likely to use CAM, whereas a score of 49 to 65 was defined as positive and being more likely to use CAM. There were 12 respondents with a positive attitude (score 49 and above) and 13 who had a negative attitude (score 48 and below) (Table 5.8). There were no differences in the number of people with positive or negative attitudes to CAM when comparing group differences for all the characteristics: gender, age, ethnicity, severity of acne and acne duration.
### Table 5.8 CAM attitudes

<table>
<thead>
<tr>
<th>CAM attitudes</th>
<th>Positive attitude N (%)</th>
<th>Negative attitude N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 25)</td>
<td>12 (48.0)</td>
<td>13 (52.0)</td>
</tr>
</tbody>
</table>

**Gender**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Positive attitude N (%)</th>
<th>Negative attitude N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n = 4)</td>
<td>1 (25)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Female (n = 17)</td>
<td>11 (64.7)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Other (n = 1)</td>
<td>0 (0.0)</td>
<td>1 (100.0)</td>
</tr>
</tbody>
</table>

$\chi^2 = 3.316, df=2, p=0.191$

**Ethnicity**

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Positive attitude N (%)</th>
<th>Negative attitude N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian (n = 11)</td>
<td>6 (54.5)</td>
<td>5 (45.5)</td>
</tr>
<tr>
<td>Asian (n = 9)</td>
<td>5 (55.6)</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>Other (n = 2)</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
</tr>
</tbody>
</table>

$\chi^2 = 0.02, df=2, p=0.990$

**Age**

<table>
<thead>
<tr>
<th>Age</th>
<th>Positive attitude N (%)</th>
<th>Negative attitude N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–24 (n = 17)</td>
<td>8 (47.1)</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td>25–45 (n = 5)</td>
<td>4 (80)</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>

$\chi^2 = 1.691, df=1, p=0.193$

**Severity**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Positive attitude N (%)</th>
<th>Negative attitude N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (n = 14)</td>
<td>8 (61.5)</td>
<td>5 (38.5)</td>
</tr>
<tr>
<td>Moderate (n = 7)</td>
<td>3 (42.9)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Severe (n = 2)</td>
<td>1 (50)</td>
<td>1 (50)</td>
</tr>
</tbody>
</table>

$\chi^2 = 0.659, df=2, p=0.719$

**Duration**

<table>
<thead>
<tr>
<th>Duration</th>
<th>Positive attitude N (%)</th>
<th>Negative attitude N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year (n = 3)</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>1–4 years (n = 9)</td>
<td>5 (55.6)</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>5+ years (n = 10)</td>
<td>6 (60)</td>
<td>4 (40)</td>
</tr>
</tbody>
</table>

$\chi^2 = 0.668, df=2, p=0.716$
5.4.4 Preferences for CM Treatment

Twenty-two respondents provided answers to their preferences on a list of herbal preparations (Table 5.9). Seventeen (77.3 per cent) chose topical cleansers as their first preference, followed by four (18.2 per cent) who chose oral pills (round pills) and one (4.5 per cent) who chose oral tablets (compressed herbs into a flat tablet). For their second preferences, one (4.5 per cent) chose cleansers, 10 (45.5 per cent) chose pills and five (22.7 per cent) chose tablets. In relation to treatment duration (Table 5.10), one (4.5 per cent) chose two weeks of treatment, six (27.3 per cent) chose four weeks of treatment and five (22.7 per cent) chose eight weeks. Five respondents (22.7 per cent) were willing to take herbs twice or three times daily and 17 (77.3 per cent) were willing to take herbs less than twice daily.

Table 5.9 Preference for herbal medicine preparation types

<table>
<thead>
<tr>
<th>Herb type</th>
<th>1st preference N (%)</th>
<th>2nd preference N (%)</th>
<th>3rd preference N (%)</th>
<th>4th preference N (%)</th>
<th>5th preference N (%)</th>
<th>6th preference N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleanser (topical)</td>
<td>17 (77.3)</td>
<td>1 (4.5)</td>
<td>2 (9.1)</td>
<td>1 (4.5)</td>
<td>0 (0.0)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Pills (oral)</td>
<td>4 (18.2)</td>
<td>10 (45.5)</td>
<td>3 (13.6)</td>
<td>0 (0.0)</td>
<td>2 (9.1)</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Tablets (oral)</td>
<td>1 (4.5)</td>
<td>5 (22.7)</td>
<td>9 (40.9)</td>
<td>2 (9.1)</td>
<td>3 (13.6)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Granules (oral)</td>
<td>0 (0.0)</td>
<td>1 (4.5)</td>
<td>4 (18.2)</td>
<td>12 (54.5)</td>
<td>2 (9.1)</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Powders (oral)</td>
<td>0 (0.0)</td>
<td>1 (4.5)</td>
<td>2 (9.1)</td>
<td>3 (13.6)</td>
<td>13 (59.1)</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Liquid (oral)</td>
<td>0 (0.0)</td>
<td>4 (18.2)</td>
<td>2 (9.1)</td>
<td>4 (18.2)</td>
<td>2 (9.1)</td>
<td>10 (45.5)</td>
</tr>
</tbody>
</table>
Table 5.10 Preferred maximum duration of herbal treatment

<table>
<thead>
<tr>
<th>Time</th>
<th>Frequency (N)</th>
<th>Per cent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>4 weeks</td>
<td>6</td>
<td>27.3</td>
</tr>
<tr>
<td>8 weeks</td>
<td>5</td>
<td>22.7</td>
</tr>
<tr>
<td>12 weeks</td>
<td>3</td>
<td>13.6</td>
</tr>
<tr>
<td>6 months</td>
<td>4</td>
<td>18.2</td>
</tr>
<tr>
<td>12 months</td>
<td>3</td>
<td>13.6</td>
</tr>
</tbody>
</table>

For acupuncture and related modalities (Table 5.11), 13 (59.1 per cent) chose acupuncture as their first preference, five (22.7 per cent) chose acupressure as their first preference, three (13.6 per cent) chose EA as their first preference and one (4.5 per cent) chose laser acupuncture as their first preference. For their second preferences, one (4.5 per cent) chose acupuncture, seven (31.8 per cent) chose acupressure, four (18.2 per cent) chose ear acupressure, six (27.3 per cent) chose EA and 5 (22.7 per cent) chose laser acupuncture.

Table 5.11 Preferences for acupuncture interventions

<table>
<thead>
<tr>
<th>Acupuncture type</th>
<th>1st preference N (%)</th>
<th>2nd preference N (%)</th>
<th>3rd preference N (%)</th>
<th>4th preference N (%)</th>
<th>5th preference N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture</td>
<td>13 (59.1)</td>
<td>1 (4.5)</td>
<td>2 (9.1)</td>
<td>3 (13.6)</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Acupressure</td>
<td>5 (22.7)</td>
<td>7 (31.8)</td>
<td>4 (18.2)</td>
<td>4 (18.2)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Ear acupressure</td>
<td>0 (0.0)</td>
<td>4 (18.2)</td>
<td>9 (40.9)</td>
<td>4 (18.2)</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>Electro-acupuncture</td>
<td>3 (13.6)</td>
<td>6 (27.3)</td>
<td>6 (27.3)</td>
<td>6 (27.3)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Laser acupuncture</td>
<td>1 (4.5)</td>
<td>5 (22.7)</td>
<td>1 (4.5)</td>
<td>5 (22.7)</td>
<td>10 (45.5)</td>
</tr>
</tbody>
</table>
Six (27.3 per cent) were willing to have acupuncture and related modalities for four weeks (Table 5.12), four (18.2 per cent) were willing to have two weeks of treatment, four (18.2 per cent) were willing to have eight weeks of treatment and three (13.6 per cent) were willing to have six months of treatment. Twelve (54.5 per cent) were willing to have weekly treatments, nine (40.9 per cent) were willing to have fortnightly treatments and one (4.5 per cent) was willing to have treatments every second day.

Table 5.12 Preferred maximum duration of acupuncture treatment

<table>
<thead>
<tr>
<th>Time</th>
<th>Frequency (N)</th>
<th>Per cent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>4</td>
<td>18.2</td>
</tr>
<tr>
<td>4 weeks</td>
<td>6</td>
<td>27.3</td>
</tr>
<tr>
<td>8 weeks</td>
<td>4</td>
<td>18.2</td>
</tr>
<tr>
<td>12 weeks</td>
<td>3</td>
<td>13.6</td>
</tr>
<tr>
<td>6 months</td>
<td>3</td>
<td>13.6</td>
</tr>
<tr>
<td>12 months</td>
<td>2</td>
<td>9.1</td>
</tr>
</tbody>
</table>

5.5 Discussion

There were 28 respondents to the survey. There were missing data from three respondents for the CAM Questionnaire for Young Adults CAM beliefs component, and from six respondents to the CM treatment preferences. Respondents were mostly female, had mild acne and were young people. There were slightly more people with acne for less than five years than those with acne for more than five years. More than 60 per cent of people had previously sought treatment for their acne.
acne and had used medically prescribed TAB and BP to treat their acne. Just under three-quarters (72.7 per cent) had used over-the-counter medications that contained salicylic acid.

The lowest score on the Acne-QoL was for self-perception and the highest was for acne symptoms. People were more emotionally affected and worried about their acne if they had moderate acne. Of note, the self-perception, role-social and role-emotional domains were scored lower in the self-reported moderate acne group compared to the mild and severe groups, although this was not statistically significant. The self-reported severe acne group had the lowest score for the acne symptoms domain. For the CAM questionnaire, just under half of the 27 respondents had not previously use CAM products. For the overall attitudes to CAM, there were approximately equal numbers of participants with a positive attitude ($n=12$) and a negative attitude ($n=13$).

Respondents preferred CHM as a topical cleanser, followed by pills and tablets, and had stronger preferences for acupuncture and acupressure than for other related interventions. For herbal medicines, they preferred to take them less than twice daily. Respondents were willing to have herbal medicines and acupuncture treatment for four to eight weeks. Responses from this survey informed the clinical trial protocol in Chapter 9.

Respondent fatigue appeared to be a factor in the completion rates for each section of the survey. The survey was structured with the consent information and consent question given first. This was followed by the Acne-QoL, then the CAM questionnaire, the CM treatment preferences and finally the demographics section. Hence as participants completed sections of the survey, the number of
participants who did not complete the survey increased. There were a total of 51 questions and this may have contributed to some participants not completing the whole survey.

There were more female respondents (17/22 who responded to the question on gender) than male (4/22) respondents in this survey. Previous studies have found more females with acne participate in research studies compared to males (228). This was also found in this survey. There were also more respondents in the youth group aged 15 to 24 who responded to their age (17/22 respondents) than the adult group (5/22 respondents). This was anticipated, as younger participants have higher androgen activity and are therefore more likely to get follicular plugging and acne formation (60). The targeted advertising at university campuses and high schools also contributed to the younger age group of respondents.

Studies have shown that the HRQoL of people with acne can be severely affected. It may have a negative impact on their psychological and emotional health, as well as their social and personal relationships, particularly in girls (220). There was a trend found in this survey that female respondents had a worse Acne-QoL score than males. Although the results are not significant in this survey (likely due to the number of respondent), females had poorer self-perception and were more emotionally and socially affected than males. The developers of the Acne-QoL survey (119-121) found females had worse Acne-QoL scores than males. An online survey conducted in female adults 25 to 45 years old with facial acne found Hispanic and Asian/other respondents had lower Acne-QoL scores compared to white and African-American participants (205). This was not found in this survey, where no significant differences were found between Asian, Caucasian and “other” ethnic groups. The mean scores in each of the domains in the study conducted by Gorelick et al.
(231) were lower in each domain compared to this study. This is likely due to significantly higher number of respondents to their survey (312 respondents).

There were only two respondents in the severe acne group, which is similar to other cross-sectional studies, which tended to have lower numbers of people with severe acne compared to those with mild and moderate acne (8, 37, 203, 222, 227). It has previously been reported that the severity of acne may not necessarily be associated with a worsening of HRQoL (69). In the study conducted by Martin et al. (121), higher reported severity was associated with a worse HRQoL score. Many other studies have also found a correlation between higher severity of acne and worse HRQoL (19, 67, 191, 222, 224). In this survey, one respondent with severe acne had a very high Acne-QoL score, which means better HRQoL, while the other one with severe acne had a much lower score, hence the large standard deviation. With only two respondents in the severe acne category, it is difficult to conclude whether there is a correlation between worse acne and worse HRQoL. Self-reported acne severity was unable to be verified by a dermatologist in this study as it was an anonymous online survey. However, with modern technology, future surveys might be able to consider requesting non-identifiable images of acne areas for verification.

People with prolonged acne duration were found to have lower Acne-QoL scores than those with shorter duration in a study of 862 respondents from different demographic groups (287). However, this was not found by Duman et al. (74), who used the AQOL (69). This study also did not find a correlation between acne duration and worse HRQoL.
Twenty-seven respondents answered questions on CAM. Approximately half were previous users of CAM and just under half had never used CAM. One-third had used CAM to prevent and treat illness, whereas the developers of the CAM Questionnaire (268) found that three-quarters of their respondents had used CAM for treating and preventing illness. The most frequently used group was alternative medical systems and, within this group, CM was the most used system. This may be related to the recruitment strategies used, including emails to student representatives of Chinese Medicine, Chiropractic and Osteopathy Disciplines. Although students were not approached directly, the study investigator is the clinical coordinator and a lecturer in the Chinese Medicine Discipline and, as a consequence, this may have resulted in more students from CM responding to the survey. CAM use varied from weekly to once per month and twice per year. CAM users were more likely to use CAM for treating illness and promote their health which is similar to the findings from the original survey conducted by Patterson and Arthur (268). In this survey, there were similar numbers of participants who had a positive attitude to CAM and a negative attitude to CAM. This is surprising, as one part of the recruitment strategy of this survey was promoted to students in the CAM areas of CM, chiropractic and osteopathy. A positive attitude to CAM was interpreted by the original authors as a higher likelihood to use CAM (268). When considering the previous use of CAM (question 20), about half \((n = 15)\) had previously used CAM and the other half had not, which may reflect this result. As this was survey was anonymous and no data on respondent study or employment status, and other recruitment strategies such as posters around the campus grounds and high schools, there is no certainty that only CAM students responded to the survey.
The original survey did not present results for each domain by demographic characteristics; therefore no comparisons are able to be made for the different domains. There were gender differences in the environmental influences and psychological comfort domains; however, due to only one “other” gender respondent, post-hoc analysis could not be performed. Based on mean scores, the differences were likely to be between males and the “other” gender and between females and the “other gender”, rather than between males and females. The environment influenced Asians and the “other” ethnicity. Environmental influences included prior knowledge about CAM treatments, whether parents, family or friends used CAM and whether coaches and teaches discussed CAM with them. Other studies looking at predictors of CAM use by children and adolescents have reported an association between female gender and parental CAM use (288-290). There were also differences between the mild and severe acne groups for the environmental influences and psychological comfort domains. The mild severity group scored higher for both domains compared to the severe group, indicating the mild group thought that family, friends, coaches and teachers influenced young people to use CAM and that young people’s reasoning behind their attitudes to CAM included physical, mental and spiritual aspects of health. Although there are no other studies on acne severity and CAM use, other studies on CAM use have shown that it can be influenced by other people, holistic health beliefs (291, 292), belief that it aided wellbeing (293) and if the user of CAM had a chronic illness (294).

In the individual questions, 21 respondents (84 per cent) agreed or strongly agreed that parents and family can influence young adults’ CAM use by exposing them to it. CAM use in children and adolescents is popular (17). In one systematic review on CAM use in children, homeopathy was the most popular CAM in Germany, the UK and Canada, with herbal product use highest in
Germany, Turkey and Brazil (17). The highest predictor for CAM use was higher parental income, education level and having older children (17). In a survey of adolescents 15 to 19 years old in Saudia Arabia, the most used CAM product was honey and the least used was acupuncture. This study also found females tended to use CAM more than males (295). CAM use in the USA also showed that the most commonly used products were non-vitamin, non-mineral natural products (15), followed by chiropractic and osteopathy. This survey showed that alternative medical systems and in particular CM (acupuncture and CHM), followed by mind-body therapies and manipulative and body-based therapies such as chiropractic and osteopathy, were more commonly used than other CAM modalities. This is likely related to the recruitment strategies, where students in the three areas of CAM taught at RMIT University were invited to participate.

There have been no previous studies identified on CM treatment preferences by people with acne. Respondents were also asked about their preferences for CM treatment methods and length and frequency of treatment. Although the numbers were low, the data provides insights into people’s preferences for CM treatment. There was a variation in what respondents were willing to take and how long participants were willing to have treatment. Topical cleansers was the most preferred of all the herb preparation types and were the only topical option in the survey. Topical herbs require no preparation time by the patient and are not orally consumed.

The most preferred preparation type for oral herbs was pills, followed by tablets. The least preferred was oral liquid (also known as decoctions), despite decoctions being the most common traditional preparation type. With decoctions, raw herbal medicines are given to patients, who take them home to boil twice and drink the liquid. They require the most preparation time by the patient,
typically between one and a half and two hours. Powders, granules and decoctions are preparations that are consumed in liquid form. Powders are made by pulverising raw herbs into fine particles or produced from the liquid extract of boiled herbs. Powder is mixed with water for drinking. A disadvantage of both decoctions and powders is that the taste of herbal medicines is obvious to the patient. The taste can be unpalatable for some people (296) and can pose issues for blinding in clinical trials.

Pills and tablets are common forms of preparation in modern clinical practice. For pills or tablets, no preparation time is required and patients swallow them whole without needing to prepare herbs or encounter the taste of the herbs. This feature appeared to be important to respondents in this survey. Capsules have the same advantages as pills and tablets, but are relatively new to modern practice. Capsules were not included in the survey, but may be an important preparation type to achieve blinding in clinical trials.

The most preferred treatment period for herbal medicine was four weeks, followed by eight weeks. This is a common treatment period encountered in clinical trials (Chapter 7). The treatment preferences component informed the development of the clinical trial protocol, as it has been shown that incorporating patient perspectives into interventions can influence participation in trials (271, 297). In taking into consideration treatment preferences, it is anticipated there would be greater adherence in trials and clinical practice (276).
5.6 Limitations of survey

People with the link to the survey could complete the survey online anonymously without verifying their identities. This is a common challenge for online surveys. The Acne-QoL survey is limited to facial acne and does not apply to acne on other parts of the body. It is a self-administered survey which was initially designed to be implemented in a dermatology office setting where researchers could be on hand to read questions to participants. If participants could not understand a question, they were instructed to use their own interpretation and respond about their feelings. The survey instructions also encouraged participants to complete all questions. As this was an anonymous online survey, such reminders were unable to be given.

The Acne-QoL survey has been validated for people between 13 to 35 years old and the CAM Questionnaire for Young adults was validated for adolescents and young adults. The age inclusion criteria for this survey included people older than 35 years old (one respondent); therefore it is unknown whether the questions were applicable for the older age group. As most of the respondents were between 15 and 24 years old (17 respondents), it is possible that the survey results are representative. Acne severity reported by respondents was unable to be verified by a dermatologist as it was an online anonymous survey.

Recruitment strategies included advertisements placed on university campuses across Melbourne, RMIT Facebook student support groups and approaches to high schools to place advertisements in their newsletters. There were two high schools that agreed to place the advertisement in their newsletters. Therefore, the age group of 20 to 24 may be overrepresented (10 respondents).
Recruitment was also an issue due to the timing of the release of the survey to the public. The initial pilot study intended for the beginning of the university semester ended up being implemented at the end of the semester. By the time the full survey was released to the public, it was semester break and fewer people were on campus to see the advertisements. There were also limited places where the advertisement could be placed online and on campus. The RMIT Facebook page and other University online websites limited the type of information that could be advertised on their websites.

The university student population receives many requests for surveys and, anecdotally, students can be “over surveyed”. With the promotion of the online survey primarily placed within university grounds, this limited the reach of the survey. Other marketing approaches such as social media were similarly unsuccessful. The creation of the survey Facebook page coincided with publicity of Facebook’s privacy issues and there were reports of a drop in the general use of Facebook during the time the page was created (286). There were eight hits on the Facebook page. Five responses were received after dissemination of the survey advertisement to healthcare practitioners later in the survey period (20 June 2018). As responses for each recruitment strategy were not recorded, it is unclear which of the advertising methods used were most effective.

The number of respondents to this survey was low. Small survey samples can lead to higher variability in results and lead to bias (298). There were few statistically significant results in this set of results and larger standard deviations. Therefore the results should be interpreted with caution and may not be generalised to the general population of people with acne.
There were no incentives given as part of the survey. Incentives may increase participation. In one survey of plastic surgeons, four different strategies were used (299): an emailed link to an online survey; regular mail; regular mail with a $1 note; and regular email with a $5 note. Of the 662 surveys sent, 608 were returned. The highest response was from those mailed with a monetary incentive and the lowest was from emails. Other innovative and timely recruitment strategies may have increased responses to the survey. These include search engine and banner advertising, monetary or other types of incentives for participants, collaboration with dermatologists and other healthcare practitioners, and applying to national or state government departments to enlist high schools to conduct research.

In the CM preferences section of the survey, no option was provided for a preference for capsules, as this is not as common traditionally. Pills and tablets may be considered similar products and some laypersons may not have understood the differences, given that no descriptions or images were provided. Researchers conducting similar surveys may consider adding capsules as an option, as this form of herbal medicine is now more popular, with many modern practices being able to manually create capsules in their private clinics. In addition, providing images or descriptions will assist participants in understanding the differences between pills, tablets and capsules. This also applies to granules and powders.

Not all sections of the survey were completed by the respondents. As participants progressed through each section, the number of respondents declined. The number of questions and the separation of sections may have contributed to the discontinuation. Future surveys may consider not separating the sections in surveys or shortening the number of questions.
5.7 Conclusions and implications

This survey showed that respondents to the survey were mostly female, young people 15 to 24 years old with mild acne. People with severe acne were more worried about their acne symptoms. Half of respondents had a positive attitude to CAM. CM treatment preferences included topical herbs for four to eight weeks and weekly acupuncture treatment. The number of respondents was low and not many statistically significant results were found. Future surveys will need to use more creative recruitment strategies and to consider other means such as ethically approved incentives to recruit more people to complete the survey. The study results therefore cannot be generalised to the Australian population with acne as a whole. The results from the CM treatment preferences section of the survey can be used as a guide on treatment preferences to help improve treatment adherence.
CHAPTER 6 : Methods for systematic reviews

Overview
The impact of acne on HRQoL has been described in Chapter 4, and Chapter 5 provided new data on the emotional, social and psychological impact of acne in young people and adults in Australia. The next step in this project was to gain an understanding of the effectiveness of CM therapies for acne vulgaris. Two systematic reviews, one of CHM for acne and one of acupuncture and related therapies was planned. This chapter describes the methods used to conduct SRs of the efficacy and safety of two types of CM interventions for acne vulgaris. The results of the first SR on the CHM formula Pi Pa Qing Fei Yin (Eriobotrya japonica Formula) will be presented in Chapter 7 and the results of the second SR on acupuncture and related techniques will be presented in Chapter 8.

6.1 Introduction
Systematic reviews provide a summary of the evidence from eligible studies and evaluate the methodological processes of included studies. They estimate clinical effects and guide clinicians on clinical decision-making by assessing the confidence in the evidence (300). SRs of RCTs are considered the highest level of evidence (Level I) according to Australia’s National Health and Medical Research Council (NHMRC) (301). The methods developed by the Cochrane Collaboration (302) are considered the best in evaluating RCTs (303).

A monograph currently in press provides a comprehensive evaluation of the evidence for acne, including CHM (168). A summary of the findings from the monograph relating to CHM and acupuncture and related techniques can be found in Chapter 3. There are currently no SRs in
English on the safety and efficacy of CHM for acne vulgaris. There have been two SRs on RCTs of acupuncture and related techniques for acne, one in Chinese (18) and one in English (185). These reviews included CM interventions, placebo and pharmacotherapies as controls, making it hard to draw reliable conclusions from current reviews. There has also been one English-language review of botanical and phytochemical therapy for acne vulgaris (20) which included Chinese and other herbal medicines.

6.2 Study design

The SRs included RCTs involving people with acne vulgaris. Non-controlled studies such as case series and case-control studies identified in the literature search were excluded.

6.2.1 Participants

Acne vulgaris begins at adolescence but can affect adults (24). It can affect any gender and ethnicity. As the onset of acne begins at adolescence and the age of puberty can be earlier than 10 years old (304-306) the SRs for the acupuncture-point stimulation and Pi Pa Qing Fei Yin (PPQFY) did not have an age limit. Acne conglobata was not excluded since some commonly used acne-grading systems included nodular acne in stage IV or severe acne (106, 107). Although PPQFY is recommended for comedonal acne, textbooks do not specify that it is used only for mild or moderate acne. Clinically, most practitioners will use it for mild to moderate acne. Therefore, there was no limit on acne severity.
6.2.2 Intervention

6.2.2.1 Inclusion criteria for PPQFY
A specific search was conducted using the formulation name in Chinese, pin yin and English variations (Table 6.1). Studies that used the original formula PPQFY or a modified version, alone, with another formula or as integrative medicine (PPQFY combined with pharmaceuticals), were included in the review. A modified PPQFY formula was defined as using the original formula with addition, removal or replacement of one or more herbs.

6.2.2.2 Inclusion criteria for acupuncture
Acupuncture trials that used body acupuncture or acupressure, auricular (ear) acupuncture or acupressure, EA, electro-stimulation (for example, transcutaneous electrical nerve stimulation), moxibustion and other forms of direct acupuncture point stimulation such as surround needling or cutaneous needling were included in the review. Other acupuncture-related techniques such as laser acupuncture and cupping or integrative medicines (pharmacotherapy) were also eligible for the review. Techniques not commonly used outside of China were excluded. Studies that included CM therapies as controls were excluded (Table 6.1).
### Table 6.1 Inclusion and exclusion criteria for systematic reviews

<table>
<thead>
<tr>
<th>PICO component</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>Diagnosis of acne vulgaris with all severity gradings (I–IV) including acne conglobata</td>
<td>Acne due to hormonal issues such as PCOS, drug-induced acneiform, acne tropica, acne infantile, acne excoriée des jeunes filles</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>PPQFY: PPQFY alone or combined with other CHM or conventional pharmacotherapy; original or modified formula</td>
<td>Other CM techniques such as acupuncture</td>
</tr>
<tr>
<td><strong>Comparators</strong></td>
<td>No treatment/waitlist, placebo control, sham acupuncture, pharmacotherapy</td>
<td>CM techniques as a control</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td><strong>Primary outcome measures:</strong> Lesion count, overall grading or severity of acne, TER</td>
<td><strong>Secondary outcome measures:</strong> Recurrence rate, HRQoL, adverse events</td>
</tr>
</tbody>
</table>

**Abbreviations:** CHM Chinese herbal medicine, CM Chinese medicine, HRQoL health-related quality of life, PCOS polycystic ovarian syndrome, PICO Participants Intervention Comparators and Outcomes, PPQFY Pi Pa Qing Fei Yin, TER therapeutic effective rate

### 6.2.2.3 Rationale for intervention selection

A project evaluating CHM for acne was being conducted in parallel to this PhD project (168). A key finding of this project was the high frequency of use of PPQY in clinical trials for acne. So as not to duplicate work already conducted, this review has focused on a PPQFY (*Eriobotrya japonica* formula), which is recommended in the China Acne Treatment Guideline to “clear heat in the Lung and Stomach” (166). PPQFY is also recommended in CM textbooks and is commonly
prescribed for comedonal acne (159). There are no standalone reviews of PPQFY in English or in Chinese. Previous reviews also included acupuncture combined with herbal medicines, did not analyse herbal medicines alone and did not focus on PPQFY in their reviews (18, 157, 185).

The second review focused on acupuncture and related therapies. Acupuncture is a common intervention used for the treatment of a range of skin conditions (155). Commonly used acupuncture techniques that directly stimulate acupuncture points include body acupuncture, auricular acupuncture and moxibustion. Previous reviews on acupuncture included studies that combined acupuncture with herbal medicines, or included studies that used CM as a comparator. Comparing acupuncture with pharmacological treatments that have already been shown to be effective provides a greater understanding of the effectiveness of acupuncture therapies than comparing with treatments with unknown efficacy. An acupuncture review specifically on the aforementioned techniques will clarify whether they are efficacious for acne. Electro-acupuncture and auricular acupuncture have been shown to decrease inflammatory mediators in various inflammation pathways (307, 308). Acupuncture has also been shown to decrease sebum production in combination with BP (309), therefore possibly affecting acne lesions. These acupuncture-related interventions are also recommended in CM textbooks. Despite the great potential for using acupuncture for the treatment of acne, there is no good evidence of its safety and efficacy.

6.2.3 Comparators

Previous systematic reviews included CM as comparators, which diluted the strength of the evidence when an unknown treatment was compared with another unknown treatment. The
comparators for PPQFY review included no treatment or a waitlist, placebo control and pharmacotherapy. Pharmacotherapy included oral medications such as antibiotics and retinoids and topical medications such as benzoyl peroxides. In addition to these comparators, the acupuncture review also included sham acupuncture as a comparator.

6.2.4 Outcome measures

There is no published consensus on outcome measures for research in acne. Lesions may be assessed using Pillsbury, Leeds, IGA, GAGS or photography (101, 104, 109, 310).

Primary outcomes included an assessment of end-of-treatment differences in:

1. lesion count
2. overall grading (either reported by physician’s assessment or self-reporting and length of time between recurrence of symptoms); and
3. therapeutic effective rate.

Lesion count is a visual count of the number of inflammatory and non-inflammatory lesions. Grading is typically assessed using an ordinal grading criterion that indicates levels of severity of the acne. Therapeutic effective rate (TER) is an outcome frequently used in studies conducted in China. Criteria for determining clinical effect vary. Two guidelines frequently referenced in clinical studies are the Clinic Research Guidelines for Chinese Herbal Medicine and New Drugs (中药新药临床研究指导原则(试行)) (311) and the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine (167). The former defines clinical effect as 50 per cent or greater improvement in lesion count and/or severity grading as effective,
while the latter uses a minimum threshold of 30 per cent or greater. Differences exist between the
criteria described in these two guidelines and there is no consensus on which is preferred. A third
guideline published in 2010 (312) also describes a minimum threshold of 30 per cent or greater
change in lesions. The details of the guidelines are below.

The TER of the 2010 guidelines recommends a change of symptoms score by 30 per cent applying
the following parameters:

1. Cure: lesions healed ≥90 per cent, no new lesions
2. Improved: lesions healed ≥30 per cent with a few new lesions
3. No improvement: no changes in lesions

The TER of the 2002 guideline recommended for trials is a change in symptom scores (severity,
location of lesions, symptom score and laboratory tests) applying the following parameters (311):

1. Cure: ≥95 per cent reduction of lesion count
2. Significant improvement: ≥70–95 per cent
3. Improvement: ≥50–70 per cent
4. No improvement: <50 per cent

The TER of the 1994 guideline recommended for trials is a decrease in lesion count applying the
following parameters (167):

1. Cure: lesions and symptoms disappear
2. Improved: ≥30 per cent lesions heal, symptoms improved
3. Not improved: <30 per cent lesions heal, symptoms not improved
A similar recommendation for drug trials is made by the Center for Drug Evaluation and Research, with a 50 per cent improvement considered a success in treatment (107). For the CHM SR, results for participants who achieved a 50 per cent or greater improvement in signs and symptoms were analysed. TER is a recommended outcome in Chinese CM research guidelines; however, there are inconsistencies and no consensus on which is superior. Therefore the acupuncture review included both criteria and analysed results based on TER of 30 per cent and 50 per cent to ascertain any differences in effect.

Secondary outcomes included recurrence rate, HRQoL and AE reports. Acne-specific and general dermatology HRQoL questionnaires were included. General health, dermatology-specific and acne-specific HRQoL questionnaires have been described in Chapter 4. Acne-specific questionnaires include the Acne-QoL (119-121), Acne-QOLI (118), ADI (70) and CADI (122). Dermatology-specific QoL included the DLQI (114), Skindex (252), Skindex-16 (115) and Skindex-29 (100).

6.2.5 Identification of search terms

A search for the definition and English synonyms for acne vulgaris was conducted in the WHO’s International Classification of Diseases version 10 (ICD-10) (97) and using medical subject headings (MeSH) terms in PubMed (313). For the Chinese terms for acne vulgaris, searches in CM dermatology textbooks (159, 165) and classical texts and medical dictionaries were conducted. Search results were compiled in an Excel spreadsheet (©Microsoft) (Appendix 13). A comparison of the terms was conducted and duplicates removed. Details of the search strategy for acupuncture
and PPQFY can be found in section 6.2.6, and the methods for identifying experimental studies are found in section 7.4.2.

### 6.2.6 Process for study selection

An electronic search of five English (PubMed, Embase, Allied and Complementary Medicine Database, Cumulative Index to Nursing and Allied Health Literature and Cochrane Library) and six Chinese-language databases (Chinese National Knowledge Infrastructure, Chongqing VIP Information Company, Wanfang Data, Chinese Biomedical Literature Database, China’s Conference Papers Database and China Dissertation database) was conducted from inception to May 2013 (and updated in February 2015) to identify RCTs of PPQFY and acupuncture. There were no language restrictions. Search terms were categorised according to intervention (CHM, traditional Chinese herbs, Chinese drugs and variants; acupuncture, acupressure, acupoint, auricular acupuncture, auricular acupressure, moxibustion electro-acupuncture, cutaneous needles and variants), condition (acne vulgaris, acne and variants) and trial design (RCT and variants) (Appendix 13). The title and abstracts were assessed to identify potential RCTs. Full texts were retrieved for eligible studies and studies where eligibility could not be determined from the title and abstract.

### 6.2.7 Data extraction

Data was extracted into a predefined file including participant characteristics, details of the intervention and comparator, outcome measures and results. Attempts were made to obtain missing data by contacting the study authors. Verification of data was conducted by an independent researcher (Iris Wenyu Zhou).
6.2.8 Statistical and meta-analysis

Systematic reviews, with or without meta-analyses are considered the highest level of evidence (301). Meta-analysis provides a statistical synthesis of the results of multiple studies to estimate a treatment effect that is not possible from reviewing results of individual studies. Consideration was given to how to group results of studies in a way that allows meaningful translation into clinical practice.

For the PPQFY SR, important features were the use of PPQFY alone, combined with other oral CHM formulas, and combined with topical CHM treatments. Each of these three combinations are suitable for clinical practice, and having evidence of the effect of each can provide reassurance for practitioners in prescribing treatments. Conversely, a lack of evidence of effect allows practitioners to understand where treatments have no evidence of benefit, which prevents unnecessary expense for patients.

The comparator drug class was an important feature relating to the comparators. Additional analyses were conducted to identify the benefits of PPQFY compared to OAB, topical BP, retinoids, and oral antibiotics. The actions of these drugs on pathophysiological pathways have been established, and included antibacterial effects, reducing hyperkeratinisation and inflammation. If PPQFY is found to be equally or more effective than acne treatments, this may provide insight into the potential mechanisms of action for PPQFY as a whole, or for individual herb ingredients.
For the acupuncture SR, analysing contributions of individual acupuncture points is possible, but is complex, and likely has little bearing on clinical practice. As all studies used a combination of points, analysing effect of single points was not possible. Diversity in points used prevented grouping of like studies for meta-analysis. Subgrouping for this review was limited to the intervention type (acupuncture, auricular acupuncture, auricular acupressure), and comparators (as described for the PPQFY SR above). Studies reported outcomes with different thresholds for effectiveness: TER of 30% or greater improvement in lesion count (according to the 1994 guideline), and TER of 50% or greater improvement in lesion count (according to the 2002 guideline). Additional subgroup analyses were conducted for these features.

Meta-analyses was conducted according to the factors outlined above. For dichotomous data, risk ratios (RR) were calculated with a confidence interval (CI) of 95 per cent. For continuous data, the mean difference (MD) with a 95 per cent CI was performed. Analysis was conducted using available data, with a random effects model used. Substantial heterogeneity was defined as $I^2$ greater than 50 per cent. Review Manager version 5.2.4 software (314) was used to analyse data for the CHM SR. An updated version (version 5.3) became available during the research and the updated version was used for the acupuncture SR. A sensitivity analysis of primary outcomes was intended to be performed by excluding studies with low risk of bias in randomisation based on sequence generation. Publication bias was intended to be explored where at least 10 trials were included in a meta-analysis by visual inspection of funnel plots for asymmetry. Subgroup analyses according to intervention and comparators were performed where possible. Details of such analyses are included in the relevant chapters. For the acupuncture review, subgroup analysis was also performed based on TER (as described above).
6.2.9 Quality assessment

Risk of bias followed the Cochrane Handbook’s Risk of Bias Assessment Tool (302). Two reviewers independently assessed the risk of bias. Trials included in the review were assessed as high, low or unclear risk based on the guidance in the handbook. The domains assessed included random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective reporting and other forms of bias such as conflicts of interest. A third assessor was consulted if disagreement occurred that could not be resolved through discussion. An assessment of unclear risk was given if there was lack of data presented in the trials.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (315) was used to assess the quality of the evidence and the strength of recommendations for the CHM SR. For the acupuncture SR, the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) (316) checklist was applied to assess the transparency of published reports and the interpretation of results.

6.3 Chapter summary

This chapter summarises the methods used for the SRs of RCTs of the CHM formula PPQFY and acupuncture and related techniques. The reviews followed the methods of the Cochrane Handbook for Systematic Reviews of Interventions (302). Studies that used guideline-recommended comparators such as pharmacotherapies, placebo and no treatment were included in both reviews. In addition, for the acupuncture review RCTs that used no treatment, sham or placebo needle treatment were also included in the review. The primary outcome measures of the SRs were
changes in lesion count, overall severity grading and therapeutic effective rate. Secondary outcomes include HRQoL outcomes and AEs.
CHAPTER 7 : Systematic review of clinical and pre-clinical evidence of Pi Pa Qing Fei Yin for acne vulgaris

Overview

Chapter 6 outlined comprehensive methods used in conducting SRs and meta-analyses for CHM and acupuncture related therapies. This chapter presents the findings from an SR and meta-analysis of RCTs of the CHM formula Pi Pa Qing Fei Yin (PPQFY) (Eriobotrya Japonica formula) for acne vulgaris. This review has been published in a modified form in the Journal of Herbal Medicine in March 2018 (317) (Appendix 14). To better understand the six PPQFY ingredients, the mechanism of actions from experimental studies are synthesised and presented in this chapter.

7.1 Introduction

Many people use CAM including CHM for skin conditions (151, 318). Despite their common use, there have been very few reviews of the efficacy and safety of CAM treatments for acne vulgaris. An SR of botanical and phytochemical treatments for acne included 23 clinical trials (20), three of which were CHM/Kampo formulations. The CHM preparations showed improvement for mild-to-moderate acne. Limitations of these clinical trials included the lack of acne-grading methods and lack of a control or placebo group. No SR have been identified in the English-language databases that have evaluated the efficacy of CHM generally, or PPQFY specifically, for acne.

An SR on acupoint stimulation (185) included combination therapy of acupuncture with herbal medicine. The review included 3453 participants from 43 trials. They found the combination of acupuncture plus herbal medicine showed significant differences in increasing the number of cured
patients compared to herbal medicine alone. They also found that acupuncture plus a herbal mask was better than a herbal mask alone. All trials were assessed as having high risk of bias.

A Cochrane review on CAM for acne that included 35 trials with 3227 participants found inconsistent effects of acupuncture and herbal medicine for acne (157). Trials comparing CHM and antibiotics showed no difference between groups for the primary outcome of change in inflammatory and non-inflammatory lesion counts or total skin lesion counts, or change in acne severity scores. Trials that compared CHM and retinoic acid did not report on lesion count reduction and only reported the secondary outcome of “remission”. The results were mixed. Xiaocuo decoction and adapalene gel were better than oral viaminate capsules, whereas Qingbu decoction was no better. Two acupuncture trials were evaluated against Western drugs. Acupuncture was significantly better than oral azithromycin and topical clindamycin phosphate gel. The other trial showed no difference between acupuncture and oral isotretinoin. The review also included a low-glycaemic diet, tea-tree oil and pollen bee venom (PBV). The authors found no clear evidence that a low glycaemic load diet had an effect on non-inflammatory lesion count between the intervention and control groups. They found that tea-tree oil and PBV reduced skin lesion count in single trials. AEs in the acupuncture group included itching, redness and pain following needle insertion. Both herbal medicines and Western drugs caused gastrointestinal upset and dizziness. Tea-tree oil also caused itchiness, dryness and flaking of the skin. None of the trials reported any SAEs. This Cochrane review only included trials that had a low risk of bias for sequence generation. They found that nearly all trials had a high risk for blinding and selective reporting. Overall, the authors concluded that the strength of evidence was low due to the small sample sizes and poor methodological designs of the trials.
7.2 **Rationale for selecting Pi Pa Qing Fei Yin**

There are currently no systematic reviews published in English on the safety and efficacy of PPQFY for acne vulgaris. PPQFY is a common CHM formula recommended by CM textbooks (159, 165). PPQFY has been used clinically to treat mild-to-moderate inflammatory comedones in people with acne. It acts to clear heat in the Lungs and cool the Blood. In a recently published evidence-based CM monograph (168), an analysis was conducted on the efficacy and safety of CHM as a whole. Overall findings of meta-analyses showed CHM to be more effective than guideline-recommended treatments in reducing acne severity, and in increasing the number of participants who achieved a clinical improvement. Given that this work was already underway, and any addition of recently published trials was unlikely to alter the results found in the 221 RCTs included in Coyle’s review (168), it was considered unnecessary to conduct a SR of CHM as a whole. In this monograph, PPQFY was the most common traditional formula tested. This finding, combined with the inclusion of PPQFY in clinical textbooks, led to the decision to focus on PPQFY for the SR.

This formula contains six herbs, *Pi pa ye* (*Eriobotrya japonica* Thunb. Lindl.), *Sang bai pi* (*Morus alba* L.), *Huang lian* (*Coptis chinensis* Franch., *Coptis teeta* Wall. or *Coptis deltoidea* C.Y. Cheng & Hsiao), *Huang bai* (*Phellodendron amurense* Rupr. or *Phellodendron chinense* Schneid.), *Ren shen* (*Panax ginseng* C.A. Mey.) and *Gan cao* (*Glycyrrhiza glabra* L. P., *Glycyrrhiza uralensis Fisch.* or *Glycyrrhiza inflata* BAT.). These herbs have anti-inflammatory, anti-lipogenic and antibacterial effects on *P. acnes* (319, 320). PPQFY has been evaluated in clinical studies; however, there are no SR evaluating the efficacy of PPQFY for acne vulgaris to date. This review evaluates the efficacy and safety of the CHM formula PPQFY alone and in combination with other
CHM in the treatment of acne vulgaris. The HRQoL of people with acne can be severely affected (190). Treatments that improve the acne symptoms also improve HRQoL. This review will also evaluate the impact of PPQFY on the HRQoL of people with acne.

7.3 Aims of the systematic review

This SR aims to:

1. Evaluate the clinical efficacy and safety of PPQFY for acne; and
2. Synthesise the findings from experimental studies of the six PPQFY ingredients in terms of actions on *P. acnes*, inflammation, hyperkeratinisation, androgen and sebum production.

7.4 Methods

7.4.1 Systematic review methods

The methods of the SR have been described in Chapter 6: Methods for systematic reviews.

7.4.2 Experimental evidence methods

A search of the electronic database PubMed was performed from inception to August 2016. The six ingredients of PPQFY were used as key words. The pharmaceutical, species, English and pin yin names for *Eriobotrya japonica* Thunb. Lindl. leaf (*Pi pa ye*), *Morus alba* L. root bark (*Sang bai pi*), *Coptis chinensis* Franch. or *Coptis teeta* Wall. or *Coptis deltoidea* C.Y. Cheng & Hsiao stem, (*Huang lian*), *Phellodendron amurense* Rupr. or *Phllodendron chinense* Schneid. cortex (*Huang bai*), *Panax ginseng* C.A. Mey. root (*Ren shen*) and *Glycyrrhiza glabra* L. P. or *Glycyrrhiza uralensis* Fisch. or *Glycyrrhiza inflata* BAT. stem (*Gan cao*) were used as search terms. These terms were combined with the terms *P. acnes*, anti-inflammatory, sebum, androgen
and hyperkeratinisation. Articles were limited to those published in English. Data was extracted into a predefined form that included the herb name, active compound in the experiment, author, year, whether the experiment was an \textit{in vivo} and \textit{in vitro} study, type of animal used, whether western blot analysis was used and the key findings of the experiment.

7.5 Results

7.5.1 Clinical evidence

7.5.1.1 Characteristics of clinical studies

The original comprehensive search (to May 2013) yielded 27,476 records, with one additional record identified through other sources. A targeted update search for studies of PPQFY (\textit{Eriobotrya Japonica} Formula) to February 2015 identified a further 143 studies (Figure 7.1). In total, 15 studies, all in Chinese, met the inclusion criteria, with 13 included in the quantitative analysis. No RCTs were found in English.

Fifteen RCTs included 1782 participants (321-334) (Table 7.1). The mean number of participants was 119 with a sample size ranging from 60 to 228. Fourteen trials included both males and females and one trial included only female participants. Participants’ age ranged from 14 to 39 years old (median age 24). All trials were conducted in China between 1997 and 2014. Treatment duration varied from two to eight weeks. Three trials reported a follow-up period which ranged from three months (334) to one year (327). The diagnostic tool used in the trials included the Pillsbury scale (321, 326, 328), Gollnick scale (329) and dermatological textbooks (323, 325, 327, 330-332, 334). The diagnostic tool was not specified in four studies (322, 324, 333, 335).
Figure 7.1 Flow chart of study selection PPQFY
All trials used the oral herbal formula PPQFY as a base formula for the main intervention (Table 7.2). Three trials combined oral PPQFY with topical herbs (325, 326, 328). Two trials used PPQFY in combination with other oral herbal formulas (326, 335). Comparators included pharmacotherapy such as topical and oral antibiotics, topical retinoids and topical BP. Topical agents vitamin E, vitamin B6 and sulfur creams were added in three trials (323, 327, 335). Three trials used viaminate as a comparator (321, 333, 334). Viaminate is a non-conventional oral retinoid derivative that is approved in China for clinical treatment of acne (166). One trial used a combination of viaminate and an antibiotic (335), which is not a common prescribing practice outside of China. None of the trials used placebo controls.
Table 7.1 Characteristics of clinical studies

<table>
<thead>
<tr>
<th>First author, publication year, country, setting</th>
<th>Study design, blinding, number of arms</th>
<th>Eligibility criteria</th>
<th>Treatment duration, follow-up duration</th>
<th>Stage, severity and duration of condition</th>
<th>No. of participants randomised/assessed</th>
<th>Age (mean (SD) or range), gender (M/F)</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen LJ, 2011 (321), China, outpatients</td>
<td>RCT, non-blinded, 2 arms</td>
<td>Acne patients, Dec 2008–Dec 2009</td>
<td>4 weeks, 0 weeks</td>
<td>NS, Pillsbury: I−IV, I: 2 (1.44) years C: 21.2 years</td>
<td>I: 53/53 C: 47/47</td>
<td>I: 24 (3.3), 27/26 C:25 (2.0), 24/23</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral)</td>
</tr>
<tr>
<td>Han SX, 2006 (322), China, outpatients</td>
<td>RCT, non-blinded, 2 arms</td>
<td>Acne vulgaris patients</td>
<td>15 days, 0 weeks</td>
<td>NS</td>
<td>I: 52/52 C: 38/38</td>
<td>I: NS, NS C: NS, NS</td>
<td>Pi Pa Qing Fei Yin (oral) + Mask (topical)</td>
</tr>
<tr>
<td>Liang XS, 2009 (323), China, outpatients</td>
<td>RCT, non-blinded, 2 arms</td>
<td>Acne patients</td>
<td>30 days, 0 weeks</td>
<td>NS, NS, 1 week–6 years</td>
<td>I: 32/32 C: 28/28</td>
<td>I: 24.5 (NS), 21/11 C: 24.5 (NS), 18/10</td>
<td>Pi Pa Qing Fei Yin Jia Wei (oral)</td>
</tr>
<tr>
<td>Liu H, 1997 (324), China, hospital, NS</td>
<td>RCT, non-blinded, 3 arms</td>
<td>Patients with acne vulgaris</td>
<td>2 weeks, 0 weeks</td>
<td>NS, NS, 2 weeks−3 years</td>
<td>I1: 60/60 I2: 60/60 C: 60/60</td>
<td>I1: 22.5 (NS), NS I2: 22.5 (NS), NS C: 22.5 (NS), NS</td>
<td>I1: Jiawei Pi Pa Qing Fei Yin (oral)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Patients</td>
<td>Duration</td>
<td>Lesion</td>
<td>I: n</td>
<td>C: n</td>
<td>Evidence</td>
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<tr>
<td>Liu HS, 2012 (325), China, outpatients</td>
<td>RCT, non-blinded, 2 arms</td>
<td>Acne patients</td>
<td>4 weeks, 0 weeks</td>
<td>NS, Lesion: I–III, 3 months–5 years</td>
<td>I: 40/40</td>
<td>C: 40/40</td>
<td>17–32, 17/23</td>
</tr>
<tr>
<td>Liu Y, 2010 (326), China, outpatients</td>
<td>RCT, non-blinded, 2 arms</td>
<td>Acne patients</td>
<td>4 weeks, 0 weeks</td>
<td>NS, Pillsbury: slight, moderate, severe</td>
<td>I: 58/58</td>
<td>C: 30/30</td>
<td>22.2 (3.6), 30/28</td>
</tr>
<tr>
<td>Ma TL, 2013 (327), China, outpatients</td>
<td>RCT, non-blinded, 2 arms</td>
<td>Acne patients</td>
<td>NS, 1 year</td>
<td>NS, NS, 7 days–5 years</td>
<td>I: 42/42</td>
<td>C: 42/42</td>
<td>24.84 (NS), 29/13</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Intervention</td>
<td>Outcome</td>
<td>Weeks</td>
<td>Baseline</td>
<td>Post-treatment</td>
<td>Comparison</td>
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<tr>
<td>Ou HB, 2012 (328), China, outpatients</td>
<td>RCT, non-blinded, 2 arms</td>
<td>Acne patients</td>
<td>3 weeks, 0 weeks</td>
<td>NS, Pillsbury: I–IV, 2 (1.5) years</td>
<td>I: 40/40 C: 40/40</td>
<td>I: 28.73 (3.59), 18/22 C: 29.12 (3.48), 19/21</td>
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</tr>
<tr>
<td>Shi XB, 2005 (335), China, outpatients</td>
<td>RCT, non-blinded, 2 arms</td>
<td>Acne patients</td>
<td>2 weeks, 0 weeks</td>
<td>NS, Moderate–severe (Lesion: II–III), NS</td>
<td>I: 82/79 C: 80/78</td>
<td>I: 23.34 (9.54), 32/50 C: 20.87 (8.67), 34/46</td>
<td></td>
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<tr>
<td>Shi XB, 2008 (329), China, outpatients</td>
<td>RCT, non-blinded, 2 arms</td>
<td>Students aged 12–30 diagnosed with acne vulgaris; and a) Gollnick I–II if not previous treatment, or b) syndrome under control if</td>
<td>8 weeks, 0 weeks</td>
<td>NS, Gollnick: I–II, NS</td>
<td>I: 39/39 (all dropouts are included as “no improvement”) C: 35/35</td>
<td>I:12–30, NS C:12–30, NS</td>
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</tr>
</tbody>
</table>

Pi Pa Qing Fei Yin Jia Jian (oral) + Dian Dao San (topical)
previously treated with viaminate and 1% clindamycin phosphate gel, or c) Gollnick I–II after treatment with tanshinone and 1% tretinoin cream; Mar 2005 to Oct 2007; Gollnick stage I–II

<p>| Wang S, 2013 (330), China, NS | RCT, non-blinded, 2 arms | Female acne patients | 1 month, 0 weeks | NS, slight–severe, NS | I: 61/61 | C: 60/60 | I: NS, 0/61 | C: NS, 0/60 | <em>Pi Pa Qing Fei Yin</em> (oral) |</p>
<table>
<thead>
<tr>
<th>Source</th>
<th>Design, Duration</th>
<th>Inclusion Criteria</th>
<th>Follow-up</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang X, 2014 (331), China, outpatients</td>
<td>RCT, non-blinded, 3 arms</td>
<td>Acne patients in outpatients department; 15–45 yo; no topical treatments in the past 7 days; no acne oral medication in the past 30 days</td>
<td>1 month, 0 weeks</td>
<td>NS</td>
<td>I: 60/60 I2: 60/60 C: 60/60</td>
<td>15–25; NS Pi Pa Qing Fei Yin (oral)</td>
</tr>
<tr>
<td>Yan LY, 2005 (332), China, outpatients</td>
<td>RCT, non-blinded, 2 arms</td>
<td>Acne patients 3 weeks, 6 months NS, light–severe, 560 days</td>
<td>15–25; NS Pi Pa Qing Fei Yin (oral)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang LL, 2006 (333), China, outpatients</td>
<td>RCT, non-blinded, 2 arms</td>
<td>Acne patients with CM diagnosis 4 weeks, 0 weeks NS, NS, I: 2 months–7 years</td>
<td>15–25; NS Pi Pa Qing Fei Yin (oral)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Duration</td>
<td>Comparator Age</td>
<td>Intervention Age</td>
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<tr>
<td>Zhang Y, 2011 (334), China, NS</td>
<td>RCT, non-blinded, 2 arms</td>
<td>Patients with acne vulgaris</td>
<td>4 weeks, 3 months</td>
<td>NS, NS, 1.5–6 years</td>
<td>I: 85/85</td>
<td>I: 14–38, 27/58</td>
</tr>
</tbody>
</table>

Abbreviations: C comparator, I intervention, NS not specified, RCT randomised controlled trial, Vit vitamin, yo years old
<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Chinese herbal medicine formula and ingredients</th>
<th>Preparation type and dosage</th>
<th>Co-intervention/control</th>
<th>Dosage and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen LJ, 2011 (321)</td>
<td><em>Pi Pa Qing Fei Yin Jia Jian</em> (oral): <em>Pi pa ye, Zao jiao ci, Zhe bei, Mu dan pi, Bai xian pi, Sang bai pi, Huang qin, Zhi zi, Ye ju hua, Jin yin hua; Bai zao xiu, Huang lian, Lu hui, Gan cao.</em> Syndrome differentiation: <em>Bai jiang cao, Bai hua she cao, Bai zhi</em> (cysts); <em>Dang gui, Bai shao, Yi mu cao</em> (irregular menstruation); <em>Chan tui, Wu she</em> (itch); <em>Shi gao, Tian hua fen</em> (dry); <em>Yi yi ren, Bai zhu</em> (oily)</td>
<td>Decoction 150ml tid</td>
<td>Viaminate capsules (oral); benzoyl peroxide gel (topical)</td>
<td>Viaminate capsules 25 mg tid.po.; benzoyl peroxide gel tid. topical</td>
</tr>
<tr>
<td>Han SX, 2006 (322)</td>
<td><em>Pi Pa Qing Fei Yin</em> (oral) &amp; mask (ext)</td>
<td>NS</td>
<td>Metronidazole (oral) &amp; roxithromycin (oral) &amp; viaminate &amp; Vit E (ext)</td>
<td>Metronidazole 0.2 g tid.po. roxithromycin 150 mg bid.po. Viaminate &amp; Vit E (ext)</td>
</tr>
<tr>
<td>Liang XS, 2009 (323)</td>
<td><em>Pi Pa Qing Fei Yin Jia Wei: Pi pa ye, Huang bai, Huang lian, Ren shen, Gan cao, Sang bai pi, Lian qiao, Bai zhi, Chuan bei, Dang gui, Da huang, Xia ku cao, Mu li, Shan zha, Yi yi ren.</em></td>
<td>Decoction 1 bid.po.</td>
<td>Erythromycin (oral) &amp; sulfur cream (ext) &amp; zinc sulfate (oral)</td>
<td>Erythromycin 0.2 g bid.po. Sulfur cream</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Chinese herbal medicine formula and ingredients</td>
<td>Preparation type and dosage</td>
<td>Co-intervention/control</td>
<td>Dosage and administration</td>
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<tr>
<td>Liu H, 1997 (324)</td>
<td><strong>Jia Wei Pi Pa Qing Fei Yin</strong>: Pi pa ye, Sang bai pi, Huang lian, Huang bai Plus Huang qin, Da huang, Dan shen, Sheng di, Zi cao, She cao, Ye ju hua, Sheng shan zha, Shen qu, Gan cao (Topical &amp; Oral) 12: Pi Pa Qing Fei Yin (ext. &amp; oral): Pi pa ye, Sang bai pi, Ren shen, Huang lian, Huang bai</td>
<td>Decoction 1 qd.po.</td>
<td>Metronidazole (topical &amp; oral)</td>
<td>qd.ext. zinc sulfate 0.2 g bid.po.</td>
</tr>
<tr>
<td>Liu HS, 2012 (325)</td>
<td><strong>Pi Pa Qing Fei Yin Jia Jian</strong> (oral): Pi pa ye, Sang bai pi, Bai mao gen, Lian qiao, Ye ju hua, Huang qin, Zhi zi, Bai hua she cao, Chi shao, Mu dan pi, Dan shen, Yi yi ren, Cang zhu, Gan cao PLUS Dian Dao San (topical): Da Huang, Liu Huang, Bai zhi</td>
<td>Decoction 200 ml bid.po.; Dian Dao San qd.ext.</td>
<td>Adapalene cream &amp; erythromycin capsules (oral)</td>
<td>Adapalene cream bid. topical. Erythromycin capsules 0.5 g bid.po.</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Chinese herbal medicine formula and ingredients</td>
<td>Preparation type and dosage</td>
<td>Co-intervention/control</td>
<td>Dosage and administration</td>
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</table>
Syndrome differentiation: *Jin yin hua*, *Bai hua she she cao* (wind and heat of Lung); minus *Ren shen*, plus *Yin chen* 15g, *Mu dan pi* (stagnation of heat and damp); minus *Huang lian* plus *Zhi ban xia*, *Bai zhu* (stagnation of phlegm and damp) | Decoction 200ml bid.po. | Vit C (oral) & roxithromycin (oral) & vit B6 cream | Vit C 0.2g tid.po.; roxithromycin 75mg tid.po.; Vit B6 cream tid. topical. |
| Ou HB, 2012 (328)             | *Pi Pa Qing Fei Yin Jia Jian* (oral): *Pi pa ye*, *Huang bai*, *Huang lian*, *Gan cao*, *Sang bai pi*, *Bai zhi*, *Fang feng*, *Fu ling*, *Dang gui*, *Chai hu*, *Chan tui*.  
<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Chinese herbal medicine formula and ingredients</th>
<th>Preparation type and dosage</th>
<th>Co-intervention/control</th>
<th>Dosage and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shi XB, 2005 (335)</td>
<td>Syndrome differentiation: <em>Lian qiao, Pu gong ying, Zi cao</em> (nodules, fester); <em>Huang qi</em> (chronic); <em>Mu li, Zhe bei</em> (white head); <em>Tao ren, E zhu</em> (chromatosis); <em>Da huang</em> (Constipation); <em>Xiang fu</em> (irritability); <em>Dan shen, Sheng di, Gui zhi, Shi chang pu</em> (pain and itch)</td>
<td>Decoction 100ml bid.po.</td>
<td>Hydrochloride capsules (oral)</td>
<td>Achromycin: 0.5 g, tid. (first course) po., 0.25 g, tid. (second course); viaminate &amp; vit E cream qd. topical.</td>
</tr>
<tr>
<td>Shi XB, 2008 (329)</td>
<td>Syndrome differentiation: <em>Gua lou, Zhi shi</em> (Constipation); <em>Pu gong ying, Zi hua di ding</em> (Heat Toxin); <em>Kun bu, Hai zao</em> (Nodules, cysts); <em>Yi mu cao</em> (Irregular menstruation)</td>
<td>Decoction 100ml qd.po.</td>
<td>Tretinoin cream (ext) and if there is inflammation will add clindamycin (topical)</td>
<td>Tretinoin cream: qd.ext.; clindamycin bid. topical</td>
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<td>Shi XB, 2004 (335)</td>
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<td>Shi XB, 2008 (329)</td>
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<td>Shi XB, 2005 (335)</td>
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</tbody>
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**Shi XB, 2005 (335)**

**Pi Pa Qing Fei Yin Bian Hua Fang** (oral): *Pi pa ye, Sang bai pi, Huang qin, Zhi zi, Pu gong ying, Dan shen, Sheng shan zha, Bai hua she she cao*

**Pi Pa Qing Fei Yin Jia Jian** (oral): *Pi pa ye, Sang bai pi, Huang qin, Zhi zi, Sheng shan zha, Pu gong ying, Dan shen, Bai hua she she cao*

Syndrome differentiation: *Gua lou, Zhi shi* (Constipation); *Pu gong ying, Zi hua di ding* (Heat Toxin); *Kun bu, Hai zao* (Nodules, cysts); *Yi mu cao* (Irregular menstruation)
<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Chinese herbal medicine formula and ingredients</th>
<th>Preparation type and dosage</th>
<th>Co-intervention/control</th>
<th>Dosage and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang X, 2014 (331)</td>
<td><strong>Pi Pa Qing Fei Yin</strong> (Oral): Pi Pa Ye, Sang Bai Pi, Huang Qin, Zhi Zi, Da Huang, Shan Zha, Dan Shen, Ku Shen, Gan Cao.</td>
<td>Decoction 250 ml bid.po.</td>
<td>Minocycline hydrochloride capsules (oral)</td>
<td>minocycline hydrochloride capsules 50 mg bid.po.</td>
</tr>
<tr>
<td>Yan LY, 2005 (332)</td>
<td><strong>Pi Pa Qing Fei Yin</strong> (oral): Pi pa ye, Huang lian, Huang qin, Sang bai pi, Jin yin hua, Mu dan pi, Gan cao</td>
<td>Decoction 50 ml bid.po.</td>
<td>Doxycycline hyclate tablets</td>
<td>0.1 g, bid.po.</td>
</tr>
<tr>
<td>Zhang LL, 2006 (333)</td>
<td><strong>Pi Pa Qing Fei Yin Jia Jian</strong> (oral): Pi pa ye 10g, Sang bai pi 15g, Huang qin 10g, Zhi zi 10g, Huang lian 10g, Da huang 10g, Mu dan pi</td>
<td>Decoction 1 bid.po.</td>
<td>Viaminate capsules</td>
<td>25 mg bid.po</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Chinese herbal medicine formula and ingredients</td>
<td>Preparation type and dosage</td>
<td>Co-intervention/control</td>
<td>Dosage and administration</td>
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<tr>
<td>Zhang Y, 2011 (334)</td>
<td>15g, <em>Jin yin hua</em> 15g, <em>Lian qiao</em> 15g, <em>Pu gong ying</em> 30g, <em>Yi yi ren</em> 30g, <em>Che qian zi</em> 15g.</td>
<td>Decoction 1 bid.po.</td>
<td>Viaminate capsules (oral)</td>
<td>25 mg bid. po.</td>
</tr>
<tr>
<td></td>
<td><em>Pi Pa Qing Fei Yin Jia Jian</em> (oral): <em>Pi pa ye</em>, <em>Bai hua she she cao</em>, <em>Jin yin hua</em>, <em>Dan shen</em>, <em>Sang hai pi</em>, <em>Lian qiao</em>, <em>Xia ku cao</em>, <em>Huang qin</em>, <em>Zhi zi</em>, <em>Ren shen</em>, <em>Shan zha</em>, <em>Gan cao</em>, <em>Huang lian</em>, <em>Da huang</em>. Syndrome differentiation: <em>Pu gong ying</em>, <em>Di ding</em> (red pimple); <em>Xuan shen</em>, <em>Hua fen</em> (dry); <em>Chai hu</em>, <em>Xiang fu</em> (irregular menstruation); <em>Chen pi</em>, <em>Ban xia</em> (cysts); <em>Chi shao</em>, <em>Dan pi</em> (blood stasis); <em>Tao ren</em>, <em>Hong hua</em> (rosacea); <em>Mang xiao</em>, <em>Huo ma ren</em> (constipation)</td>
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</tbody>
</table>
Eight trials reported effective rate based on lesion count (324, 325, 329-331, 333-335), six reported effective rate based on both lesion count and severity (321, 323, 326-328, 332) and one study did not report details of how the effective rate was calculated (322). Some studies reported using a specific criterion but modified it. For example, (336) reported using the 2002 guidelines but the actual threshold was 30 per cent to 70 per cent, which was the 1997 criterion. Four trials (325, 327, 329, 332) reported on recurrence rate. None of the trials reported on the length of time between recurrences or acne severity, and only one paper (331) reported on the HRQoL measure DLQI.

### 7.5.1.2 Risk of bias

Overall, the methodological quality of included trials was low to moderate (Figure 7.2). Two trials (328, 333) were assessed to have a low risk of bias in sequence generation as they used random number generators. Two trials (321, 331) were assessed as high risk, as Chen and Zhou used hospital record numbers (321) and Wang et al. used sequence of visit order (331). There was insufficient information reported on blinding of participants in 14 papers and these were assessed as unclear. One paper (331) was assessed to have a high risk in the blinding of participants based on the inclusion of a subjective QoL outcome measure (DLQI). As there was insufficient information reported on allocation concealment and blinding of personnel and outcome assessors, all studies were assessed as unclear risk for these domains. All trials were assessed as low risk for incomplete outcome data and selective reporting. One paper was assessed as high risk for other biases due to baseline imbalance of participants (334) with no explanation provided. No other biases such as large differences in sample size between groups or potential conflict of interests were observed in the other 14 trials (Figure 7.2).
Two studies (322, 333) were excluded from the meta-analysis as they did not report the standard effective rate of 50 per cent as outlined in the 2002 guidelines (311). The effective rate was higher in those who received PPQFY compared to pharmacotherapy (13 studies, RR: 1.30 [1.13, 1.49], I²=70 per cent) although substantial heterogeneity was detected (Figure 7.3). Analysis to account for missing data did not alter this result (13 studies, RR: 1.30 [1.13, 1.49], I²=70 per cent). Sensitivity analysis, excluding two studies (Chen LJ 2011 and Wang X 2014) assessed as having high risk of bias for sequence generation (321, 331), reduced the statistical heterogeneity to 0 per cent (11 studies, RR: 1.38 [1.21, 1.58]). When four studies that did not use syndrome differentiation were removed, heterogeneity remained substantial (9 studies, RR: 1.29 [1.08, 1.53], I²=71 per cent).

Heterogeneity was explored through subgroup analysis by interventions and comparators. When PPQFY was used alone, the effective rate was greater compared to pharmacotherapy (8 studies, RR: 1.32 [1.05, 1.65], I²=70 per cent) with considerable heterogeneity, although no benefit was
seen when PPQFY was combined with oral herbal medicines (2 studies, RR: 1.26 [0.88, 1.80], $I^2=89$ per cent) or topical herbal medicines (3 studies, RR: 1.30 [0.98, 1.73], $I^2=69$ per cent) (Figure 7.3). Again, statistical heterogeneity was detected. When studies using viaminate or viaminate combined with other comparators were excluded, the effect size was similar to the overall pool (10 studies, RR: 1.31 [1.10, 1.55], $I^2=75$ per cent), but statistical heterogeneity remained considerable.

Figure 7.3 PPQFY versus pharmacotherapy: effective rate
Studies were grouped according to comparator type for further analysis (Figure 7.4). The effective rate of PPQFY plus topical CHM was greater than those of antibiotics and BP (2 studies, RR: 1.47
Result of single studies showed PPQFY alone produced a higher effective rate than retinoids (RR: 1.35 [1.01, 1.79]) and when combined with oral CHM produced a greater effective rate than antibiotics, viaminate and supplements (RR: 1.47 [1.21, 1.79]).

### 7.5.1.4 Recurrence rate

Four studies reported on recurrence rate (325, 327, 329, 332). Two specified the time point at which the recurrence rate was assessed (327, 332) while two did not (325, 329). Results from two individual studies showed a lower recurrence rate with PPQFY (RR: 0.29 [0.16, 0.53] (332), RR: 0.17 [0.05, 0.52] (327)) while two showed no statistical significant benefit (RR: 0.25 [0.06, 1.11] (325), RR: 0.26 [0.06, 1.15] (329)).

### 7.5.1.5 Health-related quality of life

Only one study reported on HRQoL using the DLQI (331). DLQI scores after one month of treatment with PPQFY were higher, indicating poorer HRQoL, than with doxycycline (MD: 3.07 [2.42, 3.72]).

### 7.5.1.6 Adverse events

There were 107 mild AEs reported in 7 of the 15 trials (323-325, 328, 332, 335) with 33 events in the intervention groups and 74 in the control groups. There were no SAEs reported in the trials. In the intervention group, AEs included nausea, vomiting or stomach discomfort (29), itching (2),
diarrhoea (1) and burning sensation (1). In the control group, AEs included nausea or stomach discomfort (28), scaling (11), dry mouth (10), itching (9), burning sensation (8), erythema (7), nausea or vertigo (3) and erythema, itching or scaling (3).

7.5.2 Grading of Recommendations Assessment, Development and Evaluation analysis

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) is an approach adopted by the Cochrane Collaboration to assess the quality of the evidence and strength of recommendations for interventions evaluated (337). For the effective rate, 1507 participants were included from the 13 trials with a treatment range of two to eight weeks. The overall quality of the evidence was low with a relative effect of 1.30 (RR: 1.30 [1.13-1.19]). The anticipated absolute effect was 54 per 100 people treated with pharmacotherapies, indicating 54 of those would have benefit for every 100 people who received pharmacotherapies. For the intervention, there were 16 more per 100, with an average of 70 people (a range of 7 more to 27 more) benefiting from PPQFY. With the overall quality of the evidence being low, the effect was limited (Table 7.3).

The data for recurrence was unable to be pooled due to large variations in the data presented in the studies. The HRQoL assessment for 120 participants (one study) over a one-month treatment period showed the mean difference for the DLQI was 6.3 points for the pharmacotherapy group and 3.07 higher for the PPQFY, indicating worse HRQoL for the intervention group. The quality was moderate. This grading is most likely due to the low numbers included in the analysis from only one study.
### Table 7.3 GRADE analysis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>№ of participants (studies) Follow-up</th>
<th>Quality of the evidence (GRADE)</th>
<th>Relative effect (95per cent CI)</th>
<th>Anticipated absolute effects</th>
<th>Risk with pharmacotherapy</th>
<th>Risk difference with PPQFY formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective rate assessed with:</td>
<td>1507 (13 RCTs) Range 2–8 weeks</td>
<td>⨁⨁◯◯ LOW a,b,c</td>
<td>RR 1.30 (1.13 to 1.49)</td>
<td>54 per 100</td>
<td>16 more per 100 (7 more to 27 more)</td>
<td></td>
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<td>count</td>
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<tr>
<td>Recurrence rate assessed with:</td>
<td>566 (4 RCTs) Range 2–8 weeks</td>
<td>–</td>
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<tr>
<td>Quality of life assessed with:</td>
<td>120 (1 RCT) 1 month</td>
<td>⨁⨁⨁ MODERATE c</td>
<td>–</td>
<td>The mean quality of life was 6.13 points</td>
<td>MD 3.07 points higher (2.42 higher to 3.72 higher)</td>
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</table>

*The risk in the intervention group* (and its 95per cent confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95per cent CI).

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

**GRADE Working Group grades of evidence**

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations**

a. Unclear risk of bias for majority of studies
b. Substantial statistical heterogeneity
c. Small sample size

#### 7.5.3 Experimental evidence

Sebocytes and keratinocytes are both important components of the pilosebaceous glands that react to infection of *P. acnes* and stimulate inflammation (338). The androgens testosterone and 5α-dihydrotestosterone stimulate sebocytes and increase lipid droplets, increasing lipogenesis (338). Follicular keratinocytes are under androgen control (1). A combination of these factors causes
hyperkeratinisation of cells, contributing to the production of the comedones and pustules seen in
acne. Relevant to the pathogenesis of acne, the six botanicals in PPQFY were found to have anti-
inflammatory, anti-androgenic, anti-adipogenic and anti-lipogenic effects, and were antibacterial
to *P. acnes*. Key experimental studies of individual herbs identified from the PubMed search were
categorised based on the key pathogenesis described by the AAD 2016 (28) and are presented
below. There were no studies that looked a combination of these herb ingredients.

7.5.3.1 Microbial colonisation with *P. acnes*

Three of the ingredients had antimicrobial actions. *Gan cao* (*Glycyrrhiza glabra, Glycyrrhiza
uralensis*), *Huang bai* (*Phellodendron amurense*) and *Huang lian* (*Coptis chinensis*) were found
to have antimicrobial actions. The whole-herb extracts of *Glycyrrhiza glabra* and *Glycyrrhiza
uralensis* had greater antibacterial potency than erythromycin with no resistance issues (319).
Berberine, a compound common to *Phellodendron amurense* and *Coptis chinensis*, inhibited *P.
acnes* (339). The whole root extract of *Panax ginseng* prevented *P. acnes* adhesion to host human
and mouse cell lines (340).

7.5.3.2 Inflammation

All six ingredients of PPQFY had anti-inflammatory effects. The whole-herb extract of *Eriobotrya
japonica* decreased inducible nitric oxide synthase (iNOS) and the cyclooxygenase-2 (COX-2) in
lipopolysaccharide (LPS) stimulated RAW 264.7 cells (170). The whole-leaf extract of *Eriobotrya
japonica* inhibited LPS-induced interleukin-8 (IL-8), tumour necrosis factor-α (TNF-α) and IL-1β
in human lung epithelial cells (340), and regulated the production of TNF-α, IL-6 and IL-8 in mast
cells by inhibiting nuclear factor (NF)-κB, p38 mitogen-activated protein kinase (MAPK) and
extracellular signal-regulated kinase (ERK) (341). Tormentic acid from Eriobotrya japonica decreased iNOS and COX-2 in the oedematous paw by increasing the activities of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) in the liver of male ICR mice (342).

Ginsenosides from Panax ginseng inhibited the expression and production of inflammatory cytokine TNF-α (343). Ginsenoside activated the peroxisome proliferator-activated receptor gamma (PPAR-γ) nuclear receptor by directly increasing expressions of PPAR-γ2 and its targeting genes. In addition, ginsenoside sensitised insulin action and promoted the uptake and disposal of glucose by adipocytes (343, 344). Glabridin from Glycyrrhiza glabra activated PPAR-γ and bound to it. It also regulated the PPAR-γ gene expression in hepatoma cells (345). Berberine from Phellodendron amurense inhibited LPS-induced PPAR-γ overexpression and phosphorylation (346).

Glycyrrhizin from licorice root suppressed the production of cytokines through the inhibition of lipid raft accumulation and LPS-induced toll-like receptor-3 (TLR)-4 signalling, as well as suppressing LPS-induced NF-kB and interferon regulatory factor-3 (IRF3) activation (347). Glycyrrhizic acid and 18β-glycyrrhizic acid had an anti-inflammatory effect. They inhibited the production of nitrous oxide (NO), prostaglandin E2 (PGE2), TNF-α, IL-6, IL-1β and reactive oxygen species (ROS). They reduced expression of pro-inflammatory genes (iNOS and COX-2) and significantly blocked the transcription factors NF-kβ and phosphoinositide-3-kinase (PI3K), p110δ and p110γ (348).
Liquiritigenin from *Glycyrrhiza radix* blocked the induction of iNOS protein and its messenger ribonucleic acid (mRNA) at the transcriptional level and significantly inhibited LPS-induced TNF-α, IL-1β and IL-6 secretions (349). In this study, the inhibition effect was greater on TNF-α, a secondary cytokine (349). Liquiritigenin inhibited NF-kB activation in macrophages, due to its inhibition of inhibitory kappa B alpha (I-κBα) phosphorylation (349). A whole-herb extract of *Glycyrrhiza glabra* inhibited LPS-induced NO and ROS production, and expression of the cytokines iNOS, COX-2, TNF-α, IL-1β and IL-6, and protected macrophages from cell death caused by NO and TNF-α (350).

Berberine chloride, found in *Phellodendron amurense* and *Coptis chinensis*, decreased inflammation by inhibiting IL-6 and IL-8 but not TNF-α (351). However, a whole-herb extract of *Coptis chinensis* inhibited TNF-α in human keratinocytes (352). A whole-herb extract of *Phellodendron amurense* significantly suppressed the expression of iNOS and COX-2 (353-355) and decreased nuclear NF-κB and phosphorylated IκBα levels (353). In addition, the whole-herb extract inhibited IL-6, IL-1β and macrophage chemo-attractant protein-1 (MCP-1) *in vitro* and *in vivo* (353, 354). Berberine may also downregulate the cell-mediated inflammatory response by directly inhibiting T-cell activation (355). Berberine inhibited LPS-induced PPAR-γ overexpression and phosphorylation (346). Berberine reduced pro-inflammatory cytokines such as TNF-α, IL-6, C-reactive protein (CRP) and haptoglobin (HP); and reduction in the expression of LPL (lipoprotein lipase) was induced by berberine from *Phellodendron amurense* (171).
A whole-herb extract of *Morus alba* inhibited NO production in LPS-activated RAW 264.7 macrophages and decreased the production of TNF-α (356). It also inhibited NF-κB and extracellular signal-regulated kinase 1/2 (ERK1/2) activation (357).

### 7.5.3.3 Follicular hyperkeratinisation

Three ingredients had an effect on adipogenesis, lipogenesis and decreasing serum testosterone levels. *Glycyrrhiza glabra*, *Glycyrrhiza uralensis* and *Phellodendron amurense* were found to have anti-adipogenic and lipolytic actions. Glycyrrhizic acid from *Glycyrrhiza glabra* and *Glycyrrhiza uralensis* produced short-term decreases in total serum testosterone and 5α-dihydrotestosterone in human studies (358). 18β-Glycyrrhetinic acid decreased fat mass by affecting adipogenesis in maturing preadipocytes and lipolysis in matured adipocyte in 3Te-L1 cells (359). Berberine, an alkaloid of *Phellodendron amurense* and *Coptis chinensis*, reduced secretion of leptin and glycerol in 3T3-L1 adipocytes and may have reduced the mRNA expression of adipocyte-secreted inflammatory molecules (171).

### 7.5.3.4 Sebum production, anti-lipogenic and anti-adipogenic effects

Two of the ingredients had an effect on sebum. *Coptis chinensis* and *Eriobotrya japonica* had anti-lipogenic and anti-adipogenic effects. *Coptis chinensis* whole-herb extract had a greater effect on lipogenesis suppression than 0.01 per cent retinoic acid in hamster skin (319). *Eriobotrya japonica* inhibited lipid accumulation and adipocyte lipid-binding protein (aP2) (360). A whole-leaf extract of *Eriobotrya japonica* showed potent inhibition of the glucocorticoid activating enzyme 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1), an enzyme in adipose tissue (361).
7.6 Discussion

PPQFY is a common CHM formula recommended clinically for acne vulgaris in textbooks (159, 165). The clinical evidence from the results of the pooled studies on PPQFY showed that it was more effective in reducing lesion count, and the effect of the intervention was greatest when PPQFY was used alone compared to pharmacotherapy, although there was considerable heterogeneity. The effect of PPQFY varied according to the comparator type, with the highest effect seen when compared with antibiotics plus topical supplements. There were conflicting findings when PPQFY was compared with antibiotics alone and in combination with other medications. The reasons for this are unclear. Some of the studies varied the ingredients for participants based on syndrome differentiation or modified ingredients of the original formula. Future research should use original ingredients to evaluate the effect on acne. If modification is desired, justifications should be provided.

The studies included in this review were of low to moderate methodological quality with inadequate sequence generation and description of blinding procedures, which may have caused bias. There were no sample size calculations and sample size in all trials was generally small. The variability in the interventions and comparators contributed to considerable heterogeneity. The reporting of effective rate was not consistent among trials. All trials reported on lesion count, but not all reported on severity of lesions. Although not a validated outcome, reporting of lesion count and severity are widely used (362). There is a need to establish the criteria for assessing lesion count.
Few studies reported on recurrence rate and follow-up, also lacking description of withdrawals and drop-outs. None of the studies reported using intention-to-treat analyses to account for missing data. There was also large variability in comparators and the use of unconventional retinoid derivatives introduced considerable statistical heterogeneity into this review. Considering the low-to-moderate methodological quality in study design for most of the trials included in this review, the results should be interpreted with caution.

The trials used therapeutic effective rate (TER) as a primary outcome measure. TER is based on the percentage changes of lesion count and severity for improvement. A number of guidelines (162, 166, 167, 311) exist and variations of 30 per cent and 50 per cent for improvement were seen. For the PPQFY systematic review, it was decided that a threshold of 50 per cent would be used for determining clinical effect. This threshold is similar to that described in the CDER (107) Guidelines for Industry Acne Vulgaris: Developing Drugs for Treatment (107). The CDER guidelines are the standard with which drug companies in the USA must comply to obtain FDA approval for a drug (107). The CDER guidelines use the IGA scales to grade lesion severity, with lesions assessed on a five-point scale from 0 (no lesions) to 4 (severe). An improvement of two gradings is considered a success, which is similar to 50 per cent improvement in symptoms. This comparison was used since the IGA is commonly used as a scale for pharmacotherapy trials.

Meta-analysis of herb that only used PPQFY or modified from this formula was statistically significant, though heterogeneity was considerable. This was in contrast to studies that combined PPQFY with other oral or topical formulas, where no statistical significance was found. The combination of PPQFY with other herbal formulas appears to have introduced statistical
heterogeneity which may reflect clinical heterogeneity. Some studies included in this review used only two of the six original ingredients from the formula, while others used four or more ingredients. Many studies added extensively to the base formula. While this is reflective of clinical practice, variations in the formula across studies may have produced different clinical effects. Other factors that could have contributed to statistical heterogeneity include variations in the severity of disease (mild to severe) across the 15 studies. Statistical heterogeneity was also detected in several subgroup analyses, but was not able to be explored due to the small numbers of studies. Therefore, the effect of PPQFY compared with some drugs and drug combinations remains uncertain.

Acne treatment varies dependent on acne severity and cost. For mild-to-moderate acne in primary care, the combination of antibiotics with topical medications is first-line therapy (125, 140). OAB are prescribed for up to six months with 20 per cent improvement within two months and 80 per cent within six months (140). Second-line therapy includes topical or oral retinoids. This review included studies using either first- or second-line therapies as the comparator. Several studies reported acne severity ranging from mild to severe. This may have introduced clinical heterogeneity and impacted on the potential effect of PPQFY. Pharmacotherapies such as antibiotics and isotretinoin require four to six months of treatment in order to see clinical benefit (140).

The Western medicine prescribing practices for acne in the included studies, all of which were conducted in China, differed to common practices in Europe, Australia and the USA (125, 140, 363). One trial combined OAB with TAB (324). The combination of oral and topical antibiotics is
no longer a common prescribing practice due to antibiotic resistance issues (140). Four trials used an unconventional retinoid derivative (viaminate) (321, 324, 334) that is not recommended in international guidelines for acne vulgaris (28, 125, 127, 140). Though viaminate is not common outside of China, it is highly utilised in China. European, US and Australian guidelines are similar in prescribing practices for retinoids, antibiotics and topical medications. A combination of OAB with topical BP or topical isotretinoin should be prescribed depending on the severity of the acne. Photodynamic therapy is recommended in Malaysian and European guidelines, but the US and Australian guidelines indicates there is less evidence for the efficacy of these interventions.

The number of AEs was lower among those who received PPQFY than those in the control group. Few studies reported causality assessment of AEs. Monitoring of safe use of herbal products is important for public safety (364). Many of the comparators used have known side effects, such as skin irritation and dryness with topical BP (13) and burning, pruritus, scaling and erythema with topical tretinoin and adapalene (365). Based on the included studies, the formula was well tolerated by people with acne vulgaris.

There is one published review in English (20) on botanical and phytochemical treatments for acne reporting on three CHM/Kampo formulations, a herbal face mask, a Kampo formula Kaigeirengyo-to and green tea, none of which were PPQFY. Due to the differing scales used in assessing disease severity, it was not possible to explore the effect of PPQFY on severity subgroups; therefore we were unable to compare directly with the findings reported in the Fisk et al. review (20). There is one Cochrane review on CAM that included CHM compared to pharmaceuticals. None of the included trials used PPQFY. The review found herbal medicines were not better than
pharmaceuticals, and there were clinical heterogeneity between trials and incomplete data reporting. Similar limitations from these reviews such as reporting issues and non-validated outcome measures were also seen in the trials included in this review.

From the experimental studies, all six ingredients of PPQFY may have an effect in decreasing inflammation, sebum production and hyperkeratinisation. They may also have an inhibitory effect on *P. acnes*, as well as preventing *P. acnes* from adhering to host cells. *Panax ginseng* and glycyrrhizic acid from *Glycyrrhiza glabra* and *Glycyrrhiza uralensis* decreased serum testosterone (358) and encouraged lipolysis in mature adipocytes (Moon et al., 2012). *Glycyrrhiza Glabra*, *Panax ginseng*, *Phellodendron amurense* and *Coptis chinensis* all inhibited *P. acnes* growth (319, 339, 344).

Four of the six ingredients, *Glycyrrhiza glabra*, *Coptis coptidis*, *Eriobotrya japonica* and *Panax ginseng*, all inhibit PPAR-γ. *Phellodendron amurense*, *Eriobotrya japonica*, *Panax ginseng*, liquiritigenin from *Glycyrrhiza glabra* and a whole-herb extract of *Coptis chinensis* all inhibit TNF-α. NF-κB is activated in comedones and strongly expresses IL-1α, which increases hyperkeratinisation (81, 348, 353, 366). Three of the ingredients, *Phellodendron amurense*, *Morus alba* and *Eriobotrya japonica*, inhibit NF-κB cytokines and a further three of the ingredients, *Glycyrrhiza glabra*, *Phellodendron amurense* and *Eriobotrya japonica*, inhibit IL-1β but not IL-1α (348, 353, 366). Nearly all experimental evidence was from *in vivo* and *in vitro* studies. Only one study was found on the pathophysiological effects of the botanicals in people; caution is needed when translating effects to people.
7.7 PPQFY systematic review conclusions

The six ingredients of PPQFY have anti-inflammatory, antibacterial, anti-lipogenic, anti-adipogenic and anti-androgenic effects. These actions may contribute to the effects seen in clinical studies. The number of people achieving a reduction in lesion count was higher with PPQFY compared with various pharmacotherapies, although statistical heterogeneity was detected in several meta-analyses. In one study, HRQoL was worse in people who received PPQFY than in those who received pharmacotherapy. No SAEs were reported in clinical trials, suggesting that PPQFY was well-tolerated by people with acne. Rigorously designed studies that describe original formula ingredients, grade the severity of acne and report on clinically relevant outcomes such as HRQoL are needed.

7.8 Implications for future clinical research

None of the included RCTs were free from bias and methodological shortcomings are highlighted. Future research should take into consideration:

1. Proper randomisation, allocation concealment and blinding methods (see below)
2. Use of health-related quality of life questionnaires specific to acne as outcome measures
3. Minimised modification of formulations, providing reasoning if modifications are used; and
4. Comparing interventions with like controls such as placebos and, if using pharmacotherapy for controls, to use one guideline-recommended treatment at the correct dosage for the correct age group.
Randomisation is used to ensure that there is no selection bias, to control for confounders and to improve the internal validity of clinical trials (367). Rigorous randomisation procedures prevent differences between baseline characteristics of participants in different interventions groups. This is one way to prevent bias in a trial. Trials that do not use randomisation inevitably show that the intervention assessed has extremely high clinical effects (302).

Concealing group allocation from participants and the research investigators prevents the results from being influenced by personal biases and beliefs. Knowing which group one is in may lessen or increase compliance or increase drop-outs. It may make researchers behave differently towards participants, whether intended or not. Estimates of interventions can be exaggerated in studies with improper concealment (302). Blinding of participants and researchers would prevent such biases and control for unobserved cofounders and biases, hence improving the internal validity of the trial (367).

It is common in CM practice to modify formulas to address the diagnosed syndrome and tailor treatment to the individual patient as seen in the included trials in this review. This however brings heterogeneity into the meta-analyses of included clinical trials. The substantial modifications in the included trials of PPQFY may have contributed to the considerable heterogeneity found in the meta analysis. Pragmatic trial designs may be one solution to addressing individualised treatments in trials (PATSOUPOULOS 2011), This type of design requires substantial personnel to implement the trial and to make timely adjustments to herbs. This type of trial would most closely reflect real clinical practice however may increase variance in studies and efficacy of the herbs is difficult to determine.
7.9 Implications for clinical practice

From the SR and experimental review, PPQFY has the potential to decrease inflammatory and non-inflammatory acne lesions, decrease sebum and inhibit *P. acnes* growth. It may be effective for mild-to-moderate comedonal acne. All of the studies modified the original formula or added another formula as an intervention; however, the original formula may not be applicable for all lesion types or all syndromes. The herbs most commonly added to the formula were *Huang qin* (*Scutellaria baicalensis* Georgi.) followed by (Shan) *Zhi zi* (*Gardenia jasminoides* Ellis, fruit), *Mu dan pi* (*Paeonia suffruticosa* Andr., root bark) and *Da huang* (*Rheum palmatum* L. or *R. tanguticum* Maxim, et Reg. or *R. officinale* Baill.). All of these herbs are considered ‘cold’ and have actions that clear heat. *Huang qin* targets the upper and middle energisers, whereas *Huang bai* (*Phellodendron amurense* Rupr. or *P. chinense* Schneid.) from the original formula targets the lower energiser. This is considered a logical modification as the CM syndromes for acne relate to the upper and middle energisers. *Da huang* supports draining dampness, clearing heat toxicity and regulating Blood. Again, these herbs are logical choices due to the CM pathogeneses described in Chapter 3.

Clinically, the meta-analysis showed that PPQFY produced better outcomes than pharmacotherapies and with fewer AEs. It may be an alternative to pharmacotherapies for acne. The studies, however, were not free from biases. Clinicians should use their experience and patient preferences when prescribing treatment. The main AEs reported with PPQFY included gastrointestinal AEs such as nausea, abdominal discomfort and intermittent diarrhoea. This may be explained when considering the actions of the herbs. For example, *Da huang* is a purgative and may cause diarrhoea, increased abdominal peristalsis and pain. The other herbs are ‘cold’ in nature.
and may cause additional gastrointestinal discomfort. The symptoms resolved when the CHM were discontinued and, although not all trials conducted a follow-up, those trials that did reported no lingering or residual AEs from the CHM. Therefore the formula is relatively safe with a low risk of harm. Clinicians should inform patients of the possible risks and strategies to minimise AEs such as taking herbs after meals.

The trials included in this systematic review did not include integrative medicine, that is, no trials used a combination of PPQFY with pharmacotherapies compared to pharmacotherapies alone. Therefore, the safety profile of an integrative medicines was not ascertained in this review. Practitioners who see patients currently using pharmacotherapies may wish to wait until pharmacotherapy treatment has ceased before providing CM treatment, given the lack of information about safety of using CHM and pharmacotherapy concurrently.

### 7.10 Chapter summary

This chapter has provided the results of the SR and meta-analysis of the targeted CHM formula PPQFY. The effective rate of PPQFY was better than pharmacotherapies in the treatment of acne with the exception of HRQoL, although the results should be interpreted with caution due to the low methodological quality of the trials. There was also only one study that used HRQoL included in this review which showed pharmacotherapies was better than PPQFY. More studies are needed that include this outcome measure in order to improve knowledge of the impact of CHM on the HRQoL of people with acne.
CHAPTER 8: Systematic review of acupuncture for acne vulgaris

Overview

Chapter 6 outlined comprehensive methods used in conducting SRs and meta-analyses for CHM and acupuncture related therapies. Chapter 7 presented findings on the first SR and meta-analysis of CHM formula PPQFY for acne. This chapter presents the findings of the second SR of RCTs of acupuncture and related techniques for acne vulgaris (acne). The SR was published in a modified form in the journal *Evidenced-Based Complementary and Alternative Medicine* in March 2018 (368) (Appendix 15).

8.1 Introduction

Acupuncture is an umbrella term for traditional CM techniques that stimulate acupuncture points. Techniques include body acupuncture (insertion of fine needles at specific loci on the body, typically for a period of 20 to 30 minutes) and auricular acupuncture (insertion of needles in specific loci of the auricle). Acupressure is another form of point stimulation that can include using hands, fingers or other blunt instruments to apply pressure to the acupuncture point with no skin penetration. Auricular acupressure (AA), similar to body acupuncture point acupressure, is the placement of blunt instruments such as small metallic ball bearings at specific loci of the auricle. EA (mild electric stimulation of acupuncture needles) (169) can be used on body acupuncture points or auricular points. Cutaneous needling (also called plum blossom or seven-star needling) is a type of device where a cluster of five or seven short needles are spaced out in a circle or star shape and are taped around a skin lesion or along a meridian (Bertschinger et al., 1993). A form of indirect point stimulation is moxibustion (burning of *Artemisia argii* Levl. et Vant or *Artemisia*...
vulgaris leaf in a processed form) (369). These techniques for stimulating acupuncture points are commonly used in the treatment of acne vulgaris.

Several studies have suggested a potential role of acupuncture and related techniques in acne. AA and surround needling (where two to four needles are inserted superficially around the acne lesion) have been shown to reduce serum excretion rate (SER) and testosterone (176). When acupuncture was combined with BP, SER in women was reduced compared to BP alone (309). In animal studies, auricular acupuncture, auricular EA, body acupuncture and EA have been shown to decrease inflammation (308, 370-372). Auricular acupuncture may reduce acne inflammation through peripheral muscarinic receptors (370) and innate and adaptive immune responses (371, 373, 374).

Several reviews have examined the potential benefits of acupuncture techniques in clinical studies. A Cochrane review on CAM for acne (157) evaluated the efficacy of herbal medicine, acupuncture, cupping therapy, dietary modifications, purified bee venom (PBV) and tea-tree oil. The review found there was a lack of evidence to support the use of herbal medicine and acupuncture. Two SRs of acupuncture for acne have been published, one in English (185) and one in Chinese (18). Cao et al. (185) included trials which used acupuncture, cupping and other herbal medicines. While the number of “cured” cases increased when acupuncture was combined with cupping, or oral or topical herbal medicines, no benefit was found when acupuncture was compared with pharmacotherapy. The reviewers described the methodological quality of the papers as poor. Li et al. (18) included trials of manual acupuncture compared to routine conventional medicine
(isotretinoin and antibiotics) or multiple CM therapies. The authors were unable to provide conclusions due to the poor quality of the included trials.

8.2 Rationale for the acupuncture review

The abovementioned reviews included herbal medicines and acupuncture techniques not commonly used outside of China. Body acupuncture, auricular acupuncture and moxibustion are commonly used in CM clinical practice for skin conditions. Previous reviews evaluated a combination of different acupuncture therapies, or combination of herbs with acupuncture or with pharmacotherapies. They also included studies that used CM as a comparator for which evidence is lacking. Reviews of the efficacy and safety of body acupuncture, auricular acupuncture and moxibustion used alone compared with sham or placebo, or conventional acne treatments have not been identified. This chapter analyses commonly used acupuncture techniques compared to pharmacotherapies, no treatment, and sham or placebo acupuncture to evaluate their efficacy and safety for acne vulgaris.

8.3 Aims

This chapter aims to conduct an SR and meta-analysis of the efficacy and safety of acupuncture and related interventions for acne vulgaris. The methods have been described in Chapter 6: Methods for systematic reviews.
8.4 Results

8.4.1 Search Results

A total of 15,306 records were identified from database searches from inception to May 2013 (and updated in February 2015) with one additional record sourced through an online search for acupuncture-related references. After removal of duplicates, screening of titles and abstracts excluded 7,673 papers, and 2,485 full texts were reviewed (Figure 8.1).

8.4.2 Characteristics of studies

Twelve RCTs involving 1,026 participants met the inclusion criteria (174-177, 336, 375-381). Ten RCTs with 975 participants were included in the meta-analysis. The data presented from two trials could not be reanalysed due to data not being available for individual groups; these were excluded from the quantitative analysis (174, 377). The authors were contacted for additional information; however, this was unsuccessful. All trials recruited male and female participants except that of Kim and Kim (377), who recruited only male subjects. Participant age ranged from 13 to 37 with a median of 23.1 years. Details of trial location, treatment times, follow-up periods and participant stage and duration of condition are presented in Table 8.1. Most of the studies included in this SR were conducted in China, however a number of them did not explicitly state their location and therefore it is not possible to be certain of their exact location. In addition, most trials were not registered with relevant trial databases.
Figure 8.1 Study selection flow chart: acupuncture
### Table 8.1 Characteristics of studies

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<th>Treatment duration, follow-up duration</th>
<th>Stage, severity and duration of condition</th>
<th>No. of participants randomised/assessed; dropouts or withdrawals</th>
<th>Age (mean (SD) or range); gender (M/F)</th>
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| Han, 2010 (375)               | China, hospital outpatients | 8 w, 1 m                               | Stage: NS  
Severity: Pillsbury I, II  
Duration: I: 2.35±0.86; C: 2.15±0.82 | I: 50/46; 4  
C: 50/47; 3 | I: 25.83±5.25; 18/28  
C: 24.68±4.36; 14/33 |
| He, 2009 (376)                | China, hospital outpatients | 3 w, NS                                 | Stage: NS  
Severity: Slight to severe  
Duration: I: 20 d to 16 y; C: 1 m to 17 y | I: 24/24; 0  
C: 22/22; 0 | I: 25.2; NS  
C: 23.6; NS |
| Li, 2002 (176)                | NS                          | 6 d, 1 m                                | Stage: NS  
Severity: Samuelson 1–9  
Duration: I1: 14 d – 15 y, I2: 7 d – 13 y; C: 4 d – 14 y | I1:200/200; 0  
I2 : 60/60; 0 | I1: 13–37; NS  
I2:14–35; NS |
| Liu, 2011 (378)               | NS                          | 2 w, 6 m                                | Stage: NS  
Severity: NS  
Duration: I: 1 w – 14 y; C: 1 w – 10 y | I:40/40; 0  
C:40/40; 0 | I:14–41; 6/34  
C:13–30; 7/33 |
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<th>Stage, severity and duration of condition</th>
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<td>Severity: NS</td>
<td>C:38/38; 0</td>
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<td></td>
<td></td>
<td></td>
<td>Duration: NS</td>
<td></td>
<td></td>
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<tr>
<td>Tang, 2011 (287)</td>
<td>NS</td>
<td>10 d, NS</td>
<td>Stage: NS</td>
<td>I:42/42; 0</td>
<td>NS; 11/31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severity: NS</td>
<td>C:42/42; 0</td>
<td>NS; 7/35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration: 1 w – 9 y</td>
<td></td>
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<tr>
<td>Wu, 2011 (336)</td>
<td>NS</td>
<td>8 w, 2 m</td>
<td>Stage: NS</td>
<td>I:40/36; 4</td>
<td>1.24.31±4.08; 13/23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severity: NS</td>
<td>C:40/35; 5</td>
<td>C:23.91±3.83; 13/22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration: I: 11.92 ±8.93; C: 12.77 ± 9.58</td>
<td></td>
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<tr>
<td>Liu, 2015 (379)</td>
<td>NS</td>
<td>8 w, NS</td>
<td>Stage: NS</td>
<td>I: 60/50; 10</td>
<td>1:23.2; 27/33</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>Severity: NS</td>
<td>C:58/50; 8</td>
<td>C:24; 27/31</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Duration: I: 6.5 m; C: 6.1 m</td>
<td></td>
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<tr>
<td>Zhang, 2014 (175)</td>
<td>NS</td>
<td>4 w, NS</td>
<td>Stage: NS</td>
<td>I: 20/19; 1</td>
<td>1: 18–23; 2/17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severity: NS</td>
<td>C:20/20; 0</td>
<td>C: 18–24; 5/15</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Trial location</td>
<td>Treatment duration, follow-up duration</td>
<td>Stage, severity and duration of condition</td>
<td>No. of participants randomised/assessed; dropouts or withdrawals</td>
<td>Age (mean (SD) or range); gender (M/F)</td>
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<tr>
<td>You, 2014 (381)</td>
<td>NS</td>
<td>30 d, NS</td>
<td>Stage: NS</td>
<td>I: 30/30; 0</td>
<td>I: 25±5; 17/13</td>
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<td></td>
<td></td>
<td></td>
<td>Severity: NS</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Duration: 23.36 m; C: 22.81 m</td>
<td></td>
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</tr>
<tr>
<td>McKee, 2004 (174)</td>
<td>USA, outpatient clinic</td>
<td>20 w, NS</td>
<td>Stage: NS</td>
<td>I1: 6/6; 2</td>
<td>I1: F 16 (2.1); M 15 (0.7); NS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Severity: Grade I &amp; II mild to moderate non scarring facial by dermatologist; photographs grading by Cook 1979 and lesion count</td>
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<td></td>
<td></td>
<td></td>
<td>Duration: NS</td>
<td>I2: 11/11; 6</td>
<td>I2: F 21 (3.4); M 16 (3.6); NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C1: 6/6; 1</td>
<td>C1: F 19 (4.2); M 17 (1.9); NS</td>
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<td></td>
<td></td>
<td></td>
<td>C2: 6/6; 0</td>
<td>C2: F 21 (1.5); M 15 (1.2); NS</td>
</tr>
<tr>
<td>Kim, 2012 (377)</td>
<td>Korea, outpatient clinic</td>
<td>4 w, NS</td>
<td>Stage: NS</td>
<td>I:11/11, 3</td>
<td>I: Male 21.5 (3.6); NS</td>
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<td></td>
<td></td>
<td>C:11/11, 2</td>
<td>C: Male 23.3 (4.1); NS</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Trial location</td>
<td>Treatment duration, follow-up duration</td>
<td>Stage, severity and duration of condition</td>
<td>No. of participants randomised/assessed; dropouts or withdrawals</td>
<td>Age (mean (SD) or range); gender (M/F)</td>
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<td>Severity: Korean Acne Grading System</td>
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<td></td>
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<td>grades 2–4 (&gt; 10 papules, &lt; 20 nodules on face);</td>
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<td></td>
<td></td>
<td></td>
<td>Duration: &gt;3 months (chronic stage)</td>
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</tbody>
</table>

Abbreviations: d days; C control, F female, I intervention; m months, M male; NS not stated, SD standard deviation, w weeks, y years
<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Intervention type</th>
<th>Acupuncture points</th>
<th>Intervention treatment frequency</th>
<th>Control details</th>
<th>Control treatment frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han, 2010 (375)</td>
<td>Acupuncture</td>
<td>CV13 <em>Shangwan</em>, CV12 <em>Zhongwan</em>, CV4 <em>Guanyuan</em>, CV6 <em>Qihai</em>; ST24 <em>Huaroumen</em>, ST26 <em>Wailing</em>, <em>Shangfeng</em> <em>Shidian</em> (abdominal point 0.5 cun lateral and superior to ST24); KI13 <em>Qixue</em>, M-CA-23 <em>Sanjiaojiu</em> (<em>Qipang</em>)</td>
<td>30 mins, 3 times per week</td>
<td>Isotretinoin capsules (oral)</td>
<td>10 mg b.i.d. (first month); 10 mg, q.d. (second month)</td>
</tr>
<tr>
<td>He, 2009 (376)</td>
<td>Acupuncture</td>
<td>CV13 <em>Shangwan</em>, CV12 <em>Zhongwan</em>, CV4 <em>Guanyuan</em>, CV6 <em>Qihai</em>; ST24 <em>Huaroumen</em>, ST26 <em>Wailing</em>, <em>Shangfeng</em> <em>Shidian</em> (abdominal point 0.5 cun lateral and superior to ST24); KI13 <em>Qixue</em>, M-CA-23 <em>Sanjiaojiu</em> (<em>Qipang</em>), M-HN-3</td>
<td>30 mins: body points; 15–20 mins: head points Ashi Points q.d. (first week), every 2 days (2nd and 3rd weeks)</td>
<td>Metronidazole (topical)</td>
<td>b.i.d</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Intervention type</td>
<td>Acupuncture points</td>
<td>Intervention treatment frequency</td>
<td>Control details</td>
<td>Control treatment frequency</td>
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<tr>
<td>Li, 2002 (176)</td>
<td>I1 AA + SA</td>
<td>Yintang, SI18 Quanliao, ST4 Dicang, M-HN-9 Taiyang, Ashi Points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I2: AA</td>
<td>SA: Ashi points, AA: CO18 Endocrine (Neifenmi), CO14 Lung (Fei), AH6a Sympathetic (Jiaogan), CO4 Stomach (Wei), CO7 Large Intestine (Dachang), TF4 Shenmen, TF2 Internal Genitals (pin yin not identified)</td>
<td>SA: 30 min q.d.; AA: 3–5 min, b.i.d</td>
<td></td>
<td>Tetracycline (oral) 0.5 g, q.i.d</td>
</tr>
<tr>
<td>Liu, 2011 (378)</td>
<td>AP</td>
<td>Lung, Endocrine, Adrenal Gland, Ear Shen Men, Subcortex, Cheek. Large Intestine (Wind and Heat in Lung Meridian); Spleen, Stomach, Large</td>
<td>AA: 5–10 min, t.i.d</td>
<td>Benzamycin (topical)</td>
<td>b.i.d</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Intervention type</td>
<td>Acupuncture points</td>
<td>Intervention treatment frequency</td>
<td>Control details</td>
<td>Control treatment frequency</td>
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<tr>
<td>Mo, 2005 (380)</td>
<td>Acupuncture</td>
<td>Governor Meridian</td>
<td>4–5 hrs/treatment, 5 times per week</td>
<td>Viaminate capsules, vit B6 (oral)</td>
<td>Viaminate 0.25 mg t.i.d.; vit B6, 2 pills t.i.d.</td>
</tr>
<tr>
<td>Tang, 2011 (287)</td>
<td>Acupuncture + SA</td>
<td>Manual: ST36 <em>Zusanli</em>, ST40 <em>Fenglong</em>, ST45 <em>Lidui</em>, LI11 <em>Quchi</em>, LI10 <em>Shoushanli</em>, LI4 <em>Hegu</em>; SA: Ashi Points</td>
<td>30 min q.d.</td>
<td>Erythromycin, zinc sulfate (oral); sulfur (topical)</td>
<td>Erythromycin 0.2 g b.i.d.; zinc sulfate 0.2 g b.i.d.; sulfur (topical) q.d.</td>
</tr>
<tr>
<td>Wu, 2011 (336)</td>
<td>Acupuncture + moxibustion</td>
<td>Acupuncture: CV11 <em>Shangwan</em>, CV12 <em>Zhongwan</em>, CV4 <em>Guanyuan</em>, CV6 <em>Qihai</em>; ST24 <em>Huaroumen</em>, ST26 <em>Wailing</em>; <em>Shangfeng Shidian</em> (abdominal point 0.5 cun lateral and superior to ST24); KI13</td>
<td>Acupuncture and moxibustion: 3 times per week</td>
<td>Isotretinoin capsules (oral)</td>
<td>10 mg, b.i.d.</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Intervention type</td>
<td>Acupuncture points</td>
<td>Intervention treatment frequency</td>
<td>Control details</td>
<td>Control treatment frequency</td>
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</tr>
<tr>
<td>Liu, 2015 (379)</td>
<td>Acupuncture</td>
<td>Qixue; Moxa: CV4 Guanyuan, CV6 Qihai.</td>
<td>q.d. (total 56 treatments)</td>
<td>Isotretinoin (oral)</td>
<td>10 mg, b.i.d. – t.i.d.</td>
</tr>
<tr>
<td>Zhang, 2014 (175)</td>
<td>EA</td>
<td>GB14 Yangbai, SI18 Quanliao, GV14 Dazhui, LI4 Hegu, LI11 Quchi, ST44 Neiting</td>
<td>Twice per week (total 15 treatments)</td>
<td>Tretinoin (topical)</td>
<td>b.i.d.</td>
</tr>
<tr>
<td>You, 2014 (381)</td>
<td>Acupuncture</td>
<td>Governor meridians, M-BW-35 Huatuojiaji and Bladder through the first lateral line (BL13 Feishu, BL21 Weishu BL25 Dachangshu)</td>
<td>q.d. (total 15 treatments)</td>
<td>Tretinoin (topical)</td>
<td>q.n.</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Intervention type</td>
<td>Acupuncture points</td>
<td>Intervention treatment frequency</td>
<td>Control details</td>
<td>Control treatment frequency</td>
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<tr>
<td>McKee, 2004 (174)</td>
<td>Auricular acupuncture and EA</td>
<td>GV14 Dazhui, LI11 Quchi, LI4 Hegu, ST36 Zusanli, KI3 Taixi, LU9 Taiyuan</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>I1: Oleson’s Shenmen, Allergy point, Skin Disorder Point F, Point Zero, Lung 1 and 2, Endocrine point, Genital Control Point, Face Point bilateral ears; I2: points as I1 plus EA 8–16 sec on 5–80 Hz</td>
<td>20 min weekly</td>
<td>C1: 9 Sham points on helix auricular ridge</td>
<td>20 min weekly</td>
</tr>
<tr>
<td>Kim, 2012 (377)</td>
<td>Acupuncture</td>
<td>ST2 Sibai, ST6 Jiache, ST36 Zusanli, LI20 Yingxiang, LI11 Quchi, PC6 Neiguan, HT8 Shaofu, SP3 Taibai, SP6 Sanyinjiao, SP10 Xuehai, LR3 Taichong, and/or Ashi points randomly</td>
<td>Twice weekly for 4 weeks</td>
<td>Waitlist – no treatment</td>
<td></td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Intervention type</td>
<td>Acupuncture points</td>
<td>Intervention treatment frequency</td>
<td>Control details</td>
<td>Control treatment frequency</td>
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<tr>
<td></td>
<td></td>
<td>selected at papules and nodules on the face by acupuncture practitioner</td>
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</tbody>
</table>

Abbreviations: AA auricular acupressure, b.i.d. twice daily, C control, EA electro-acupuncture, Hz: hertz, I intervention, q.d. one time per day, q.i.d four times daily, qn once nightly, SA surround acupuncture, sec seconds, t.i.d. three times daily
8.4.2.1 Acupuncture interventions used

The intervention most frequently used was acupuncture (six trials) (177, 375, 376, 379-381) followed by AA (two trials) (176, 378). One trial used EA (and plum blossom needling) (175) and one trial used acupuncture combined with moxibustion (336). The comparators are described in Table 8.2. Kim and Kim (377) included three treatment arms, one of acupuncture alone, one of herbal medicine alone and one where herbal medicine was combined with acupuncture. These three groups were compared with a waitlist control. Only the data for the acupuncture arm was included in this analysis. McKee et al. (174) included two treatment arms, auricular acupuncture and auricular EA, which were compared to placebo control groups, sham auricular acupuncture and sham auricular EA, respectively.

There was large variation in the acupuncture points used (Table 8.2). Three studies (336, 375, 376) used CV13 Shangwan, CV12 Zhongwan, CV4 Guanyuan, CV6 Qihai, ST24 Huaroumen, ST26 Wailing, Shang Feng Shi Dian (an abdominal point 0.5 cun lateral to ST 24 Huaroumen) and KI13 Qixue (Table 8.3). Most of the studies used a standardised set of acupuncture points, with one study using a semi-standardised approach (378). Four studies used Ashi points (176, 177, 336, 376) for which the location was not specified and two used needles around acne lesions (surround acupuncture; (176, 177)).
### Table 8.3 Frequency of acupuncture points used

<table>
<thead>
<tr>
<th>Acupuncture point</th>
<th>Pinyin / Chinese characters</th>
<th>Frequency</th>
<th>Point function*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point near a comedone</td>
<td><em>Ashi</em> 阿是穴</td>
<td>4</td>
<td>A local area or point chosen for “pain” and can be considered a trigger point (Birch, 2003)</td>
</tr>
<tr>
<td>CV12</td>
<td><em>Zhongwan</em> 中脘</td>
<td>4</td>
<td>Harmonises the middle energizer (<em>zhong jiao</em>) and descends rebellion; tonifies the Stomach and fortifies the Spleen; regulates <em>qi</em> and alleviates pain.</td>
</tr>
<tr>
<td>CV4</td>
<td><em>Guanyuan</em> 关元</td>
<td>3</td>
<td>Fortifies original <em>qi</em> (<em>yuan qi</em>) and benefits essence (<em>jing</em>); tonifies and nourishes the Kidneys; warms and fortifies the Spleen; benefits the uterus (<em>zi gong</em>) and assists conception; regulates the lower jiao and benefits the Bladder; regulates Small Intestine <em>qi</em>; restores collapse.</td>
</tr>
<tr>
<td>CV6</td>
<td><em>Qihai</em> 气海</td>
<td>3</td>
<td>Fosters original <em>qi</em> (<em>yuan qi</em>); tonifies <em>qi</em>; tonifies the Kidneys and fortifies yang; rescues collapse of yang; regulates <em>qi</em> and harmonises Blood.</td>
</tr>
<tr>
<td>CV13</td>
<td><em>Shangwan</em> 上脘</td>
<td>3</td>
<td>Harmonises the Stomach and regulates <em>qi</em>; descends rebellion and alleviates vomiting; regulates the Heart.</td>
</tr>
<tr>
<td>KI13</td>
<td><em>Qixue</em> 气穴</td>
<td>3</td>
<td>Regulates the Penetrating and Conception vessels; regulates the lower energizer (<em>xia jiao</em>).</td>
</tr>
<tr>
<td>LI4</td>
<td><em>Hegu</em> 合谷</td>
<td>3</td>
<td>Regulates defensive <em>qi</em> and adjusts sweating; expels wind and releases the exterior; regulates the face, eyes, nose, mouth and ears; activates the meridian and alleviates pain; induces labour; restores the yang.</td>
</tr>
<tr>
<td>Acupuncture point</td>
<td>Pinyin / Chinese characters</td>
<td>Frequency</td>
<td>Point function*</td>
</tr>
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</tr>
<tr>
<td>LI11</td>
<td>Quchi 曲池</td>
<td>3</td>
<td>Clears heat; cools the Blood, eliminates wind, drains damp and alleviates itching; regulates qi and Blood; activates the meridians and alleviates pain.</td>
</tr>
<tr>
<td>SI18</td>
<td>Quanliao 颧髎</td>
<td>3</td>
<td>Eliminates wind and alleviates pain; clears heat and reduces swelling.</td>
</tr>
<tr>
<td>ST24</td>
<td>Huaroumen 滑肉門</td>
<td>3</td>
<td>Transforms phlegm and calms the spirit (shen); harmonises the Stomach and alleviates vomiting.</td>
</tr>
<tr>
<td>ST26</td>
<td>Wailing 外陵</td>
<td>3</td>
<td>Regulates qi and alleviates pain.</td>
</tr>
<tr>
<td>Upper wind-damp point (an abdominal point 0.5 cun lateral to ST24 Huaroumen)</td>
<td>Shang Feng Shi Dian 上风湿点</td>
<td>3</td>
<td>Functions not identifiable. Indications: postoperative complaints in the wrist joint and palm, pain, swelling, limitation of movement and numbness of wrist and pain in the palm (Sun, 2007).</td>
</tr>
</tbody>
</table>

* Point indications sourced from Deadman, 2009 (382) unless otherwise indicated.

8.4.3 Risk of bias

The methodological quality of the trials was generally low (Figure 7.2). Four trials (176, 376, 380, 381) were assessed as having high risk of bias in the domain of sequence generation as they used sequence of visit for randomisation. Five trials (175, 336, 375, 377, 379) were assessed as low risk as random number generators were used. Three trials were assessed as unclear as there was insufficient information (174, 177, 378). All trials were assessed as having unclear risk in blinding of participants. Two trials were assessed as low risk for blinding of outcome assessors (174, 377) and ten were at unclear risk due to insufficient information. One trial was assessed as having
unclear risk for incomplete data (379) as it did not report drop-out data. One trial, Zhang et al. (175), reported on drop-outs but data was reported only for those who completed the trial; thus it was assessed as high risk for incomplete outcome data. Ten trials were assessed as low risk for incomplete data. Two trials were assessed as high risk for selective outcome reporting. McKee et al. (174) stated they would include data on AEs but no such data was presented. Kim and Kim indicated in their protocol (377) the use of the VAS scale to measure acne severity (0 for no symptoms up to 100 for severe symptoms) but no data was reported. The remaining ten trials were assessed as unclear, as there were no trial protocols published or trial registrations identified (175-177, 336, 375, 376, 378-381).

A summary of the assessment of reporting of STRICTA conducted for this review is found in Appendix 16. For studies included in this review, several items were reported well in all trials: the type of acupuncture used, standard acupuncture name and/or locations of acupuncture points, the number and duration of treatment sessions, and precise descriptions of the controls or comparators.
(Table 8.2). The trials conducted in China did not provide information about the practitioners, the setting and context of treatment, the instructions to practitioners, or the information and explanations to the patients.

### 8.4.4 Primary outcome: therapeutic effective rate

One trial (176) reported on TER based on lesion count and severity, and also reported on serum testosterone and recurrence rate. Four trials (336, 375, 379, 381) reported on TER according to the 2002 *Guideline for New Chinese Herbal Medicine in Clinical Practice and Research* (中药新药临床研究指导原则 (试行)) (311). Three trials (175, 376, 380) used the 1994 CM research guidelines (167). One trial did not refer to a guideline for judgement of TER but indicated that an improvement in lesions of 95 per cent was a cure and 60 per cent was a significant improvement; this data was included in the meta-analysis (378). Another trial (177) also did not specify a guideline for judgement of TER and indicated no lesions as a cure, 80 per cent as significant improvement and >30 per cent as improvement; this data was also included in the meta-analysis (177). The criteria for determining clinical effect are described in Table 8.4. Only one trial reported measuring QoL, using the Skindex-29 (377).

Figure 8.3 presents the forest plot for the meta-analysis of TER ≥30 per cent change in symptoms. Meta-analysis showed the chance of achieving a 30 per cent or greater change in lesion count in the acupuncture group was not different to the combined pharmacotherapy group (retinoids, antibiotics and other supplements) (four studies, RR: 1.07 [95 per cent CI 0.98, 1.17], I²=8 per cent) (175, 177, 376, 380) with low heterogeneity. Subgroup analysis of studies where the comparator was antibiotics plus other supplements showed the chance of a 30 per cent or greater
change in lesion count was not different between the acupuncture and the topical/oral antibiotics and supplements groups (two studies, RR: 1.03 [95 per cent CI 0.91, 1.16], I²=14 per cent) (177, 376) with low heterogeneity. In a subgroup analysis of the chance of a change of 30 per cent or greater in lesion count, acupuncture was as effective as the retinoids groups (viamine and tretinoin) (two studies, RR: 1.13 [95 per cent CI 1.00, 1.28], p=0.06, I²=0 per cent) with no heterogeneity (175, 380).

Table 8.4 Therapeutic effective rate criteria and secondary outcomes reported

<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Therapeutic Effective Rate Criteria</th>
<th>Secondary outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han, 2010 (375)</td>
<td>2002 guideline(^1)</td>
<td>Adverse events</td>
</tr>
<tr>
<td>He, 2009 (376)</td>
<td>Cure: All lesions disappear; Significant improvement: &gt;60% lesions disappear; Improvement: &gt;30% lesions disappear; No improvement: &lt;30% lesions disappear, or clinical symptoms worsen.</td>
<td>Not stated</td>
</tr>
<tr>
<td>Li, 2002 (176)</td>
<td>Samuelson grading system(^2)</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

\(^1\) 2002 Guideline: Cure: 90% lesions disappear, all clinical symptoms disappear; Significant improvement: 60%–89% lesions disappear, clinical symptoms significantly improved; Improvement: 30–59% lesions disappear, clinical symptoms improved; No Improvement: <30% lesions disappear, or clinical symptoms worsen.

\(^2\) Samuelson Grading: If grading \(\geq 3\): Significant improvement: grading decrease 3 levels; Better improvement: grading decrease 2 levels; Improvement: grading decrease 1 level; No improvement: grading no change; Worsen: if grading increase 1–2 levels.

If grading \(< 3\): Significant improvement: lesion count decrease 90%; Good improvement: lesion count decrease more than 70%; Improvement: lesion count decrease more than 50%.
<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Therapeutic Effective Rate Criteria</th>
<th>Secondary outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu, 2011 (378)</td>
<td>Cure: &gt;95% lesions disappear; Significant improvement: &gt;60% lesions disappear; Improvement: &gt;20% lesions disappear; No improvement: &lt;20% lesions disappear.</td>
<td>Not stated</td>
</tr>
<tr>
<td>Mo, 2005 (380)</td>
<td>Standard of Diagnosis and Therapeutic Effect of TCM Diseases¹ 中医病证诊断疗效标准</td>
<td>Not stated</td>
</tr>
<tr>
<td>Tang, 2011 (287)</td>
<td>Cure: All lesions disappear; Significant improvement: &gt;80% lesions disappear, new lesions &lt;5, improvement of oily face, slight itchy sensation; Improvement: &gt;30% lesions disappear, new lesions &lt;10, slight improvement of oily face and itchy sensation; No improvement: &lt;30% lesions disappear, or clinical symptoms worsen.</td>
<td>Adverse events</td>
</tr>
<tr>
<td>Wu, 2011 (336)</td>
<td>2002 guideline</td>
<td>Adverse events</td>
</tr>
<tr>
<td>Liu, 2015 (379)</td>
<td>2002 Guideline</td>
<td>Not stated</td>
</tr>
<tr>
<td>Zhang, 2014 (175)</td>
<td>1994 Guideline²</td>
<td>Adverse events</td>
</tr>
</tbody>
</table>

¹ Standard of Diagnosis and Therapeutic Effect of TCM Diseases: Cure: all lesions disappear, all clinical symptoms disappear; Significant improvement: >70% lesions disappear, clinical symptoms significantly improved; Improvement: 30–70% lesions disappear, clinical symptoms improved; No improvement: <30% lesions disappear, or clinical symptoms worsen.

² 1994 Guideline: Cure: lesions and symptoms disappear; Improved: ≥30% lesions heal, symptoms improved; Not improved: <30% lesions heal, symptoms not improved.
<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Therapeutic Effective Rate Criteria</th>
<th>Secondary outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>You, 2014 (381)</td>
<td>2002 Guideline</td>
<td>Severity grading: Global Acne Grading System</td>
</tr>
<tr>
<td>McKee, 2004 (174)</td>
<td>Not applicable</td>
<td>Photographic grading.</td>
</tr>
<tr>
<td>Kim, 2012 (377)</td>
<td>Not applicable</td>
<td>Skindex-29; photographic grading; Korean Acne Severity Scale.</td>
</tr>
</tbody>
</table>

**Figure 8.3 Forest plot of TER ≥30 per cent change in symptoms acupuncture**

One study (380) used viaminate (a retinoid vitamin A derivative), which is only recommended in Chinese treatment guidelines. When this study was excluded from the meta-analysis of TER ≥30 per cent change in symptoms, there were only minor differences in the results, although
heterogeneity increased fourfold (three studies, RR: 1.07 [95 per cent CI 0.93, 1.23], \( I^2=36 \) per cent, compared to four studies, RR: 1.07 [95 per cent CI 0.98, 1.17], \( I^2=8 \) per cent).

Figure 8.4 presents the forest plot for TER \( \geq 50 \) per cent change in symptoms. In the meta-analysis of the data from the trials that used \( \geq 50 \) per cent TER, the chance of a 50 per cent or greater change in lesion count in the acupuncture group was not statistically different to the pharmacotherapy group (retinoids and antibiotics) (six studies, RR: 1.07 [95 per cent CI 0.98, 1.17], \( I^2=50 \) per cent) (176, 336, 375, 378, 379, 381); however, there was moderate to substantial heterogeneity. In the subgroup analysis, the chance of a 50 per cent or greater change in lesion count in the acupuncture group was not different to the retinoid group (isotretinoin and topical tretinoin) in four studies (four studies, RR: 1.05 [95 per cent CI 0.93, 1.17], \( I^2=59 \) per cent) with moderate to substantial heterogeneity (336, 375, 379, 381). Two AA trials were not combined in subgroup analysis due to differences in comparator types (one comparator was an oral pharmaceutical and the other was a topical preparation). AA was more effective compared to oral tetracycline for TER \( \geq 50 \) per cent (one study, RR: 1.15 [95 per cent CI 1.02, 1.31]) (176); however, there were four times more participants in the intervention group compared to the comparator group with no reasons provided. Another study of AA found no benefit compared to topical benzamycin (one study, RR: 1.12 [95 per cent CI 0.88, 1.43]) (378).

### 8.4.5 Secondary outcomes

The study by Kim and Kim (377) was the only trial to report on HRQoL, using Skindex-29 score. The data was not presented in a way that permitted re-analysis, so the effects remain unclear. This study included four arms: CHM Keigai-rengyo-to alone, acupuncture alone, Keigai-rengyo-to plus
acupuncture and a wait-list control. The authors combined the results and did not separate the herbal results and the acupuncture results. The study authors were contacted but no response was received. The study authors concluded that the use of acupuncture and Chinese herbal medicine *Keigai-rengyo-to* could be used for inflammatory acne lesions but that further research was required.

A total of 127 AEs were reported in three trials (177, 336, 375). The other nine trials did not mention any AEs. There were more AEs in the control group (98 in the control group, 29 in the intervention group). AEs in the intervention group included painful sensation (11 cases), ecchymosis (9 cases), flushing (5 cases) and itchy sensation after needle withdrawal (4 cases), which are common AEs seen after needle penetration and acupressure (383, 384). In the control
group, AEs that included dry mouth (75 cases), dry skin and desquamation (17 cases) and gastrointestinal discomfort (6 cases) are also common AEs following topical benzoyl peroxide and retinoid treatment (28, 385). No SAEs were reported in the included trials.

8.5 Discussion

This SR showed that the chance of ≥30 per cent and ≥50 per cent improvement in acne symptoms with body acupuncture, EA and AA was not statistically different from that of pharmaceuticals for acne vulgaris. Interestingly, the magnitude of the treatment effect and the 95 per cent CI were the same for the primary meta-analyses, regardless of which criteria were used to measure clinical change. There were more AEs in the pharmacotherapy/control group than in the acupuncture/intervention group. Based on the included studies, acupuncture was well tolerated by participants with acne vulgaris.

TER is a common measure of effect in CM trials. The TER for acne vulgaris is a subjective outcome that includes a change in lesion count and/or severity. It is not clear whether this outcome measure has been validated. The Chinese research guidelines for acne from 2002 (311) suggest a ≥50 per cent change in lesion count or severity, whereas the 1994 guidelines (167) suggested ≥30 per cent change in lesion count and symptoms. In this review, acupuncture was as effective as antibiotics in trials that used the TER criterion of a ≥30 per cent improvement in symptoms. In the trials that used a ≥50 per cent improvement in symptoms, AA was as effective as antibiotics, and acupuncture was as effective as topical and oral retinoids. There is currently no consensus on outcome measures for acne, although there are efforts underway to standardise them (99). There was only one trial that reported on an HRQoL measure, the Skindex-29, even though there is
mounting evidence that sufferers of acne vulgaris may experience a considerable psychological and emotional burden (59).

All trials in the quantitative analysis used retinoids or antibiotics as the comparator. Retinoids and antibiotics have demonstrated efficacy for acne (28); however, long-term antibiotic use can contribute to antibiotic resistance (386). Retinoids have SAEs such as teratogenicity and should be used with caution in people of childbearing age (13). Acupuncture and AA were shown in this analysis not to be statistically different to guideline-recommended treatments but with fewer side effects, and may be an option for those wanting an alternative treatment to pharmaceuticals. Treatment times varied considerably across the trials. Such variations in treatment times could have introduced clinical heterogeneity. The typical treatment duration for body acupuncture is 20 to 30 minutes for each treatment and treatment frequency may vary from one to five times per week depending on the local clinical practice environment. Fibromyalgia and tension headache studies have found 20 to 30-minute needle retention, repeated stimulation on acupuncture points (the de-qi sensation) and daily or twice weekly treatment to have better clinical outcomes compared to less needle retention time and once-weekly treatment (387, 388).

The findings of this review are similar to those of previous reviews (18, 185); however, previous reviews included trials that compared CM interventions against each other such as acupuncture compared to herbal medicines. This review faced the same limitations as the others in terms of the methodological quality of the included trials. The methodological quality of the included studies was low, with four of the twelve studies assessed as having high risk of bias and three unclear in...
the domain of sequence generation. There was also insufficient information on the blinding of outcome assessors and participants.

Sample sizes were small and none of the included studies reported sample size calculations. Not all trials reported on the severity of lesions. There were no follow-up assessments in the included trials. Statistical heterogeneity was also detected in several subgroup analyses, but was not able to be explored due to the small numbers of studies. Detailed reporting of trial information was lacking; none of the trials addressed all items from the Consolidated Standard of Reporting Trials (CONSORT) (389) or STRICTA (316) standard reporting conventions. The STRICTA guidelines are important in order to improve the transparency of intervention reporting in acupuncture clinical trials. The lack of standardised reporting in included studies can pose an issue with the reproducibility of studies and may be a source of bias. Reporting of such details would enhance accurate analysis and interpretation of data, and improve research reliability in acupuncture interventions (390). GRADE was not applied to the acupuncture SR due to time constraints at the time of publication of the manuscript.

8.6 Conclusions

There was no statistical difference in the efficacy of acupuncture compared to pharmacotherapies for acne vulgaris; however, acupuncture interventions reported fewer AEs. Poor methodological quality of trial designs and lack of consistent reporting of outcome measures from some trials were found in this review; therefore results should be interpreted with caution. Future trials should include rigorous methodological design and reporting should follow standard reporting
conventions such as CONSORT and STRICTA. QoL measures and further investigation of the mechanisms of acupuncture on acne should also be considered in future studies.

8.7 Implications for future research

Many of the limitations of the studies included in this review were also identified in the SR of *Pi Pa Qing Fei Yin* (see Chapter 7). The key considerations for studies of both CHM and acupuncture include:

1. Proper randomisation, allocation concealment and blinding methods (see below)
2. Use of health-related quality of life questionnaires specific to acne as outcome measures
3. Comparing interventions with like controls such as sham acupuncture or placebo needling and, if using pharmacotherapy for controls, use of guideline-recommended treatments at the correct dosage for the correct age group as controls.

For further discussion of these issues, see section 7.8 in Chapter 7.

In addition to the above items, future acupuncture studies should provide reasoning for the selection of acupuncture points, and consider a standardised time for treatment duration and treatment period. Standard acupuncture needle retention time and treatment frequency in Australia are normally 20 to 30 minutes every day for ten treatments (391). One study had a 4 to 5-hour treatment duration five times per week. Having standard treatment times may help to reduce clinical heterogeneity and facilitate translation of research findings into clinical practice. Having interventions and controls that appear the same or similar is recommended for rigorous evaluation
of treatment efficacy (392-394). Future trials should consider using placebo needles or sham acupuncture as controls.

8.8 Implications for clinical practice

The meta-analysis of results showed that there was no statistical difference between acupuncture and related manual techniques and pharmacotherapies. Acupuncture may be an alternative treatment for those seeking treatment other than pharmacotherapies. Acupuncture had fewer AEs than pharmacotherapies. AEs with acupuncture were similar to those encountered in acupuncture practice. Acupuncture AEs included bleeding, bruising and itching at needle sites. Minimising pain and bleeding while performing acupuncture is a common goal for practitioners. Strategies such as using the correct needle size for the patient, improving acupuncture skills and using a longer duration of applying pressure to the acupuncture point upon needle withdrawal, particularly when using face points, will minimise pain, bleeding and bruising.

Both auricular acupuncture/acupressure trials and body acupuncture trials featured in this review. Results were similar for both; therefore practitioners should consider using AA for those who have a fear of needles. Acupuncture points featured in the review include textbook-recommended acupuncture points such as CV13 Shangwan, CV12 Zhongwan, CV4 Guanyuan, CV6 Qihai. Ashi points were also used in four studies, which conforms with clinical practice using points on or near the affected area. Common auricular points included CO18 Endocrine (Neifenmi), CO14 Lung (Fei), AH6a Sympathetic (Jiaogan), CO4 Stomach (Wei), CO7 Large Intestine (Dachang), TF4 Shenmen and may be an alternative to body acupuncture points.
8.9 Chapter summary

This chapter summarises the findings of the SR and meta-analysis conducted of RCTs of common acupuncture and related techniques for acne vulgaris. Overall, acupuncture was no different to pharmacotherapies for the treatment of acne, although the methodological quality of the included studies was low. As with the PPQFY review, only one trial used HRQoL as an outcome measure. More studies are needed in order to understand the impact of acupuncture and related manual techniques on the HRQoL of people with acne.
CHAPTER 9: Pi pa qing fei yin for acne vulgaris: A trial protocol

Overview

This project has reviewed the current literature and has summarised the epidemiology, diagnosis, pathophysiology and treatments for acne vulgaris (Chapter 2). The project also described CM theory underpinning acne vulgaris and summarised the different types of CM treatments prescribed for acne (Chapter 3). Chapter 4 showed that many people who have acne vulgaris may be significantly affected by their acne emotionally, socially or psychologically. There are numerous instruments used to measure the impact of HRQoL however there is no consensus on which instrument should be used in clinical practice and for research.

A survey was conducted to provide current data on how acne affects HRQoL of Australian young people and adults (Chapter 5). It also acquired data on the types of CM treatments people with acne would find acceptable. The respondents to the survey were under 45 years old, most with mild to moderate acne. People with self-reported moderate acne were more emotionally affected and worried about their acne. Chinese medicine treatment preferences suggested that CHM or acupuncture treatment for four to eight weeks would be acceptable, which reflects clinical practice. The SRs (Chapters 7 and 8) have shown that CHM formula PPQFY has a greater effective rate than pharmacotherapies though acupuncture is no better but no worse than pharmacotherapies. Both reviews found the quality of the included trials were low with many methodological issues identified in the trials. This chapter focuses on a trial protocol to address the methodological issues highlighted in the SRs, such as randomisation and allocation of participants, blinding of participants and researchers, using appropriate controls, and herbal medicine quality control. The use of syndrome differentiation will assist translation of trial findings into clinical practice, and
the primary outcome will be HRQoL. The formula PPQFY will be used as an exemplar for conducting a CM trial.

9.1 Introduction

People with acne can be emotionally, socially and psychologically affected by their skin condition (190, 192, 216). There is a negative perception of acne (200) and it can have a significant impact on HRQoL (74). Improving HRQoL should be a goal of healthcare in clinical treatment (395). Using patient HRQoL information can lead to optimised care and help with decisions on treatment (126, 222) and facilitate patient-centred care (395).

There has been a Cochrane review on CAM for acne which included CM modalities (157), two systematic reviews on CM for acne (18, 185) and two conducted as part of this project. All reviews found that the randomised trials included in the reviews were mostly of low quality. Many of the studies compared CHM to CHM or other acupuncture related techniques, comparing unknown effects against others. There were also poor randomisation and blinding procedures in the included trials. Therefore, more rigorously designed studies are needed to address these methodological flaws and to confirm the clinical efficacy of acupuncture and CHM for acne. All reviews also found few trials used HRQoL as an outcome measure. Therefore, there is a need for a rigorously designed trial to assess the efficacy of CM treatment in reducing acne severity and improving the HRQoL of people with acne.

Chapter 5 details the preferences of survey participants in relation to CM treatments. In terms of acceptability of treatment, there was a slightly higher preference for CHMs (topical) over
acupuncture treatment. Participants preferred topical treatments (cleansers) over oral pills or tablets (72.2 per cent). Respondents also preferred oral pills and tablets over granules and raw herbs. This is similar to clinical practice. Pills and tablets are more popular than raw herbs. Raw herbs require more time for preparation and both raw herbs and granules are less palatable to some, whereas swallowing pill and tablets is quick and the taste of herbs is not as strong. Participants preferred taking herbs once daily. In clinical practice, oral CHM would be prescribed twice to three times daily depending on the different forms of herbs. Oral decoction is prescribed twice daily, and capsules, pills and tablets are usually three times daily. For treatment length, survey respondents preferred four weeks (26.1 per cent) to eight weeks (21.7 per cent) of CHM treatment, which is similar to the length of time used in the trials included in the SR (Chapter 7). Treatment duration in clinical practice is dependent on acne severity. A typical course of herbal treatment for acne is twice daily herbs over one to three months (159). In acupuncture preferences, 60.9 per cent preferred body acupuncture and 95.7 per cent would like the treatment to be weekly or fortnightly. More participants also preferred a treatment period of four to eight weeks for acupuncture. The frequency and duration of treatment are similar to clinical practice.

The methodological issues outlined in Chapters 7 and 8 included lack of proper randomisation, no sample size calculations, lack of blinding of participants and personnel, and lack of reporting against recommended trial guidelines. This trial protocol is developed, using PPQFY as a case example, to improve the quality of evidence for CM effects on HRQOL in people with acne. There have also been no SRs published in English and none on Pi Pa Qing Fei Yin (PPQFY) alone without modification of the original ingredients. The SR described in Chapters 7 and 8 showed that PPQFY-based treatments achieved a higher reduction in lesion count than various
pharmacotherapies, while acupuncture showed no difference. In addition, the subgroup analysis of PPQFY alone (which included herbs from the original formula and modifications based on syndrome differentiation) showed greater improvement than pharmacotherapies, whereas, studies that combined other topical or oral formulations did not. Although the first preference in Chapter 5 was for topical CHM, the evidence from the systematic review for PPQFY was for the oral route of administration, and not topical. Oral herbal medicine was the second preference from survey respondents. Therefore, with the evidence from the SRs, the trial protocol will include oral PPQFY.

This chapter presents an RCT protocol and details the steps used to develop the protocol. The findings from the survey described in Chapter 5 have informed the design of this trial protocol, as have the SRs of CHM and acupuncture described in Chapters 7 and 8.

9.2 Trial justification

The SRs in Chapter 7 and Chapter 8 have highlighted methodological shortcomings in previous research. These include a lack of rigorous study design and a lack of reporting against guidelines such as STRICTA and CONSORT. This trial protocol will improve on trial design by including more rigorous randomisation procedures, sample size calculations, allocation concealment and blinding procedures, which were rarely described in the trials included in the SRs. This trial protocol will follow the recommendations on reporting according to CONSORT and in particular the CONSORT Extension for Chinese Herbal Medicine Formulas (396).
In addition, there were only two CM RCTs in the SRs that used HRQoL as an outcome measure (331, 377). The HRQoL instruments used were not acne-specific. There is a need to fill this gap in acne research in CM. The gaps identified in the SRs relating to trial design are addressed to improve the quality of CHM research in acne vulgaris. Details of the trial design can be found in section 9.5.

9.3 Aims

This trial protocol aims to:

1. Develop rigorous trial procedures informed by existing evidence and consumer preferences; and

2. Ensure the trial protocol meets the reporting standards of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).

9.4 Research questions

1. Does the Chinese herbal medicine *Pi Pa Qing Fei Yin* improve the health-related quality of life of people with acne vulgaris compared to placebo?

2. Does the Chinese herbal medicine *Pi Pa Qing Fei Yin* decrease lesion count and severity in people with acne vulgaris?

3. Does *Pi Pa Qing Fei Yin* decrease the *Propionibacterium acnes* count on the skin of people with acne vulgaris?

4. Is *Pi Pa Qing Fei Yin* safe to use in people with acne vulgaris?
9.5 **Trial design**

This protocol is for a prospective, randomised, double-blind, placebo-controlled trial using PPQFY as the intervention. A summary of the inclusion criteria for participants, the interventions, controls and outcome measures and the rationale for selection are described. The implementation of the trial does not form part of this PhD project. Prior to undertaking this trial, researchers will be responsible for obtaining funding and complying with all ethical and regulatory requirements for a clinical trial.

9.5.1 **Participant inclusion and exclusion criteria**

The target study group is people:

1. Diagnosed with mild-to-moderate facial acne vulgaris (with or without other areas affected) as defined by the American Academy of Dermatology (AAD): an inflammatory disease of the pilosebaceous units in the skin of the face, neck, chest and upper back (28)
2. Of any gender
3. Who are adolescents and young people (15 to 24 years old), as defined by the United Nations (UN) (United Nations, 2008) or adults (25 to 45 years old)
4. Who meet the Chinese medicine diagnosis criteria of heat in the Lung; and
5. Who give written consent to participate in the trial.

Participants will be excluded if they:

1. Are under the age of 15 or over the age of 45
2. Are unable to read or speak English
3. Are unable to give informed consent or obtain consent from parents or guardians to participate in the trial
4. Have endocrine-related acneiform (polycystic ovarian syndrome, PCOS), rosacea, chloracne, acne varioformis, acne tropica, acne venenata, acne necrotica miliaris or acneiform eruptions from drugs
5. Have acne severity greater than 4 using the Comprehensive Acne Severity Scale (CASS)
6. Have used any Chinese herbal medicines within the previous three months
7. Have known allergies to the Chinese herbal medicine or placebo ingredients
8. Are females who are pregnant or planning to become pregnant during the trial, or females who are breastfeeding; or
9. Have severe medical conditions including heart, liver or kidney disease.

9.5.2 Participants

Eligible participants will be people aged 15 to 45 with facial acne diagnosed according to the AAD guidelines and the CM syndrome of heat in the Lung.

9.5.2.1 Rationale for participant selection

Acne begins at adolescence but can continue into adulthood, with higher occurrence of acne reported in 15- to 17-year-olds (22, 23). According to Australian legislation, children under 18 years old have limited competence or capacity to make independent decisions about their health care (397). However, a child between 14 (South Australia) and 16 (New South Wales) can validly consent to their own treatment in some states in Australia as they may be “capable of understanding
the nature, consequences and risks” involved in medical treatment (397, 398). Consent to participate in a trial from a parent or guardian would still be required.

Acne is reported to be most prevalent in the 12- to 24-year-old age group, but reports of adult onset acne are increasing (1), with acne reported in 64 per cent of adults in their 20s and 43 per cent in their 30s (76). It is rare for people over 45 to have acne. They are also more likely to have other medical conditions and higher risk of comorbidities (399). Therefore, due to the prevalence and capability of adolescents to understand the medical intervention, adolescents 15 years and older, young people and adults between 25 and 45 will be the target participant group.

9.5.2.2 Chinese medicine diagnostic criteria

The CHM PPQFY used in this trial is traditionally prescribed to people with the CM diagnosis of heat in the Lung (see Chapter 3) (159), which corresponds to the comedonal type acne. In this syndrome, open and closed comedones (including red papules and pustules) are distributed mainly around the cheeks, forehead and nose, and may also involve the chest and back. Shiny, oily skin and a dry mouth and nose may also be present. The tongue body is red with a thin yellow coating and the pulse is floating.

CM practitioners use a synthesis approach to diagnosis compared to WM practitioners who use a reductive approach (400). In evaluating evidence for CM trials, practitioners may find modern research methods reductive and at odds with the traditional concepts of CM. Syndrome differentiation is a key concept (see Chapter 3, section 3.5) and individualised treatment according to syndrome differentiation is the cornerstone of CM treatment. Including syndrome differentiation
as an inclusion criterion in modern trials may be one way to bridge this disconnect from research to clinical practice (401).

Using syndrome differentiation as part of the inclusion criteria will limit the number of participants included in the trial, but will ensure that the results are relevant to clinical practice. As this trial protocol aims to be acceptable to participants and relevant to clinical practice, where syndrome differentiation is common, syndrome differentiation is a desired component of this protocol. The intervention proposed for this protocol is PPQFY (9.5.3), which addresses the CM syndrome heat in the Lung; therefore this syndrome will be an inclusion criterion.

The CM syndromes heat in the Stomach, stagnation of qi and Blood, and imbalance of Thoroughfare (Chong) and Conception (Ren) vessels describe lesions similar to those described for heat in the Lungs. However, the ingredients of PPQFY have not traditionally been used for these three syndromes; other herbs for these three syndromes are described in Chapter 3. Additional syndromes identified in Chapter 3 included damp toxins with Blood stasis and Blood stasis with binding of phlegm. Lesions seen with the syndrome damp toxins with Blood stasis include nodules and cysts that are deep, painful, inflamed and pus-filled. Lesions with the syndrome Blood stasis with binding of phlegm include nodules and cysts that are 3–5 mm, red to purple in colour and soft on palpation. The description of these lesions would correspond to the severe acne severity grading. Therefore people diagnosed with these syndromes will be excluded.

Acne vulgaris is defined as a “chronic inflammatory dermatosis notable for open or closed comedones (black and whiteheads) and inflammatory lesions, including papules, pustules and
nodules (also known as cysts)” (28). Although many of the trials in the SR in Chapter 7 did not exclude participants with severe acne, the intended Chinese herbal formula PPQFY is traditionally used for mild-to-moderate comedonal acne. The symptoms listed in the above syndrome differentiation correspond to mild-to-moderate severity gradings (see Chapter 2) in the IGA tool (107), the GAGS (106) and the CASS (108). Therefore, to reflect clinical practice, the participant inclusion criteria will be mild-to-moderate acne. Severity grading will be made by a study dermatologist using the CASS (108), which is a modified and validated version of the IGA tool (107). Acne conglobata, acne venenata and acne necrotica miliaris are considered to be greater than grade 4 severity on the CASS (108).

9.5.3 Intervention

The intervention will be the Chinese herbal formula Pi Pa Qing Fei Yin (PPQFY).

9.5.3.1 Rationale for intervention selection

The intervention was selected based on the SRs described in Chapters 7 and 8, and after considering participant preferences in Chapter 5. In the literature review of CHM (Chapter 3), PPQFY was recommended in key CM clinical guidelines and textbooks, and was also the most frequently used in clinical studies (168). The SR on CHM PPQFY (Eriobotrya Japonica Formula; see Chapter 7) found the number of people achieving a reduction in lesion count was higher with PPQFY compared with various pharmacotherapies. The greatest effect was found when the original formula was modified, rather than combined with other formulations of CHM (for example, topical or oral). There were no SAEs reported, suggesting that the formula was well tolerated. Experimental studies also showed that all six ingredients of PPQFY may have an effect
in decreasing inflammation, sebum production and hyperkeratinisation. These herbs showed an inhibitory effect on *P. acnes*, as well as preventing *P. acnes* from adhering to host cells *in vivo* and *in vitro* (Chapter 7).

Clinically, patients are frequently prescribed oral CHM and topical CHM at the same time. The SRs did not find evidence that the combination of topical applications and oral CHM was more effective than pharmacotherapies. Further, there was only one experimental study identified relating to the mechanisms of action of topical herbs with topical *Ren shen* (*Panax ginseng* C.A. Mey.) preventing *P. acnes* from adhering to host cells (340). Therefore, topical CHM will not be included in this protocol (159, 165).

The second SR was conducted on acupuncture and acupressure for acne. This review found that there was no statistical difference in the efficacy of acupuncture compared to pharmacotherapies; however, acupuncture interventions reported fewer AEs. Again, the quality of the evidence was low. In the subgroup analysis of AA compared to oral tetracyclines, AA was more effective than tetracycline; however, there were four times the number of people in the AA group compared to the tetracycline group. Acupuncture has been found to decrease inflammation in animal studies (371, 372) and auricular acupuncture may reduce acne inflammation through regulating innate and adaptive immune responses (370). As the SR found more promising evidence for PPQFY than for acupuncture, acupuncture was not selected as the intervention for this trial protocol. Clinically and in CM textbooks (159, 165), CHM is considered the main treatment method and acupuncture is used as an adjunct therapy.
PPQFY oral capsules will be used (see 9.7.1 for details of ingredients and dosing). Each capsule will contain 0.5 g of the granulated herbal ingredients (refer to section 9.7.1). Adult participants 18 to 45 years old will be prescribed four capsules twice daily (total of 4 g daily) over an eight-week treatment period. An eight-week treatment period was a common period encountered in previous trials (Chapter 7) and it was also the preferred period by respondents in the survey conducted in this project (Chapter 5). A recent protocol also considered the effect time of the intervention (although no details were given on how this was determined) and tolerability and compliance by participants (402). The CHM Advanced Textbook on Traditional Chinese Medicine and Pharmacology, Volume II (403) age-to-dose guidelines suggests a dose range of two-thirds to the total adult dosage for children aged 14 to 18 years. Two capsules is half the adult dosage and, as it is not possible to give half-capule dosages, younger participants 15 to 17 years of age will be given three-quarter dosage, that is, three capsules twice daily (total of 3 g daily). This is still within the recommended dosing for this age group.

All capsules will be wholly enclosed opaque capsules to prevent tampering and decrease visibility of the ingredients inside the capsules in order to maximise blinding. Having wholly enclosed capsules will also decrease the risk of the capsules breaking open and the ingredients being identified. Although the respondents from the survey preferred pills and tablets, capsules are another form of preparation which is swallowed whole and are a similar size and shape to tablets. Capsules are generally softer than tablets and pills, and so easier to swallow. They also mask the smell of herbs better than tablets or pills. One study looking at the blinding of capsules of ginger compared to placebo found the participants were not able to determine which type of capsule they received, but were able to distinguish them from the smell inside of the bottles (404). The study
suggested using blister packs to prevent the smell of ginger from breaking the blinding. In a pharmacokinetic study comparing the bioequivalence of pirfenidone tablets and capsules, the investigators found the larger 801 mg tablet was similar to three 267 mg capsules (405). Bioequivalence in this example was dependent on the dosage of tablets and capsules, and not the type of preparation. In extension, there is no difference in the bioavailability of capsules compared to tablets. Therefore, for this study, using smaller capsules will improve blinding, making them easier to swallow in order to improve compliance.

CHM is traditionally prescribed in raw form. With modern processing methods, granulated and powder concentrated herbs are now commonly prescribed. The convenience of not having to boil up herbs is more acceptable to patients in clinical practice and compliance is higher. Granulated and powdered herbs are extracted using water or alcohol extraction methods usually at an average concentration ratio of 5:1. Based on the calculations of the herb ingredients (section 9.7.1), the daily dosage of the herbs would be 4 g per day for adults and 3 g per day for children aged 15 to 17.

Capsules come in various sizes and the smallest is 0. As children will be included in the trial, the smallest size is more appropriate as they would be easier to swallow. Since the smallest size would hold less herbs, around 0.5 g, adult participants would need to take four capsules twice daily and participants aged 15 to 17 would need to take three capsules twice daily. Most people would not be amenable to taking eight capsules at a time. Traditionally, the recommended dosing for CHM is twice to three times daily (403). In modern practice, twice daily is more common as most patients would be at either school or work and so would have less opportunity or forget to take a dose in
the middle of the day. Thus, practitioners in clinical practice prescribe twice daily, at breakfast and dinner time. In addition, given that most AEs reported in the CHM review (Chapter 7) were gastrointestinal symptoms, taking eight capsules at a time can increase the chance of AEs. Therefore, to minimise the risk of gastrointestinal AEs and to improve compliance, four capsules twice daily will be prescribed for adults and three capsules twice daily for participants aged 15 to 17.

9.5.4 Comparator

The comparator will be placebo capsules made from a vegetable corn/potato starch that does not include any active constituents. Placebo capsules will look, taste and smell the same and be the same colour as the intervention.

9.5.4.1 Rationale for comparator selection

Most studies in the SR of PPQFY used active controls of current guideline-recommended treatments. Actively controlled studies require more participants for statistical power (406). The number of participants in individual CHM trials for acne described in the Evidence-based Clinical Chinese Medicine monograph (168) ranged between 30 and 320 (median 90). For some trials, the number of participants may not have enough statistical power to determine non-inferiority to current treatment controls. In pragmatic study designs, multiple interventions or comparators can be used (see Figure 9.1 for example). Pragmatic study designs are ideal, but require larger numbers of participants and so are more expensive to conduct (407, 408). Pragmatic study designs also increase variance in studies and so it is more difficult to determine efficacy (407). It is suggested
that pragmatic study designs would be useful for determining dosing in real-life situations, rather than determining efficacy (409).

Figure 9.1 Example of pragmatic design for acne (adapted from Buch et al. (409))

Another patient-centred study design is the Bayesian and adaptive study design, which suggests calculating results throughout the study and adapting the study according to the results as the trial progresses. This would lessen the time to determine benefits (410) and is particularly useful for assessing rare diseases or subgroups of participants underrepresented in recruitment. Acne is a polymorphic multiple pathogenesis condition and a very common dermatological condition. Adaptive trials such as the Bayesian design are resource intensive and require significant investment in planning, modelling and statistical analysis. It is also difficult to create a balance between patient needs and determining efficacy in a trial. Therefore the Bayesian model will not be suitable for this trial, which is aiming to determine the efficacy of PPQFY.
Efficacy (explanatory) trial designs have limitations in extrapolating findings to real-life situations (409). Explanatory trials are considered the gold standard, as they minimise confounders and bias, are able to provide clear comparison of experimental intervention compared to control, and determine clinical equivalence (409, 410). Clinical trials using like interventions with like controls provide a rigorous evaluation of treatment efficacy (392-394). Although CHM has been used in clinic settings for millennia, this does not necessarily indicate efficacy.

The recommendations for determining efficacy are to compare like interventions with like controls (393, 394). Only a few studies from both the CHM and acupuncture reviews (Chapters 7 and 8) used placebo controls. As this trial aims to determine the efficacy of PPQFY, a placebo control treatment arm will be used. Therefore, this trial design will use PPQFY as the intervention and a placebo as the control. The comparator will be a placebo capsule with vegetable starch that has no active ingredients and has a similar appearance, packaging, colour, smell and taste to the intervention to reduce bias (396, 411).

The NHMRC’s National Statement on Ethical Conduct in Human Research update in 2018 states that it is unethical to withhold treatment if there is known risk of significant harm in the absence of treatment (412). Acne is not considered a life-threatening condition, although it does have a large impact on HRQoL. Not everyone with acne will seek medical treatment and some will use over-the-counter products only (222). Therefore a lack of treatment with an active control such as pharmacotherapies is unlikely to pose serious harm and therefore a placebo control is considered an appropriate comparator.
9.5.5 Primary outcome measures

The primary outcome measure will be HRQoL using the Acne-QoL (119, 121, 205). The change in domain scores from baseline (week 0) to end of treatment (week 8), and from baseline to end of follow-up (week 12), will be compared between the two groups.

9.5.5.1 Justification of selection of primary outcome

Acne-QoL is the most used HRQoL tool in clinical trials (228). It is a validated tool that assesses the HRQoL of people with facial acne. It has 19 questions in four domain areas: self-perception, role-social, role-emotional and acne symptoms, which assesses feelings about acne, medication usage and social interaction. Questions include how unattractive, embarrassed, self-conscious or upset people feel about their acne. The questions use a seven-answer code ranging from 0 (‘extremely’ or ‘extensively’) to 7 (‘not at all’ or ‘none’). The domains of self-perception, role-emotional and acne symptoms are scored from 0 to 30, and the role-social domain has a maximum score of 24. Higher scores indicate better HRQoL. Acne-QoL is a self-administered tool that takes approximately 10 minutes to complete. After permission for use has been obtained, administration of the Acne-QoL will follow the instructions given by the developers. The Acne-QoL is recommended by the European Academy of Dermatology and Venereology Task Force on Quality of Life and Patient Oriented Outcomes and Acne, the Rosacea and Hidradenitis Suppurativa (228) and other reviewers of acne HRQoL instruments (253, 254). Therefore the Acne-QoL is well suited to assessing the HRQoL outcome of this trial.

There is one other acne-specific validated HRQoL instrument for facial acne, the Acne-QOLI (118). It is more commonly used for clinical purposes than for research (254). Other acne-specific
and dermatological HRQoL tools have been recommended by the above organisations and publications. The Skindex-29 and DLQI are dermatology-specific tools validated for acne. However, they are not specific to acne and include questions that may not be relevant to acne, such as about itching (refer to Chapter 4). The CADI has also been used in acne trials and is recommended for routine clinical practice and trials (228), but it is not specific to facial acne.

9.5.6 Secondary outcome measures

Secondary outcomes will include photographic lesion counts, severity grading using the CASS, self-reported current medications, \(P.\text{acnes}\) levels present on the skin and AEs.

9.5.6.1 Lesion count

Lesion count will be assessed using photographs at baseline (week 0), end of treatment (week 8) and follow-up (week 12). Changes in lesion count will be compared between the two groups. Lesion count includes the entire face and the chin, and excludes the neck. The different types of non-inflammatory lesions (open comedones and closed comedones) and inflammatory lesions (papules, pustules and nodules) will be recorded.

9.5.6.1.1 Justification for including lesion count as a secondary outcome measure

Lesion count is a common objective outcome assessment used in clinical practice and research trials. Lesion counts include counting the number of open and closed comedones, papules, pustules and nodules, and inflammation. A table listing the different types of lesions will be used to record the count. Lesions are categorised into inflammatory and non-inflammatory, and a total count will be recorded at each visit. Inflammatory lesions are ruptured papules, pustules and nodules (open
comedones) that are often painful. Non-inflammatory lesions include closed comedones (papules, pustules and nodules) that have no redness or pain.

The process of identifying a lesion and counting can vary from assessor to assessor, as can severity assessment. Photographs of participants’ skin lesions may differ if the lighting or other factors change at each visit. This will be minimised by taking photographs at the same location with appropriate lighting and using the same equipment each time. To minimise the variability in assessment, standard definitions of lesion types and an image with a description will be used as standard examples. Research investigators will be given training on identifying and counting lesion types in order to improve reproducibility (111). An independent researcher will be responsible for lesion count.

9.5.6.2 Severity grading

The CASS will be used to grade acne severity. Severity will be assessed at baseline (week 0), end of treatment (week 8) and follow-up (week 12). Changes in severity from baseline to end of treatment and follow-up will be compared between the two groups.

9.5.6.2.1 Justification for assessing severity using Comprehensive Acne Severity Scale

The AAD has suggested that grading systems need to be reproducible, easy to use and accepted by dermatologists (145). Severity grading includes lesion size, density, type and the distribution and intensity of involvement of affected sites (413). The CASS was developed from the IGA by Tan et al. (108). The CASS can be used for lesions on the face, neck, chest and upper back. It has an ordinal grading scale that assesses overall severity based on the dominant lesions and extent of
inflammation and lesion distribution. Scoring ranges from 0 (no lesions or barely noticeable lesions) to 5 (very severe acne with highly inflammatory acne covering the affected area with nodules and cysts present).

The CASS also recommends photographic grading to provide an opportunity for review of lesions if there are discrepancies and for independent assessment. With modern photographic equipment and good lighting, photographic inconsistencies can be minimised. This grading scale has a high correlation with the Leeds photonumeric system and has a positive correlation with the Acne-QoL. As Acne-QoL will be used as a primary outcome measure for this study, this severity scale will be a suitable tool for severity grading.

The CASS includes both descriptive and numerical scales that have clear descriptions for assessing severity. It is flexible and comprehensive. A key advantage is that it does not rely on lesion count like other severity scales that grade severity. As the protocol already intends to record lesion count as a secondary outcome, this will not need to be repeated for determination of severity. It has been recommended for severity grading by the Malaysian MOH’s Management of Acne Clinical Practice Guidelines (126). To date, the CASS (108) is the only validated acne severity grading scale. Permission to use the CASS should be sought by researchers.

Various other instruments used for severity grading include photographs, descriptive text and ordinal scales such as 0 (mild) to 4 (severe) with descriptions, or a combination of these criteria (a summary can be found in Chapter 2). The Leeds system requires a more complicated photonumeric scale including 16 facial, 8 chest and 8 back categories which may be time-consuming to
administer. The CASS was better able to differentiate between the “clear” and “mild” categories compared to the Leeds system (108).

The GEA Scale (111) has a similar grading scale as the CASS with an ordinal scale of 0 (residual pigmentation and erythema may be seen) to 4 (entire face is involved, covered with many papules and pustules, open or closed comedones and rare nodules). It is a photographic evaluation of severity for juvenile facial acne. This trial will include participants from 15 to 45 years old; therefore the CASS is more suitable for this age group. The GAGS (106) separates the area of assessment into regions. Each region is given a numerical value of 1 to 4 based on the most severe lesion within that location. That number is then multiplied by the number of lesions in the region to allocate a global severity score. It does not take into consideration the density or intensity of lesions and is less suitable for grading in this trial.

**9.5.6.3 Propionibacterium acnes identification**

*P. acnes* count will be assessed at baseline (week 0), end of treatment (week 8) and follow-up (week 12) using the surface scrub technique. The changes in *P. acnes* will be compared between the two groups.

**9.5.6.3.1 Justification for Propionibacterium acnes collection technique**

*P. acnes* is a commensal gram-negative bacterium that lives on human skin. It is well documented that *P. acnes* is present in acne lesions (134, 414, 415) and may initiate inflammation that forms microcomedones (81). Skin punch biopsy is recommended to investigate the presence of *P. acnes* in the epidermis and hair follicles; this is a minor surgical procedure performed by a dermatologist
This technique is not feasible for this trial, as it is cumbersome and exposes the skin to chemicals, which can cause cross-contamination (415).

Gel biopsy is another technique used to collect skin samples. A gel is placed on the skin to form a polymerised adhesive. Due to variation in skin humidity, pH and environmental factors, this technique is hard to standardise (415). Sebum can also cause uncertain effects; therefore gel biopsy is not suitable for this trial. Materials that have direct contact with the skin such as pads or stripping tape have also been previously used to obtain *P. acnes* samples. This is non-invasive and able to obtain 14 layers of stratum corneum. Variation in tapes can lead to differences in the number of stratum corneum layers being removed, making it difficult to standardise the method (415).

A skin swab is quick and easy to perform, and provides useful information on the skin surface stratum corneum microbiota if the sample is taken directly from lesions (415); however, it is hard to standardise.

The surface scrub technique is non-invasive, using a blade to gently scrape the skin surface of a lesion in the same site in triplicate to minimise the quantification variations and make it easier to quantify. At each visit, sample sites will be chosen depending on the locations of lesions. Scrapings will be placed in a sterile, sealed pathology bag and sent for laboratory analysis. This technique will be used for this trial. The total number of *P. acnes* from the scrapings will be counted. As laboratories require patient samples be labelled with the patient’s details, the samples will be sent to a person not involved in conducting the trial to enter the data in order to ensure the blinding of assessors. A mean change in *P. acnes* count from baseline to end of treatment will be calculated.
(416) and the changes in *P. acnes* will be compared between groups. Appendix 17 provides an example of the *P. acnes* data collection form.

### 9.5.6.4 Medications used during the trial

Co-medication or concomitant medications will be allowed during the study period with the exception of prescribed oral isotretinoin. Oral isotretinoin is usually prescribed for people with severe acne. The inclusion criterion is mild-to-moderate acne and it is anticipated that people who are on oral isotretinoin will be excluded. Other oral and topical medications commonly prescribed for mild-to-moderate acne will be allowed. Oral prescription medications include antibiotics and contraceptive pills. Topical prescription medications such as BP with antibiotics or retinoids (Stieva A Cream) may also be used. Participants will be allowed to use other over-the-counter products such as Clearasil® or ProActive®. Participants will be required to record co-medications and other over-the-counter products used during the trial period.

### 9.5.6.5 Adverse events and safety monitoring

AEs will be documented on the case record form (CRF) by trial researchers. AEs will be categorised as expected or unexpected. An expected AE is a reaction known to be associated with the use of the herbs as reported in CHM pharmacopeia (369). An unexpected AE is defined as a reaction not identified or consistent with the use of the herb. SAEs are defined by the Australian Therapeutic Goods Administration (TGA) (417) as follows:

- results in death
- is life-threatening
- results in inpatient hospitalisation or prolonged hospitalisation
• results in persistent or significant disability or incapacity
• is associated with a congenital anomaly or birth defect; or
• is a medically important event or reaction.

Based on the SR of PPQFY, oral herbal medicines can cause some gastrointestinal discomfort including nausea or vomiting, stomach discomfort, diarrhoea and dry mouth. Another reported symptom is vertigo. Participants will be instructed to report AEs at any time during the trial to researchers, who will refer them to the trial doctor. The trial doctor will assess whether the AE is possibly, likely or unlikely to be related to the intervention. Participants will be referred to relevant medical intervention from their general practitioner, dermatologist or hospital as required. SAEs will be reported to the product manufacturer, the relevant institution Human Research Ethics Committees and the TGA as per the Good Practice Guidelines. They will also be recorded in each participant’s CRF. SAE reports will also be reviewed by the trial doctor, as will other AEs, to ensure participants are directed to the medical care needed.

For safety, participants will be requested to have a full blood examination incorporating renal and liver function tests at baseline and at follow-up. If an abnormal blood result is present at baseline, the investigators will refer the participant to the trial doctor to review their results and to assess whether it is safe for the participant to proceed in the trial or needs to be excluded from the trial. The trial doctor will determine whether the patient should also be referred to their relevant medical practitioner for further follow-up.
Liver and kidney functions tests will be conducted again at follow-up. The trial doctor will assess the clinical implications and determine the appropriate medical steps to take or refer as required. The participant will be followed up until the AEs have resolved or stabilised to ensure there are no further issues. Trial insurers should be notified to ensure future care needs are met.

9.5.6.6 Procedures for breaking codes

Emergency 24-hour access to the participant identification and treatment codes will be made available to authorised study investigators at the site of study. Should the need arise to unmask the treatment code, an authorised study investigator will have access to the treatment code with confirmation from one other researcher. Emergency unblinding will be documented.

9.6 Trial procedures

Trial participation will be for 12 weeks (Table 9.1). Participants will be asked to attend a total of four visits during this time. There will not be a run-in period, as the life cycle of acne lesions varies from week to week, and hence is unlikely to stabilise. The treatment period will be eight weeks, which is in line with other current CHM trials for acne (402) and was the preferred duration from the survey results. The recommended duration of treatment with interventions such as antibiotics is up to three months, with a change in treatment if there is little or no improvement after three months (126). The survey identified eight weeks as the preferred treatment duration (refer to Chapter 5). Many trials included in the SR also provided treatment for eight weeks (Chapter 7); this duration is considered a reasonable timeframe to see changes in acne.
9.6.1 Recruitment

Participant recruitment will include electronic and printed advertisements distributed through online and printed media. Printed advertisements will be sent with letters of introduction to general practices and dermatology specialists in the local Melbourne and wider metropolitan area informing them of the trial. Recruitment can be an issue, as indicated in Chapter 5. Additional strategies such as advertising in search engines, banner advertising on websites and other types of incentives for participants such as reimbursements or vouchers can improve recruitment (418).

Table 9.1 Trial schedule

<table>
<thead>
<tr>
<th>Assessment or procedure</th>
<th>Baseline (week 0)</th>
<th>Mid-treatment (week 4)</th>
<th>End of treatment (week 8)</th>
<th>Follow-up (week 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Screening &amp; randomisation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Informed consent</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CM diagnosis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Confirmation of eligibility &amp; randomisation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Acne-QoL</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lesion count</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CASS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>P. acnes</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Current medications</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Adverse events</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Medication dispensing</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Participant guess of blinding</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Individuals may contact the trial coordinators to obtain further information and the participant information and consent form (PICF). Interested individuals will attend initial assessment of eligibility and provide written informed consent.

9.6.2 Eligibility screening

Eligibility of participants will be checked against the inclusion criteria. Randomisation will be performed after confirming eligibility at the initial assessment. Individuals who meet the inclusion criteria and agree to participate in the study by signing the consent form will be assigned a participant number.

CM syndrome differentiation can vary between assessors (419). Procedures will be put in place to minimise assessor variation by using a participant-completed questionnaire about symptoms and signs. Study practitioners can then make a diagnosis using the information provided. Inter-rater reliability of the instrument will be conducted to determine the reliability of the CM diagnosis of the syndrome heat in the Lung. A number of different types of inter-rater reliability methods have been reported (420-423). Good inter-rater reliability requires practitioner training before trial commencement on the use of the questionnaire-based checklist and calibration of results between assessors using methods such as the Delphi process (424). Study investigators should discuss and calibrate their diagnoses prior to intake of participants. Based on previous studies, this may need to be done up to six times before a reduction in variability is seen (422).
9.6.3 Informed consent

Participants will be given a written plain-language statement and a verbal explanation of the study at the initial assessment. Prior to participants signing the consent form, any questions they have will be answered and signed written consent will be given in front of a witness. Participants who are under 18 years old will require a parent or guardian in attendance. Both the child and the parent or guardian will be given the written plain-language statement and the verbal explanation of the study. The consenting parent or guardian will sign the consent form in front of the witness with the agreement of the child.

9.6.4 Baseline assessment

Participants will be asked to fill out four questionnaires:

1. General information (demographics, general health status regarding current medical conditions, medical history, current and previous medications)
2. Screening questionnaire
3. Acne-QoL; and

Participants will also be asked to do a blood test for full blood examination, and liver and kidney function. As there is limited data on herbal medicine safety in pregnancy, serum human chorionic gonadotropin will also be measured in females of reproductive age to exclude pregnancy. Pregnancy is an exclusion criterion for the trial. The study investigators will take photographs of the face to perform the lesion count, assess acne severity using the CASS and take skin samples for *P. acnes* assessment at baseline assessment.
9.6.5 Sequence generation and allocation concealment

Participants will be randomly assigned to the intervention group (PPQFY) or control group using block randomisation, with block sizes of four and six with a ratio of 1:1. The randomisation schedule will be computer-generated by an independent researcher who will hold the password-protected list. Randomisation numbers will be placed into sealed, numbered envelopes to ensure they stay in sequence order and are opened in sequential order. Each envelope will contain a randomisation and medication number that is concealed to the treatment allocation. A study investigator will provide the participant with the study medication (PPQFY or placebo) based on the number allocated. Participants will also be given the medication diaries and AE diaries, and instructed on how to fill out the forms daily to monitor adherence and AEs. The dispenser, who will also be blinded to group allocation, will dispense oral capsules sufficient for four weeks of use.

Due to the length of time between visits, adherence may be an issue. In one review on acne treatment adherence, the reviewers found a weak physician–patient relationship, fear of adverse reactions, lack of results, complex regimens and forgetfulness as hurdles to adherence (425). To improve adherence, participants will be given detailed verbal and written instructions with a ‘frequently asked questions’ brochure on how to take the medications and how to fill out the forms.

Modern technology can also help with engagement (426). A website will be developed with the same information given to participants and a contact form within the website for participants to easily ask questions of research investigators. Electronic recording of adherence will reduce the
burden on participants to attend the trial site. Every two weeks, participants will be sent personalised email reminders to take the trial medication. By using secure online forms, participants will have easier access to forms and there will be less risk of losing hardcopy forms (426). Participants will be provided with the contact details of investigators should they have any further questions during the trial period.

9.6.7 Blinding

This is a double-blind trial design. The randomisation sequence and allocation will be unknown to the participants, the study investigators (who will conduct scheduled visits and outcome assessment) and the trial medication dispenser. The data will be analysed by a statistician who is blind to the treatment codes using a two-stage unblinding process. The final unblinding will be conducted after the completion of the statistical analysis. At week eight and at follow-up, study participants will be asked whether they thought they were in the real or placebo group, or whether they were unsure of their group allocation. The Bang blinding index will be used to assess the degree of blinding, response bias and different behaviour between the two study arms. The Bang blinding index is scaled to an interval of $-1$ to 1, 1 being complete lack of blinding, 0 being consistent with perfect blinding and $-1$ indicating opposite guessing, which may be related to unblinding (427). This will support the credibility of the blinding process.

9.6.8 Treatment phase

Visit 1 (week 0)

After completion of baseline assessments (section 9.6.4), participants will be dispensed the first four weeks of trial medication.
Visit 2 (week 4)

Week four is the middle of the treatment phase. Participants will be asked to return any unused oral capsules. The study researchers will record the amount of remaining oral capsules in the CRF. Participants will be dispensed the final four weeks of the oral capsules. The mid-treatment visit will be used to encourage participants’ adherence in taking the oral capsules. It will also be used to check for AEs and to take any appropriate action as required. AEs and SAEs will be recorded on the CRF. SAEs will be notified to the manufacturer, the relevant institution ethics committees and the TGA using the relevant forms.

Visit 3 (week 8)

Week eight ends the treatment phase. Participants will be asked to return any unused herb capsules. They will be asked to complete the Acne-QoL, have their photographs taken for lesion count and severity grading, and have skin scrapings taken of the affected areas. The study researchers will record the amount of remaining oral capsules, the results of the lesion count and severity assessment, and the photographs in the CRF. Blood tests for liver and kidney function and full blood examinations will also be conducted. A check for AEs will be conducted and any appropriate action taken as required. AEs and SAEs will be recorded on the CRF. SAEs will be notified to the manufacturer, relevant institution ethics committees and TGA using the relevant forms. No new oral capsules will be dispensed. Participants will be reminded of the follow-up period in four weeks.
9.6.9 Follow-up phase

Visit 4 (week 12)

Participants will be asked to visit the trial site again for follow-up assessment, including the Acne-QoL, photographs for lesion count and severity grading, and skin scrapings of affected areas. The study researchers will record the results of the lesion count and severity assessment, and the photographs taken at the time of the visit on the CRF. AEs will be checked for the final time. AEs and SAEs will be recorded on the CRF. SAEs will be notified to the manufacturer, relevant institution ethics committees and TGA using the relevant forms.

9.7 Treatment

9.7.1 Pi Pa Qing Fei Yin

The intervention will be PPQFY in capsule form (Table 9.2). This formula contains six herbs, Pi pa ye (Eriobotrya japonica Thunb. Lindl.), Sang bai pi (Morus alba L.), Huang lian (Coptis chinensis Franch., Coptis teeta Wall. or Coptis deltoidea C.Y. Cheng & Hsiao), Huang bai (Phellodendron amurense Rupr. or Phellodendron chinense Schneid.), Ren shen (Panax ginseng C.A. Mey.) and Gan cao (Glycyrrhiza glabra L. P., Glycyrrhiza uralensis Fisch. or Glycyrrhiza inflata BAT.). All ingredients act on at least one of the four pathophysiolgies described for acne (Chapter 7).
### Table 9.2 PPQFY ingredients

<table>
<thead>
<tr>
<th>CHM</th>
<th>Raw dosage (g)</th>
<th>Ratio</th>
<th>Total dosage for 8 w</th>
<th>Daily dose</th>
<th>Capsules (4 bd)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pi pa ye</em> (Eriobotrya japonica Thunb. Lindl., leaf)</td>
<td>6</td>
<td>5:1</td>
<td>67.2 g</td>
<td>1.2 g</td>
<td>0.15 g</td>
</tr>
<tr>
<td><em>Sang bai pi</em> (Morus alba L., root bark)</td>
<td>6</td>
<td>5:1</td>
<td>67.2 g</td>
<td>1.2 g</td>
<td>0.15 g</td>
</tr>
<tr>
<td><em>Huang lian</em> (Coptis chinensis Franch., stem)</td>
<td>3</td>
<td>5:1</td>
<td>33.6 g</td>
<td>0.6 g</td>
<td>0.075 g</td>
</tr>
<tr>
<td><em>Huang bai</em> (Phellodendron amurense Rupr. or Phellodendron chinense Schneid., cortex)</td>
<td>3</td>
<td>5:1</td>
<td>33.6 g</td>
<td>0.6 g</td>
<td>0.075 g</td>
</tr>
<tr>
<td><em>Ren shen</em> (Panax ginseng C.A. Mey., root)</td>
<td>1</td>
<td>5:1</td>
<td>11.2 g</td>
<td>0.2 g</td>
<td>0.025 g</td>
</tr>
<tr>
<td><em>Gan cao</em> (Glycyrrhiza uralensis Fisch., stem)</td>
<td>1</td>
<td>5:1</td>
<td>11.2 g</td>
<td>0.2 g</td>
<td>0.025 g</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>224 g</strong></td>
<td><strong>4 g</strong></td>
<td><strong>0.5 g</strong></td>
</tr>
</tbody>
</table>

Abbreviations: bd twice daily, g grams, w weeks

### 9.7.1.1 Processing of herbs

The intervention will be a herbal extract of the six ingredients in granule form placed in wholly enclosed opaque capsules. Granulated herbs will be encapsulated prior to packaging. The capsules will be vegetarian capsules each containing 0.5 g PPQFY. They will be packed in sealed, plain bottles with appropriate labelling to maintain blinding. The capsules will be produced by a
manufacturer that holds a TGA-approved good manufacturing practice (GMP) certificate. Each capsule of PPQFY will contain granulated herbs as detailed in Table 9.2.

9.7.1.2 Authentication, quality control and safety testing of herbs

As advised by the CONSORT Extension for Chinese Herbal Medicine Formulas, CHM formulas should ensure quality control of each ingredient in the formula (396). Herbs will be analysed to confirm authenticity of each ingredient using DNA fingerprint analysis to identify constituents. Herbs will be tested for contaminants such as pesticides, heavy metals and microbiota. High-performance liquid chromatography (HPLC) or other techniques such as ultra-performance liquid chromatography will identify the chemical constituents of herbs and whether the active ingredients of the herbs are present (428).

Processing of herbs will follow good manufacturing processes for granulated herbs and methods will provide maximum yield of active constituents. The manufacturer should have the ability to identify active ingredients, and have risk management and quality process controls in place (428).

9.7.1.3 Placebo

The comparator will be a placebo made from a vegetable corn/potato starch that does not include any active constituents. Artificial pigments will be added to the starch to mimic the colour of the PPQFY ingredients. The manufacturer should have a GMP certificate approved by the TGA.
9.7.1.4 Dosage and frequency

The dosage of the capsules will be four capsules twice daily for adult participants aged 18 to 45 years, and three capsules twice daily for participants aged 15 to 17 years. Participants will be asked to take the capsules with warm water twice daily after food (preferably after breakfast and dinner). Capsules should not be taken with tea or coffee, as there is no data about the interaction or clearance from the body of CHM when taken with diuretics. Participants will be asked to record the consumption of the herbs in their medication diary. There must be a minimum of four hours between dosages; however, the exact time of consumption is not required. Participants may prefer to take capsules after lunch and dinner, or after lunch and before bed.

9.7.2 Dispensing and monitoring

A medication dispenser who will be blinded to group allocation will instruct participants on the consumption of the trial medication. Participants will also receive an information leaflet detailing instructions and frequently asked questions. Online support materials will also be made available to participants.

9.7.3 Co-medication data collection method

Co-medication or concomitant medications are allowed during the trial, with one exception (refer to 9.5.6.4). Study participants will be asked to provide a list of daily use of current medications in their daily diary of medications. These can include guideline-recommended treatments and over-the-counter oral or topical products. Face-washing is a usual routine for people with or without acne. Data collected will include the name of the medication, the dosage and frequency, and the face-washing products used and frequency. This will help monitor if using PPQFY can reduce the
need for other medications or other products used for acne. Participants will be requested to continue using their current medications during the trial and any changes are to be recorded in the participant medication usage form. Participants who do not take or use any products will be asked not to begin them during the twelve-week trial period.

9.8 Data collection and storage

Data and results collected will be entered into Microsoft® Excel spreadsheets for cleaning and transferred into the statistical analysis software package Statistical Package for the Social Sciences (SPSS) software (IBM SPSS®) or other similar software for further analysis. Only de-identified aggregated data will be published.

All electronic and hardcopy data will be stored according to the research data storage policy of the investigators’ institutions. The International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Guideline with the TGA Good Practice Guidelines addendums (429) suggests that data be kept for two years after study completion; however, some institutions, including RMIT University, require data to be kept for 15 years. For children, the records will be kept until they are 25 years old. States and territories of Australia may require longer periods (or indefinite periods for trials that include children) (430). Electronic data will be password-protected and stored on a secure internet server. Hardcopy data will be stored in locked cabinets at the trial site during the trial. At the end of the trial, hardcopy data will be transferred to institution archives. After 15 years, data will be destroyed following the relevant institution procedures.
9.9 Sample size calculations

Sample size calculation will be based on the primary outcome, the Acne-QoL (119-121). The effect size will be taken as the change from baseline to end of treatment. With 80 per cent power, the required number of participants for each group, with allowances for drop-outs, will be calculated using the software G*Power (431). Fehnel et al. (119) reported the responsiveness of the Acne-QoL to treatment with Estrostep® (norethindrone acetate/ethinyl estradiol) for moderate acne vulgaris in placebo-controlled clinical trials. The mean changes in Acne-QoL subscale scores (acne symptoms) were 7.21+/-5.81 and 4.25+/-6.00 for the intervention and placebo groups, respectively, giving a Cohen’s D’s effect size of 0.49. Using G*Power 3.1.2 with 80 per cent power, this suggests a sample size of 134 with 67 in each group (Figure 9.2). For missing data (refer to 9.12), an intention-to-treat (ITT) analysis will be applied; therefore the sample size does not include loss to follow-up.
Figure 9.2 Sample size calculations using the effect estimated from Fehnel et al. (119)

9.10 Withdrawals and dropouts

Participants may withdraw from the study at any time without providing any reasons and without repercussions. Participants will be asked if they want to stop the medication and continue with the study or withdraw completely from the trial. Participants who become pregnant during the study will be withdrawn by the investigators, as they will be deemed medically unsafe to continue with the study. Participants who have started new medications or over-the-counter products during the trial will be withdrawn. There will not be replacements of participants who drop out.
9.11 Trial adherence and preventing drop-outs

The researchers should try to minimise drop-outs. In one review of acne treatment adherence, factors such as lack of knowledge, confusion about the usage or application, and fear of adverse reactions were reported. Other factors included complex regimens, busy lifestyles and forgetfulness (425). Adherence to treatment was shown to improve in one trial if the adolescent was educated about the condition and had a good understanding of acne. In addition, experiencing fewer side effects and being satisfied with the treatment provide motivation for adherence (432). Clear instructions on dosing and consumption, and regular reminders can also improve adherence (425).

Involving participants in trial design is considered good practice, as it prevents exploitation and maximises partnerships (433). By using survey data from the target participant group on preferences for treatment types, treatment duration and medication frequency, it is anticipated that trial participation and adherence will improve (426). Creating a caring and supportive environment, ensuring patients are accountable for their compliance and maintaining continuous communication can improve adherence (434). Building trusting relationships between study researchers and study partners can also improve recruitment and adherence (435).

This study includes verbal and written instructions with a ‘frequently asked questions’ fact sheet to improve understanding. Modern technology such as secure online forms for ease of access and personalised email reminders will be implemented to try to improve engagement and adherence (426, 432).
9.12 Missing data

An ITT analysis will be applied to minimise bias in the results. For the primary outcome, the Acne-QoL, missing data will be imputed as per the developers’ instructions. A minimum of three items must be answered for each domain in order for domain scores to be calculated. The mean value within the domain of the answered items should be calculated and the mean value replaces the missing values. If the minimum number of items is not obtained, the domain score should not be calculated. For the secondary outcomes, missing responses will be imputed using the method of the last observation carried forward.

9.13 Data analysis

Data analysis will be conducted by an independent statistician blinded to group allocation. Baseline demographic comparisons of the two groups will be analysed by using Chi-square or Student’s t-test and non-parametric tests as appropriate. A test for normality will be performed. Outcome measures will be presented as means and standard deviations, and the differences between the two groups will be analysed using repeated-measure ANOVA at baseline, at end of treatment and at follow-up.

For the primary outcome, the Acne-QoL, a change score for each of the four domains from the baseline to the end of treatment and from baseline to the end of follow-up will be compared between groups. Scores for each domain will be calculated by summing scores for all item responses in each domain. Missing values should be replaced as per the user manual. Routine scoring checks by checking the range, correlation analysis and manual calculation of domain scores are also suggested by the developers. For secondary outcome measures, the change score
from baseline to the end of treatment and baseline to the end of follow-up will be compared between groups. Significance is calculated at a probability value of less than 0.05.

9.14 Early termination of trial

An independent data and safety committee will be formed and will meet in the implementation phase at three months or six months depending on recruitment, and then as necessary. In the event of an SAE reported during the trial, the independent data and safety monitoring committee will review data and SAEs. If the SAE is related to the intervention, the independent data and safety monitoring committee will make a determination on the continuation of the trial.

9.15 Reimbursements

Covering the minimum cost for attending the trial site during the trial period (for example, AU$100 per participant) is a reasonable expectation and highly recommended. Reimbursements may be an incentive for trial adherence.

9.16 Reporting

Reporting of the trial results will follow the CONSORT statement and extension for herbal interventions (396). Results should be disseminated through peer-reviewed journals and conferences.

9.17 Ethical approval

Ethics approval should be sought from the RMIT Human Research Ethics Committee (HREC) or another HREC, and is the responsibility of the investigators who conduct the research.
9.18 Trial registration

The trial should be registered with the relevant trial registration authorities, such as the Australian and New Zealand Clinical Trial Register (ANZCTR) (www.anzctr.org.au).

9.19 Trial compliance

This trial should comply with the following:

- ICH, Harmonised Guideline Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice – Annotated with Therapeutic Goods Administration (TGA) comments E6(R2) (429)
- ICH, General Considerations for Clinical Trial (CPMP/ICH/291/95) (436)
- ICH, Statistical Principles for Clinical Trial (CPMP/ICH/363/96) (437)
- NHMRC, National Statement on Ethical Conduct in Research Involving Humans (430); and

9.20 Discussion

This trial protocol illustrates how methodological issues found in the reviews and the lack inclusion of HRQoL in clinical trials for acne can be addressed, using PPQFY as an example. Evidence from the literature review of CM and the SRs of RCTs of PPQFY and acupuncture has informed the development of this trial protocol. The study design improves on the methodological shortcomings found in the SRs relating to randomisation and blinding procedures. It also takes into consideration patient treatment preferences in order to improve participant adherence. Having
a rigorous study design will minimise bias in results and so practitioners can have confidence in the study results. Taking into consideration the CM treatment preferences of people with acne in the trial design makes the trial relevant to them, and using syndrome differentiation and targeting participants with mild-to-moderate acne ensure the research findings can be translated into practice. The study design has also taken into consideration participant preferences for CM treatment types and acceptable treatment frequency and duration from the survey conducted in this project.

The primary outcome is HRQoL using the Acne-QoL. There were only two previous trials that reported on QoL as an outcome measure in the SRs. Both trials used general dermatology HRQoL instruments: Skindex-29 (377) and the DLQI (331). Kim and Kim (377) found no statistically significant reduction within groups or between groups using the Skindex-29. Wang et al. (331) found higher DLQI scores (indicating poorer QoL) after one month of treatment with PPQFY than with doxycycline. Neither the Skindex-29 or DLQI include descriptions of lesions specific to acne; generic descriptions of skin lesions are included that could be applicable to any skin disease (253). This trial will provide data on the impact of a common CHM formula, PPQFY, on QoL for people with acne using a validated, acne-specific HRQoL instrument.

The secondary outcome measures include lesion count, severity grading, *P. acnes* and AEs. Lesion count is a common visual outcome measure to rate improvement. It is also used as part of grading of the severity of acne. The CASS is used for severity grading which includes overall assessment of lesions and photographic evidence. Lesion count and the CASS can be done concurrently. Both lesion count and grading will be used as inclusion criteria and as outcome measures. Photographic
evidence can be used to standardise study investigators’ perceptions of lesion types and severity, and allow for independent assessment or review at a later stage. Having severity grading as an inclusion criterion and as an outcome measure will also provide information on whether the intervention, PPQFY, is efficacious for mild and/or moderate acne as specified in dermatology textbooks.

*P. acnes* is one of the identified pathogeneses of acne. Experimental studies have shown the herbal ingredients for PPQFY decrease inflammation specifically caused by *P. acnes* (438), suppress *P. acnes* growth (319, 339) and prevent it from adhering to the host (340). Using *P. acnes* as an outcome measure will provide information on the potential mechanisms of action of PPQFY.

As this trial aims to determine the efficacy of PPQFY, an efficacy trial design has been chosen over a pragmatic design. Efficacy trials require a smaller number of participants compared to pragmatic designs and are less expensive. A placebo control has been chosen over an active control in the trial protocol as it is the most rigorous test for efficacy (392). Most of the trials encountered in the SRs used guideline-recommended treatments as active controls and very few placebo-controlled trials have evaluated the efficacy of PPQFY. Active controlled trials are used to determine equivalence or superiority, rather than efficacy (392).

Syndrome differentiation has been chosen as an inclusion criterion in the trial design to align with the traditional use of PPQFY for heat in the Lung. This also coincides with mild-to-moderate acne in CM (159). Including syndrome differentiation alongside selection of patients with mild and moderate acne will enable easier translation from research into clinical practice. This may limit
the numbers of patients included in the trial. Based on the prevalence of acne severity types presented in the literature review (Chapter 2) and predictive factors for HRQoL in people with acne (Chapter 4), most people with acne have mild-to-moderate acne, rather than severe acne. Therefore, the implications of this limitation are not anticipated to affect trial recruitment. Trial adherence strategies outlined in this trial protocol and consideration of recruitment strategies during the planning process will help to minimise drop-outs (439).

9.21 Limitations

This is a trial protocol using the most current information acquired during the project. The narrow inclusion criteria included in this protocol will not be generalisable to all people with acne, in particular those with severe acne, cyclical acne or acne scars. It will be generalisable to those with mild-to-moderate acne. There are a number of pathophysiological processes involved in acne. These include \textit{P. acnes} infection, increased levels of sebum causing follicular plugging of the pilosebaceous gland and hyperkeratinisation, increased androgen activity and inflammation. This trial does not include serum hormone testing and will not be generalisable to those with hormone-influenced acne such as PCOS, acne in rosacea or cyclical acne. This trial will determine if PPQFY alters \textit{P. acnes} count on the skin. \textit{P. acnes} can initiate inflammation and alter keratinisation of the skin (79). There will be visual inspection for inflammation as part of the lesion count, but there will not be laboratory tests to determine the mechanisms of action of the herbs in humans. Instead, the protocol will focus on clinical efficacy and safety.

The SR on PPQFY found there was considerable heterogeneity in the results. This was detected in the groups that used PPQFY as the main formula but with modifications, whether they were small
modifications or substantial. Modifications includes removing one or more of the original ingredients and adding other ingredients or using the original formula and adding more herbs. This modification reflects clinical practice but may produce different results. Having evidence for the original six ingredient version of PPQFY can shed light on the effect of making specific modifications to formulas, as has been done in existing clinical trials.

The survey included 22 participants who indicated their preferences for CHM route of administration, trial frequency and duration. This small number may limit generalisability to the whole of the population of people with acne. However, the preferred herbal treatment type and the treatment frequency and duration of participants align closely with clinical practice; therefore the results may be generalisable to those with mild and moderate acne.

9.22 Conclusions

This CHM trial protocol takes into consideration stakeholder preference on treatment type and length of time. The trial design uses rigorous methods such as adequate randomisation techniques, sample size calculations and blinding of participants and outcome assessors. It follows the recommendations of the CONSORT Extension for Chinese Herbal Medicine Formulas on trial design (396) and meets the reporting standards of SPIRIT (Appendix 18). Finally, it addresses the current lack of evidence for CHM on acne-specific HRQoL.
10.1 Introduction

Acne is not a trivial adolescent disease. It is a chronic disease that affects adolescents and adults up to 50 years old (24), and increasingly affects older women (43). Acne produces visible lesions on the face that can significantly impact on patients’ HRQoL, with reports of poor self-esteem and depression (189). Pharmacotherapies used for acne can provide relief of symptoms; however, some are associated with unwanted AEs that may reduce tolerability (139).

CAM are increasingly popular in the community; however, there is a lack of evidence on the efficacy and safety of CAM products for acne (151). CM, including body and auricular acupuncture and CHM, have been commonly used in CM clinical practice to treat acne.

A small number of SRs have evaluated the efficacy and safety of CHM or acupuncture for acne. Limitations were identified in published SRs. This includes limited numbers of databases searched and methodological weaknesses in trial designs, such as comparing two CM interventions, applying outcome measures that have not been validated and inconsistent reporting of acne severity and AEs. There were also statistical analysis issues, such as lack of ITT analysis to account for missing data. This project has addressed these gaps through rigorous SR procedures. SRs involved a comprehensive search of five English and four Chinese databases. Identified citations were screened against strict inclusion criteria. Reviews were guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (302) and assessed the strength and quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE)
(315). The reviews also assessed the trial design and reporting standards of the included trials against CONSORT and STRICTA.

This project has also conducted an online survey to determine the impact of facial acne on QoL in an Australian population. It also explored stakeholders’ CM treatment preferences. A rigorous trial protocol has been developed. The findings of the SRs informed the decision on the intervention, and the findings from the survey guided decisions about treatment frequency and duration. Incorporating patient preferences into trial design will promote adherence to the trial protocol. The aim of the trial protocol is to evaluate the efficacy and safety of *Pi Pa Qing Fei Yin* (PPQFY), thereby providing new clinical evidence for the treatment of acne.

### 10.2 Project summary

This thesis includes six components:

1. A general introduction to acne;
2. A review of acne from a CM perspective;
3. A review of the HRQoL of people with acne;
4. An online survey of people of impact of acne on HRQoL, attitudes to CAM and CM treatment preferences;
5. One SR of the Chinese herbal formula *Pi Pa Qing Fei Yin* and one SR of acupuncture; and
6. Development of a trial protocol to address the issues highlighted in this research project.

A general literature review was conducted (Chapter 2: Acne vulgaris). Acne affects younger adolescents, with severity increasing in older adolescents (19, 23) and is more likely to be seen in
Caucasians (46) from a Western background (5). The global burden of disease is high, with acne second only to eczema in years lost due to disability in dermatological conditions (61). The pathophysiology of acne is complex, with infections from \textit{P. acnes}, inflammation, androgen activity, hyperkeratinisation and follicular plugging due to sebum production (28). Both pharmacological agents and non-pharmacological therapies such as CAM (157), photodynamic therapy (28) and diet (86) have been described for the treatment of acne. The review highlighted the multiple number of severity grading instruments encountered in clinical trials for acne. There is no consensus on one acne grading tool and no consensus on the outcome measures used to evaluate acne in clinical trials, though there are efforts underway (263). A uniform set of agreed outcome measures will reduce the uncertainty when evaluating effectiveness of interventions for acne.

A summary of the CM literature for acne was also conducted (Chapter 3: Chinese medicine). CM therapies include topical and oral CHM, and body and auricular acupuncture. CM treatment is based on syndrome differentiation. CHM formulas include PPQFY for the syndrome wind-heat stagnating in the Lung meridian, \textit{Xiao Cuo Tang} for \textit{yin} deficiency generating internal heat and \textit{Tao Hong Si Wu Tang} for clearing heat from the Blood, tonifying Blood and clearing pathogenic heat (159, 165). The main syndromes described and evaluated in trials in the literature include wind-heat stagnating in the Lung meridian and PPQFY was used to addresses this syndrome (168). Body acupuncture and auricular acupuncture are commonly used to address similar syndromes.

The HRQoL of people with acne can be affected psychologically, emotionally and socially (Chapter 4: Quality of life). People with acne have reported depression, suicidal ideation and
attempts, poor self-esteem and avoidance of social activities (190, 192). Acne on the face and severe acne have a correlation with worse HRQoL scores (74). There are many HRQoL instruments used in the evaluation of people with acne. There were 16 general HRQoL questionnaires, 7 dermatology-specific questionnaires and 7 acne-specific questionnaires identified in the literature. General health instruments such as the Medical Outcome Study 36-item SF-36, dermatology-specific instruments such as the DLQI and the acne-specific CADI are commonly used to evaluate HRQoL in people with acne. Again, there needs to be agreed upon instruments used to evaluate HRQoL of people with acne. The use of acne-specific instruments would provide more accurate meaningful data to people with acne than general health instruments. Instruments that are age specific may also be beneficial as issues for children, adolescents with acne have been shown to be different for adults with acne. Despite the importance of HRQoL for acne patients, this review found few CM trials used HRQoL as an outcome measure. This is an important outcome measure that should be included in future CM studies.

The online survey (Chapter 5) included three components: the Acne-QoL, CAM Questionnaire and CM preferences for CM trial design. Recruitment for the study was suboptimal and the response rate was lower than anticipated. There were 28 respondents; 22 completed the whole survey and a further 6 partially completed the survey. For data that was available, there was a greater number of female respondents than males (17 female, 4 male) and most were between 15 to 24 years old. Results for the Acne-QoL showed the lowest score was for the self-perception domain, compared to the highest score for the acne symptoms domain. For the CAM use component, the mean domain score was highest for positive beliefs and lowest for psychological comfort. Most respondents preferred topical cleansers as their first treatment preference, followed
by pills and tablets. Weekly acupuncture treatment for between four and eight weeks was the acupuncture treatment frequency and duration preferred by most respondents. The survey participants were low. This may have brought some bias and larger variation into the results, and may not represent all people with acne. There were recruitment issues associated with the survey and future surveys may need to consider alternative strategies or incentives to improve recruitment. There were also a large number of questions in the survey. Future surveys may consider separating each of the components into three separate surveys.

The survey finding that females had worse scores on the Acne-QoL than males was also found by the survey developers (119-121). Few other studies that assessed HRQoL with the Acne-QoL have done so in populations similar to those who completed this survey. Given the small sample size highlighted above, it is difficult to say whether results for this population are the same or different to other populations.

The number of survey respondents with favourable attitudes to CAM in was similar to the number with unfavourable attitudes. Findings by Magin et al (155) found positive attitudes in 26 people who had used CAM for their acne. Use of CAM was perceived as more efficacious in their study, and was associated with greater self-efficacy. The difference between the results of this study and those of Magin et al may be due to several reasons. Firstly, this study examined attitudes to CAM through a survey, while Magin et al conducted interviews. Secondly, approximately half of the survey respondents in this study had not previously used CAM, which may affect their attitude toward CAM. Thirdly, the survey used was an existing survey that did not specifically ask about
use of CAM for acne. Finally, it was not possible to examine attitudes to CAM for people in this study who had previously used CAM due to the low response rate (268).

Two SRs were conducted for this project. The first review examined the efficacy and safety of the CHM formula PPQFY for acne (Chapter 7: Systematic review of Chinese herbal medicine for acne vulgaris). This contains ingredients that clear Lung heat, clear Stomach heat, resolve phlegm and tonify qi. Experimental studies have shown inhibition of growth of *P. acnes* (319), anti-inflammatory effects (353) and anti-adipogenic effects (440), which may address different acne pathophysiology pathways. Results of the meta-analysis of the included trials in the SR found there is some evidence that PPQFY may be effective for acne, with fewer AEs reported compared to pharmacotherapies. The DLQI (114) was included as an HRQoL outcome measure in one PPQFY trial (331). There were methodological flaws found in the included trials, including in relation to randomisation procedures, allocation concealment, blinding procedures and sample size calculations.

Results in CHM PPQFY meta-analysis showed PPQFY to have a greater effect than pharmacotherapy though there was considerable heterogeneity. The variation and modification of ingredients used in trials as well as the inclusion of people with mild to severe acne may have contributed to this. Only the main ingredients of CHM PPQFY were evaluated in the experimental studies, and actions included anti-inflammatory (353, 356) and antimicrobial actions (319, 339, 340), and reducing follicular hyperkeratinisation (358, 359) and sebum production (360, 361). Other herbal medicines may have other physiological effects such as hormonal, endocrinological or other effects that future reviews may need to investigate.
The monograph on acne by Coyle et al evaluated the efficacy of CHM (168). There was some evidence to show CHM was effective for acne though many comparisons of lesion count and acne grading show no difference between CHM and pharmacotherapy. Using effective rate in CM trials is common but may cause some statistical analysis variations as shown in the monograph. This may be resolved by using standard agreed upon outcome measures in acne trials to resolve this issue.

Results from the monograph showed CHM may be as effective as guideline recommended treatments for acne. In comparison, oral PPQFY had a greater effective rate than pharmacotherapies, in particular for when compared to BP and antibiotics and compared to retinoids alone. Both the monograph and this review of PPQFY found fewer AEs with CHM than with pharmacotherapy. The lack of evaluation of HRQoL was also common to both the monograph and the PPQFY SR. There needs to be more CM studies evaluating this important outcome in acne.

The second SR evaluated acupuncture for acne (Chapter 8: Systematic review of acupuncture for acne vulgaris). The acupuncture SR found there was no difference between people receiving acupuncture compared with pharmacotherapies, with low statistical heterogeneity. There were also fewer AEs in the acupuncture group compared to the pharmacotherapy group. Skindex-29 (100) was an HRQoL outcome measure used in one acupuncture trial (377). The same shortcomings found in the PPQFY included trials were also found in the acupuncture included trials. The acupuncture review in this project included studies that evaluated common acupuncture techniques such as body acupuncture, auricular acupuncture, electroacupuncture and moxibustion. The reviews conducted by Li et al (18), Cao et al (185) and the Cochrane systematic review (157)
included other techniques that stimulated acupuncture points. They also included studies that combined acupuncture with CHM interventions and compared interventions with controls that included CM therapies. This review only included comparators that were of known efficacy such as pharmacotherapies and or studies that used no treatment/waitlist or placebo. All studies reported the quality of the included studies were low and methodological issues with the trials. Again, only one trial measured HRQoL. HRQoL should be given more consideration in future trials to improve the understanding of the impact CM has on this important outcome for people with acne.

The final component of the project was the trial protocol (Chapter 9). The trial protocol addresses the methodological issues found in previous trials for PPQFY by using SPIRIT and the CONSORT Extension for Herbal Interventions as a guide (396). Issues included lack of randomisation in trials, blinding of personnel and participants, and substantial modification of herbal formulas. As the evidence from Chapter 7 shows, PPQFY was effective in reducing acne lesion count, and so this formula was selected as the intervention for the trial protocol. Participants included in the trial will have mild-to-moderate acne using the proposed validated severity tool CASS (108). Taking into consideration the survey results of participant preferences, the treatment phase of the trial will run for eight treatment weeks with follow-up assessment at twelve weeks.

The trial will use an acne-specific HRQoL instrument (the Acne-QoL) as the primary outcome measure, to address the lack of trials evaluating HRQoL and to provide meaningful data relevant to patients and clinical practice. It also outlines the trial procedures for recruitment, eligibility screening and obtaining of informed consent. Randomisation and blinding procedures were lacking in previous trials and this protocol addresses these gaps. There were also no sample size
calculations in many of the included trials and no details on the CHM quality control procedures. The protocol will also address these issues. Herbs will undergo authentication and safety testing using a manufacturer that adheres to good manufacturing practices (417). To maintain blinding, placebo capsules that look and smell the same as the intervention will be used. Blinding will be assessed using the Bang blinding index (427). There are different trial designs that may be suitable for evaluating the efficacy of herbal medicine. These include Bayesian, pragmatic and randomised controlled trials. Bayesian and pragmatic trial designs do not address efficacy as well as randomised controlled trials. Pragmatic and Bayesian trial designs require substantial personnel. Bayesian designs are adaptive and require a smaller sample size, but are more beneficial for diseases that are rare. They are resource intensive and require substantial modelling, design and statistical analysis. Pragmatic trials reflect real clinical setting scenarios however efficacy has yet been established for PPQFY and pragmatic designs will introduce variances that make it difficult to determine efficacy. Given the limitations of pragmatic and Bayesian trial designs, a two-arm placebo controlled, randomised controlled trial was considered the most appropriate study design to address the issues found in the SRs. A randomised controlled trial with adequate blinding and randomisation procedures was presented, using the traditional formula PPQFY as the intervention. Such a design will improve the reliability of the data and confidence of the efficacy of PPQFY for people with mild to moderate acne.

10.3 Limitations

The search for both SRs was restricted to Chinese and English databases. Articles were restricted to these two languages due to the availability of project members who could read and write in these languages. During the project, English abstracts of articles in other languages such as Korean,
Japanese and European languages were encountered. Other databases may contain clinical evidence that has not been included in this project. Future studies should consider broadening database searches in other languages to gain a more comprehensive picture of the clinical evidence for acne.

This project evaluated the efficacy and safety of one CHM formula, PPQFY, which is frequently used in clinical practice. Future research focusing on other CHM formulas will provide further evidence of the efficacy of specific CHM formulas for acne. The findings of the SRs are limited by the low methodological quality of the included trials. Biases were identified in included trials due to few studies providing information on sequence generation, allocation concealment or blinding procedures for both participants and assessors. This reduces the reliability of the clinical outcomes reported. The variation in acne severity in included participants and the variation in the interventions and comparators included in the trials contributed to considerable heterogeneity, further reducing the reliability of reported clinical outcomes.

In theory, the advantages of an online survey include ease of use, accessibility, low cost and reduction of researchers’ time and effort (418). Survey recruitment was challenging. Only two of the secondary schools approached allowed the survey to be advertised in their newsletters, with the majority declining due to the limited number of research studies each institution could support. The online strategies used and the direct mailout to practitioners did not appear to increase recruitment. Other recruitment strategies may also be a consideration for future research. These could include banner advertisements, search engine promotions and applying to national or state-
based high schools’ education governance departments in order to collaborate with groups of schools, rather than approaching individual schools.

The low number of participants limits the survey results and they are not able to be generalised to the Australian population. There is still a need to obtain more data on the HRQoL of people with acne in Australia in order to gain more contemporary information and to improve the understanding of the HRQoL of people with acne in Australia.

10.4 Implications for research

10.4.1 Systematic reviews

There were methodological flaws found in the trials included in the SRs. There was a lack of detail on randomisation or randomisation that was based on hospital record numbers or sequence of hospital visits. Allocation concealment detail was not reported. There was also a lack of detail on blinding procedures for both participants and assessors. Some trials in the PPQFY SR used comparators not recommended by treatment guidelines, such as TAB combined with OAB, and there was considerable modification of the original ingredients of the formula without justification. Few studies reported follow-up, with a lack of description of withdrawals and drop-outs. None of the studies reported using ITT analyses to account for missing data. Further, many trials did not report AEs. Transparent AE reporting would help to properly assess the safety profile of herbal medicines (396, 401).

The trials also used the therapeutic effective rate (TER) as a primary outcome measure. The TER is based on the percentage of change in symptoms such as lesion count and severity, and does not
appear to have been validated for acne. Thresholds for improvement were based on two CM research guidelines: *Guideline for New Chinese Herbal Medicine in Clinical Practice and Research (Vol. 1)* (2002) (311) and *Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine* (1994) (167). The 2002 guideline suggests a 50 per cent change in symptoms as an improvement threshold and the 1994 guideline suggests a 30 per cent improvement threshold. This lack of consensus on the threshold for improvement could bring confusion to the review results and so the findings of the SRs need to be interpreted with caution. There was also subjectivity in how the trial authors interpreted descriptions for the different levels of improvement from the encountered guidelines that trials reported using. In addition, not all trials followed these guidelines. Although Wu et al. (336) reported using the 2002 guidelines (which describe improvement of 50 per cent or greater), the actual threshold used to assess improvement in trial participants was 30 to 70 per cent, which corresponds to the 1994 guidelines (167).

The acupuncture trials included in the SR had the same issues as the PPQFY review. The acupuncture SR included subgroup analysis of trials that used a 30 per cent threshold for improvement and those that used a 50 per cent threshold for improvement. Surprisingly, the results for both subgroups were the same. There is no clear explanation for this occurrence. This may mean the descriptions are sufficiently subjective that the tool is not able to discriminate between the two levels. This may also indicate that there is no difference in the two thresholds, whether at 30 per cent or at 50 per cent. In the 2010 research guidelines, the threshold for improvement is 30 per cent (312).
10.4.2 Trial designs

Many of the trials encountered in the SRs were assessed as having high risk of bias for sequence generation. Nearly all were assessed as unclear in relation to allocation concealment. Future trials should be designed with rigorous randomisation and allocation-concealment procedures. One trial had three times the number of participants in the first intervention group \( n = 200 \) compared to the second intervention group \( n = 60 \) and the control group \( n = 60 \) with no explanation (176). Imbalance in the number of participants in the intervention and control groups can bring bias to results. Trials need to have sample size calculations.

Few of the trials reported on acne severity. Severity can be based on the number of lesions or the type of lesions, such as inflamed or non-inflamed comedones, or nodules and cysts. Eight validated acne-severity grading scales were found in the literature, but none of the included trials in the SRs used any of the validated scales. Severity grading in the included trials used scales developed by trial investigators or did not give details. Given that severity also can affect HRQoL, using a validated severity scale may help to standardise reporting of results.

Many of the trials were assessed as unclear in relation to blinding of assessors and participants. Trials should follow standard reporting conventions such as STRICTA (316). A more rigorous trial design to address these issues is presented in this project (Chapter 9).

10.4.3 Outcome measures

Despite increasing reports of people’s HRQoL being affected by acne, HRQoL did not feature prominently in the CM trials evaluated in the two SRs conducted for this project. None of the trials
used acne-specific HRQoL outcome measures. Using an acne-specific HRQoL outcome measure may give a more accurate picture of the impact of the intervention evaluated for the acne. Although the DLQI and Skindex-29 have been validated in people with acne and are recommended by the EADV TF on QoL (228), the DLQI has questions that may not be relevant to someone with acne, such as about itchiness, and the Skindex-29 also asks questions on itching, burning and stinging. An acne-specific HRQoL tool would provide meaningful data about people with acne and make it easier for data to be compared across trials (441).

Attempts have been made to gain consensus for this outcome measure in research, but no consensus has been achieved (99). There are efforts underway to standardise the outcome measures used in acne research. CM researchers should consider standardised outcome measures as well as the TER rate for future trials in order to improve data collection and reduce clinical heterogeneity when comparing trials. The Acne Core Outcome Research Network (ACORN) is attempting to standardise the outcome measures used in clinical trials (263) as part of the Core Outcome Measures in Effectiveness Trials (COMET) initiative. Preliminary identification of measures is underway; these may include physician and patient assessment of signs and symptoms, global acne severity and HRQoL measures. The next steps for the group are to identify or develop the outcome measures set for acne vulgaris.

10.5 Implications for practice

10.5.1 Pi Pa Qing Fei Yin

The ingredients of PPQFY have potential to address the five main pathophysiological pathways of acne, including inhibiting *P. acnes*, reducing inflammation and sebum and thus reducing
hyperkeratinisation, and affecting androgen activity. The meta-analysis showed that PPQFY was superior to pharmacotherapies in reducing lesion count though there were many modifications and additions to the formula. Although there were limitations in the methodological designs, PPQFY had fewer AEs than pharmacotherapies and appeared to be better tolerated by people with acne. There is some evidence that PPQFY may be effective for acne, with relatively lower numbers of AEs than pharmacotherapies. The review found that PPQFY in the included trials was modified frequently, which reflects clinical practice. *Huang qin* was commonly substituted for *Huang bai*, which changes the focus from the lower energiser (*Huang bai*) to the upper energiser (*Huang qin*) to address the syndrome for wind-heat stagnating in the Lung meridian. The original ingredients of the formula addresses mild-to-moderate acne and is the intervention for the trial protocol.

### 10.5.2 Acupuncture and related therapies

The meta-analysis of the included acupuncture trials found there was no difference between acupuncture and other common manual therapies such as moxibustion and auricular acupuncture compared to pharmacotherapies. Although it was not more effective than pharmacotherapies, the effect size was comparable regardless of the threshold used for TER assessment for those receiving acupuncture compared to pharmacotherapies. Again, the same methodological design issues were found in the acupuncture review as in the PPQFY review. Acupuncture and related techniques had fewer AEs than pharmacotherapies and the reported AEs, such as bruising and pain at the needle insertion site, are known AEs from acupuncture. Acupuncture may be an alternative for people who cannot tolerate the AEs from pharmacotherapies such as dryness and burning of the skin and gastrointestinal disturbances.
10.5.3 Health-related quality of life

Findings from the survey show acne has a significant impact on HRQoL. For clinical practice, the inclusion of HRQoL tools can help to inform decision-making for treatment. For example, if patients are severely affected although their acne is assessed as mild to moderate, they may benefit from a multidisciplinary approach to treatment rather than just one modality. Practitioners should be mindful of the impact acne can have on HRQoL and this line of questioning may be appropriate as part of the therapeutic consultation. Addressing patients’ HRQoL early will improve patients’ health. A short, easy-to-use tool such as the CADI is recommended in clinical practice by the EADV TF (228) and other reviewers of HRQoL tools for acne (253, 254).

10.6 Conclusions

This thesis summarises the literature on CM therapies for acne and identifies HRQoL as an important factor in acne research. The clinical evidence of CM therapies shows PPQFY was more effective than pharmacotherapies for acne and there was no difference between acupuncture and pharmacotherapies for acne. PPQFY and acupuncture may be alternatives for those who want alternatives to conventional medicines. This clinical evidence should be interpreted with caution due to the methodological flaws of the included studies. This project has attempted to obtain recent data on how acne impacts the Australian population’s HRQoL and their CM treatment preferences. A rigorous trial protocol has been designed incorporating stakeholders’ preferences for CM treatment and addressing the methodological flaws in previous trials to inform future research.
REFERENCES


182. Liu W, Shen D, Song P, Xu X. Clinical observation in 86 cases of acne vulgaris treated with Compound Oldenlandis Mixture. Journal of traditional Chinese medicine = Chung i tsa chih


286. Solon O. Teens are abandoning Facebook in dramatic numbers, study finds. The Guardian. 2018.


322. Han SX. [Pi Pa Qing Fei Yin Combines with Chinese Medicine Mask to Treat Acne Vulgaris in 90 Patients]. 2006:266. [In Chinese: 韩守信. 插把清肺饮配合中药面膜治疗寻常痤疮 90 例. 河北省崇礼县妇幼保健院]


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### APPENDICES

#### Appendix 1 Oral Chinese herbal medicines formulas and herb ingredients

<table>
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<tr>
<th>Oral formulas</th>
<th>Ingredients (Pinyin, Chinese characters and species name)</th>
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<tr>
<td><strong>Chai Hu Shu Gan Wan modified (柴胡疏肝丸) plus ingredients from Xiao Cuo Tang</strong> (Fan et al., 2008)</td>
<td><strong>Chai hu</strong> 柴胡 (<em>Bupleurum chinense</em> DC.)&lt;br&gt;<strong>Yu jin</strong> 郁金 (<em>Curcuma wenyujin</em> Y.H. Chen et C. Ling)&lt;br&gt;<strong>Bai shao</strong> 白芍 (<em>Paeoniae lactiflora</em> Pall.)&lt;br&gt;<strong>Nu zhen zi</strong> 女真子 (<em>Ligustrum lucidum</em> Ait.)&lt;br&gt;<strong>Han lian cao</strong> 旱莲草 (<em>Eclipta prostrata</em> L.)&lt;br&gt;<strong>Yu xing cao</strong> 鱼腥草 (<em>Houttuynia cordata</em> Thunb.)&lt;br&gt;<strong>Pu gong ying</strong> 蒲公英 (<em>Taraxacum mongolicum</em> Hand)&lt;br&gt;<strong>Dan shen</strong> 丹参 (<em>Salvia miltiorrhiza</em> Bge.)&lt;br&gt;<strong>Shan zha</strong> 山楂 (<em>Crataegus pinnatifida</em> Bge. var. major N.E. Br.)&lt;br&gt;<strong>Gan cao</strong> 甘草 (<em>Glycyrrhiza uralensis</em> Fischer)</td>
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<td><strong>Chu Shi Jie Du Tang</strong> (升阳解毒汤) (Shen et al., 1995)</td>
<td><strong>Bai xian pi</strong> 白鲜皮 (<em>Dictamnus dasycarpus</em> Turcz.)&lt;br&gt;<strong>Dou juan</strong> 豆卷 (<em>Glycines mas</em> (L.) Merr.)&lt;br&gt;<strong>Yi yi ren</strong> 薏苡仁 (<em>Coix lachryma-jobi</em> L.)&lt;br&gt;<strong>Tu fu ling</strong> 土茯苓 (<em>Smilax glabra</em> Roxb.)&lt;br&gt;<strong>Shan zhi zi</strong> 山栀子 (<em>Gardenia jasminoides</em> Ellis)&lt;br&gt;<strong>Mu dan pi</strong> 牡丹皮 (<em>Paeonia suffruticosa</em> Andr.)&lt;br&gt;<strong>Jin yin hua</strong> 金银花 (<em>Lonicera japonica</em> Thunb.)&lt;br&gt;<strong>Lian qiao</strong> 连翘 (<em>Forsythia suspense</em> (Thunb.) Vahl)&lt;br&gt;<strong>Zi hua di ding</strong> 滑石 (<em>Hydrated magnesium silicate</em>)&lt;br&gt;<strong>Gan cao</strong> 甘草 (<em>Glycyrrhiza uralensis</em> Fischer)</td>
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<td><strong>Cuo Chuang Jian Ji Tang</strong> (川芎健脾汤) (Chinese characters not identified) (Shen et al., 1995)</td>
<td><strong>Jin yin hua</strong> 金银花 (<em>Lonicera japonica</em> Thunb.)&lt;br&gt;<strong>Lian qiao</strong> 连翘 (<em>Forsythia suspense</em> (Thunb.) Vahl)&lt;br&gt;<strong>Huang qin</strong> 黄芩 (<em>Scutellaria baicalensis</em> Georgi)&lt;br&gt;<strong>Chuan xiong</strong> 川芎 (<em>Ligusticum chuanxiong</em> Hort.)&lt;br&gt;<strong>Dang gui</strong> 当归 (<em>Angelica sinensis</em> (Oliv.) Diels)&lt;br&gt;<strong>Jie geng</strong> 桔梗 (<em>Platycodon grandiflorum</em> (Jacq.) A. DC.)&lt;br&gt;<strong>Niu xi</strong> 牛膝 (<em>Achyranthes bidentata</em> Bl.)&lt;br&gt;<strong>Ye ju hua</strong> 野菊花 (<em>Chrysanthemum indicum</em> L.)</td>
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<td><strong>Modified Dan Zhi Xiao Yao San (丹栀逍遥散加减)</strong> (State Administration of TCM, 1994)</td>
<td><strong>Mu dan pi</strong> 牡丹皮 (<em>Paeonia suffruticosa</em> Andr.)&lt;br&gt;<strong>Zhi zi</strong> 咀子 (<em>Gardenia jasminoides</em> Ellis)&lt;br&gt;<strong>Chai hu</strong> 柴胡 (<em>Bupleurum chinense</em> DC.)&lt;br&gt;<strong>Dang gui</strong> 当归 (<em>Angelica sinensis</em> (Oliv.) Diels)&lt;br&gt;<strong>Bai shao</strong> 白芍 (<em>Paeoniae lactiflora</em> Pall.)&lt;br&gt;<strong>Bai zhu</strong> 白术 (<em>Atractylodes macrocephala</em> Koidz.)&lt;br&gt;<strong>Fu ling</strong> 茯苓 (<em>Poria cocos</em> (Schw.) Wolf)&lt;br&gt;<strong>Zhi gan cao</strong> 炙甘草 (<em>honey fried Glycyrrhiza uralensis</em> Fischer)</td>
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<td><strong>Modified Er Xian Tang (二仙汤) plus Zhi Bai Di Huang Wan (知柏地黄丸)</strong> (Xiang, 2015)</td>
<td><strong>Er Xian Tang:</strong>&lt;br&gt;<strong>Xian mao</strong> 仙茅 (<em>Curculigo orchioides</em> Gaertn.)&lt;br&gt;<strong>Yin yang huo</strong> 泻羊藿 (<em>Epimedium grandiflorum</em> Morr., <em>E. sagittatum</em> (Sieb. et Zucc.) Maxim or <em>E. brevicornum</em> Maxim)&lt;br&gt;<strong>Ba ji tian</strong> 巴戟天 (<em>Morinda officinalis</em> How)</td>
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<tr>
<td>Oral formulas</td>
<td>Ingredients (Pinyin, Chinese characters and species name)</td>
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| **Huang bai 黄柏** (Phellodendron amurense Rupr.)  
**Zhi mu 知母** (Anemarrhena asphodeloides Bge.)  
**Dang gui 当归** (Angelica sinensis (Oliv.) Diels)  
**Zhi Bai Di Huang Wan: Zhi mu 知母** (Anemarrhena asphodeloides Bge.)  
**Sheng di huang 生地** (Rehmannia glutinosa (Gaertn.) Libosch.)  
**Shan zhu yu 山茱萸** (Cornus officinalis Sieb. et Zucc.)  
**Shan yao 山药** (Dioscorea opposita Thunb.)  
**Fu ling 茯苓** (Poria cocos (Schw.) Wolf)  
**Mu dan pi 牡丹皮** (Paeonia suffruticosa Andr.)  
**Ze xie 泽泻** (Alisma orientalis (Sam.) Juzep.)  
**Hai Zao Yu Hu Tang (海藻玉壶汤)** (Xu, 2004)  
Hai zao 海藻 (Sargassum pallidum (Turn.) C. Ag.)  
Kun bu 昆布 (Laminaria japonica Aresch.)  
Zhe bei mu 浙贝母 (Fritillaria thunbergia Miq.)  
Zhi ban xia 制半夏 (Pinellia ternate (Thunb.) Breit.)  
Chen pi 陈皮 (Citrus reticulata Blanco, C. tangerine Hort. Et Tanaka or C. erythrosa Tanaka)  
Lian qiao 连翘 (Forsythia suspense (Thunb.) Vahl)  
Dang gui 当归 (Angelica sinensis (Oliv.) Diels)  
Chuan xiong 川芎 (Ligusticum chuanxiong Hort.)  
Du huo 独活 (Angelica pubescens Maxim)  
Gan cao 甘草 (Glycyrrhiza uralensis Fischer)  
Xia ku cao 夏枯草 (Prunella vulgaris L.)  
Long gu 龙骨 (Fossilised bone - various species)  
Mu li 牡蛎 (Ostrea gigas Thunb.)  
Qing pi 青皮 (Citrus reticulata Blanco)  
Ju he 聚合 (Citrus reticulata Blanco)  
**Modified Hai Zao Yu Hu Tang (海藻玉壶汤) plus Tao Hong Si Wu Tang (桃红四物汤)** (China Association of CM 2012; Xiang, 2015)  
**Hai Zao Yu Hu Tang:**  
Hai zao 海藻 (Sargassum pallidum (Turn.) C. Ag.)  
Kun bu 昆布 (Laminaria japonica Aresch.)  
Hai dai 海带 (Laminaria japonica J.E. Areschoug)  
Zhe bei mu 浙贝母 (Fritillaria thunbergia Miq.)  
Zhi ban xia 制半夏 (Pinellia ternate (Thunb.) Breit.)  
Du huo 独活 (Angelica pubescens Maxim)  
Chuan xiong 川芎 (Ligusticum chuanxiong Hort.)  
Dang gui 当归 (Angelica sinensis (Oliv.) Diels)  
Qing pi 青皮 (Citrus reticulata Blanco, C. tangerine Hort. Et Tanaka or C. erythrosa Tanaka)  
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Lian qiao 连翘 (Forsythia suspense (Thunb.) Vahl)  
Gan cao 甘草 (Glycyrrhiza uralensis Fischer)  
**Tao Hong Si Wu Tang:**  
Tao ren 桃仁 (Prunus persica (L.) Batsch.)  
Hong hua 红花 (Carthamus tinctorius L.)  
Shu di huang 熟地 (Rehmannia glutinosa (Gaertn.) Libosch.)  
Dang gui 当归 (Angelica sinensis (Oliv.) Diels)  
Bai shao 白芍 (Paeoniae lactiflora Pall.) |
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<th>Oral formulas</th>
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<td>Liang Xue Qing Fei Yin (凉血清肺饮) (Shen et al., 1995; Xu, 2004)</td>
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</tbody>
</table>
| **Tao Hong Si Wu Tang** (桃红四物汤) (Fan et al., 2008; Shen et al., 1995; Xu, 2004) | Chen pi 陈皮 (Citrus reticulata Blanco, C. tangerine Hort. Et Tanaka or C. erythrosa Tanaka)  
Zhi gan cao 炙甘草 (honey fried Glycyrrhiza uralensis Fischer)  
Tao ren 桃仁 (Prunus persica (L.) Batsch.)  
Hong hua 红花 (Carthamus tinctorius L.)  
Shu di huang 熟地黄 (Rehmannia glutinosa (Gaertn.) Libosch.)  
Dang gui 当归 (Angelica sinensis (Oliv.) Diels)  
Bai shao 白芍 (Paeoniae lactiflora Pall.)  
Chuan xiong 川芎 (Ligusticum chuanxiong Hort.) |
| Modified **Tao Hong Si Wu Tang** (桃红四物汤) plus **Er Chen Tang** (二陈汤) (Xiang, 2015) | Tao ren 桃仁 (Prunus persica (L.) Batsch.)  
Hong hua 红花 (Carthamus tinctorius L.)  
Shu di huang 熟地黄 (Rehmannia glutinosa (Gaertn.) Libosch.)  
Dang gui 当归 (Angelica sinensis (Oliv.) Diels)  
Bai shao 白芍 (Paeoniae lactiflora Pall.)  
Chuan xiong 川芎 (Ligusticum chuanxiong Hort.)  
Er Chen Tang:  
Zhi ban xia 制半夏 (Pinellia ternate (Thunb.) Breit.)  
Chen pi 陈皮 (Citrus reticulata Blanco, C. tangerine Hort. Et Tanaka or C. erythrosa Tanaka)  
Fu ling 茯苓 (Poria cocos (Schw.) Wolf)  
Zhi gan cao 炙甘草 (honey fried Glycyrrhiza uralensis Fischer) |
| **Tiao Wei Cheng Qi Tang** (调胃承气汤) (Shen et al., 1995; Xu, 2004) | Da huang 大黄 (Rheum palmatum L.)  
Gan cao 甘草 (Glycyrrhiza uralensis Fischer)  
Mang xiao 芒硝 (Hydrated sodium sulfate) |
| Modified **Wu Wei Xiao Du Yin** (五味消毒饮) plus **Tao Hong Si Wu Tang** (桃红四物汤) (State Administration of TCM, 1994) | Wu Wei Xiao Du Yin:  
Jin yin hua 金银花 (Lonicera japonica Thunb.)  
Pu gong ying 潘公英 (Taraxacum mongolicum Hand. -Mazz.)  
Zi hua di ding 紫花地丁 (Viola yedoensis Mak.)  
Ye ju hua 野菊花 (Chrysanthemum indicum L.)  
Zi bei tian kui 紫背天葵 (Begonia fimbristipulata Hance or Semiaquilegia adoxoides (DC.) Mak.)  
Tiao Wei Tang:  
Tao ren 桃仁 (Prunus persica (L.) Batsch.)  
Hong hua 红花 (Carthamus tinctorius L.)  
Shu di huang 熟地黄 (Rehmannia glutinosa (Gaertn.) Libosch.)  
Dang gui 当归 (Angelica sinensis (Oliv.) Diels)  
Bai shao 白芍 (Paeoniae lactiflora Pall.)  
Chuan xiong 川芎 (Ligusticum chuanxiong Hort.) |
| Modified **Xian Fang Huo Ming Yin** (仙方活命饮) (State Administration of TCM, 1994) | Jin yin hua 金银花 (Lonicera japonica Thunb.)  
Gan cao 甘草 (Glycyrrhiza uralensis Fischer)  
Zhe bei mu 浙贝母 (Fritillaria thunbergia Miq.)  
Tian hua fen 天花粉 (Trichosanthes kirilowii Maxim.)  
Dang gui 当归 (Angelica sinensis (Oliv.) Diels)  
Chi shao 赤芍 (Paeonia veitchii Lynch)  
Ru xiang 乳香 (Boswellia carterii Birdw.)  
Mo yao 没药 (Commiphora myrrha Engl.)  
Fang feng 防风 (Ledebouriella divaricata (Turcz.), L. seselides (Hoffin.) or Saposhnikovia divaricata (Turcz.) Schischk |
### Oral formulas

<table>
<thead>
<tr>
<th><strong>Ingredients (Pinyin, Chinese characters and species name)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bai zhi 白芷 <em>(Angelica dahurica (Fisch. Ex hoffm.) Benth. Et Hook f. or A. dahurica (Fisch. Ex Hoffm.) Benth. Et Hook. F. var. taiwaniana (Boiss.) shan et Yuan, or A. anomala Lallem.)</em></td>
</tr>
<tr>
<td>Chuan shan jia 穿山甲 <em>(Manis pentadactyla L.)</em></td>
</tr>
<tr>
<td>Zao jiao ci 皂角刺 <em>(Gleditsia Sinensis Lam.)</em></td>
</tr>
<tr>
<td>Chen pi 陈皮 <em>(Citrus reticulata Blanco, C. tangerine Hort. Et Tanaka or C. erythrosa Tanaka)</em></td>
</tr>
<tr>
<td>Xiao Cuo Tang (消痤汤) (Fan et al., 2008)</td>
</tr>
<tr>
<td>Nu zhen zi 女贞子 <em>(Ligustrum lucidum Ait.)</em></td>
</tr>
<tr>
<td>Han lian cao 旱莲草 <em>(Eclipta prostrata L.)</em></td>
</tr>
<tr>
<td>Zhi mu 知母 <em>(Anemarrhena asphodeloides Bge.)</em></td>
</tr>
<tr>
<td>Huang bai 黄柏 <em>(Phellodendron amurense Rupr.)</em></td>
</tr>
<tr>
<td>Yu xing cao 鱼腥草 <em>(Houttuynia cordata Thunb.)</em></td>
</tr>
<tr>
<td>Pu gong ying 蒲公英 <em>(Taraxacum mongolicum Hand. -Mazz.)</em></td>
</tr>
<tr>
<td>Lian qiao 连翘 <em>(Forsythia suspense (Thunb.) Vahl)</em></td>
</tr>
<tr>
<td>Sheng di huang 生地黄 <em>(Rehmannia glutinosa (Gaertn.)</em></td>
</tr>
<tr>
<td>Libosch.)*</td>
</tr>
<tr>
<td>Dan shen 丹参 <em>(Salvia miltiorrhiza Bge.)</em></td>
</tr>
<tr>
<td>Gan cao 甘草 <em>(Glycyrrhiza uralensis Fischer)</em></td>
</tr>
<tr>
<td>Xiao Yao San (逍遥散) (Xiang, 2015)</td>
</tr>
<tr>
<td>Chai hu 柴胡 <em>(Bupleurum chinense DC.)</em></td>
</tr>
<tr>
<td>Dang gui 当归 <em>(Angelica sinensis (Oliv.) Diels)</em></td>
</tr>
<tr>
<td>Bai shao 白芍 <em>(Paeoniae lactiflora Pall.)</em></td>
</tr>
<tr>
<td>Bai zhu 白术 <em>(Atractylodes macrocephala Koidz.)</em></td>
</tr>
<tr>
<td>Zhi gan cao 炙甘草 <em>(honey fried Glycyrrhiza uralensis Fischer)</em></td>
</tr>
<tr>
<td>Modified Yin Chen Hao Tang (茵陈蒿汤加减) (China Association of CM 2012; Xiang, 2015)</td>
</tr>
<tr>
<td>Yin chen hao 茵陈蒿 <em>(Artemisia capillaris Thunb. Or A. scoparia Waldst. Et Kit.)</em></td>
</tr>
<tr>
<td>Zhi zi 栀子 <em>(Gardenia jasminoides Ellis)</em></td>
</tr>
<tr>
<td>Da huang 大黄 <em>(Rheum palmatum L.)</em></td>
</tr>
</tbody>
</table>

* May contain herbs that are restricted in Australia (Rebera, 2018)

**Abbreviations:** CM Chinese medicine, TCM Traditional Chinese medicine
### Appendix 2 Topical Chinese herbal medicines formulas and herb ingredients

<table>
<thead>
<tr>
<th>Topical formulas</th>
<th>Ingredients (Pinyin, Chinese characters and species name)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cuo Chuang Xi Ji</strong></td>
<td><em>Liu huang</em> 硫黄 (Sulfur)<em>&lt;br&gt; <em>Zhang nao</em> 樟脑 (Cinnamomum camphora (L.) Presl)</em>&lt;br&gt; <em>Xi huang qi jiao</em> 西黄芪胶 (Bummi Tragacanthi)&lt;br&gt; Lime water 柠檬水</td>
</tr>
<tr>
<td><strong>Dian Dao San</strong></td>
<td><em>Da huang</em> 大黄 (Rheum palmatum L.)&lt;br&gt; <em>Liu huang</em> 硫黄 (Sulphur)</td>
</tr>
<tr>
<td><strong>Du Jiao Lian Gao</strong></td>
<td><em>Bai fu zi</em> 白附子 (Typhonium giganteum Engl.)&lt;br&gt; <em>Bai zhi</em> 白芷 (Angelica dahurica (Fisch. ex Hoffm.) Benth. Et Hook f.)&lt;br&gt; <em>Zao jiao ci</em> 皂角刺 (Gleditsia sinensis L.)&lt;br&gt; <em>Fang ji</em> 防己 (Aristolochia fangchi Wu. or Stephania tetrandra S. Moore).<em>&lt;br&gt; <em>Lian qiao</em> 连翘 (Forsythia suspensa (Thunb.) Vahl)&lt;br&gt; <em>Jin yin hua</em> 金银花 (Lonicera japonica Thunb.)&lt;br&gt; <em>Hai tong pi</em> 海桐皮 (Erythrina variegata L. var. orientalis (L.) Merr.)&lt;br&gt; <em>Sheng nan xing</em> 生南星 (Arisaema consanguineum Schott)&lt;br&gt; <em>Su mu</em> 苏木 (Caesalpinia sappan L.)&lt;br&gt; <em>Ci wei pi</em> 刺猬皮 (Pellis Erinacei)&lt;br&gt; <em>Hai da i</em> (Kun bu) 昆布 (Laminaria japonica Aresch.)&lt;br&gt; <em>Huo ma ren</em> 火麻仁 (Cannabis sativa L.)</em>&lt;br&gt; <em>Xue yu tan</em> 血余炭 (Homo sapiens L. (charred human hair))&lt;br&gt; <em>Xi xian cao</em> 豨莶草 (Siegesbeckia pubescens Makino)&lt;br&gt; <em>Gan chan</em> 干蟾 (Bufo siccus)&lt;br&gt; <em>Ru xiang</em> 乳香 (Boswellia carterii Birdw.)&lt;br&gt; <em>Mo yao</em> 没药 (Commiphora myrrha Engl.)&lt;br&gt; <em>Xiang you</em> 香油 (Sesamum indicum DC.)&lt;br&gt; <em>Biao ye xian</em> 飞燕草 (Sphenomeris japonica (Thunb.) Maxim.)&lt;br&gt; <em>Zhang nao</em> 樟脑 (Cinnamomum camphora (L.) Presl)</td>
</tr>
<tr>
<td><strong>Hei Bu Yao Gao</strong></td>
<td><em>Lao hei cu</em> 老黑醋 (Acetum atrum vetum)&lt;br&gt; <em>Wu bei zi</em> 五倍子 (Rhus chinensis Mill.)&lt;br&gt; <em>Wu gong</em> 蜈蚣 (Scolopendra subspinipes mutilans L. Koch.)*&lt;br&gt; <em>Bing pian</em> 冰片 (Dryobalanops aromatica Gaertn.)&lt;br&gt; <em>Feng mi</em> 蜂蜜 (Mel)</td>
</tr>
<tr>
<td><strong>Qu Ban Gao</strong></td>
<td><em>Da feng zi</em> 大风子 (Hydnocarpus anthelmintica Pierre ex Laness)&lt;br&gt; <em>Xing ren</em> 桃仁 (Prunus armeniaca L. var. ansu Maxim.)*&lt;br&gt; <em>Hong fen</em> 红粉 (Mecuric oxide)&lt;br&gt; <em>Zhang nao</em> 樟脑 (Cinnamomum camphora (L.) Presl)</td>
</tr>
<tr>
<td><strong>San Huang Xi Ji</strong></td>
<td><em>Ku shen</em> 苦参 (Sophora flavescens Ait.)&lt;br&gt; <em>Da huang</em> 大黄 (Rheum palmatum L.)&lt;br&gt; <em>Huang qin</em> 黄芩 (Scutellaria baicalensis Georgi)&lt;br&gt; <em>Huang bai</em> 黄柏 (Phellodendron amurense Rupr.)</td>
</tr>
<tr>
<td><strong>Si Huang Gao</strong></td>
<td><em>Huang qin</em> 黄芩 (Scutellaria baicalensis Georgi)&lt;br&gt; <em>Huang lian</em> 黄连 (Coptis chinensis Franch.)&lt;br&gt; <em>Huang bai</em> 黄柏 (Phellodendron amurense Rupr.)</td>
</tr>
<tr>
<td>Topical formulas</td>
<td>Ingredients (Pinyin, Chinese characters and species name)</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td><em>Tu da huang</em> 士大黄 (<em>Rumex madaio</em> Mack.)</td>
<td><em>Ze lan</em> 泽兰 (<em>Lycopus lucidas</em> Turcz.)</td>
</tr>
<tr>
<td><em>Huang la</em> 黄蜡 (<em>Cera Aurea</em>)</td>
<td><em>Xiang you</em> 香油 (<em>Sesamum indicum</em> DC.)</td>
</tr>
</tbody>
</table>

* May contain herbs that are restricted in Australia (Rebera, 2018)
‡ May contain herbs that are on the CITES list
## Appendix 3 Impact on HRQoL and instruments used

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Sample size (n)</th>
<th>Instrument used</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akyazi et al., 2011</td>
<td>61</td>
<td>DLQI</td>
<td>DLQI was worse in people with acne compared to health controls. Also worse in severe acne group compared to mild acne group</td>
</tr>
<tr>
<td>Bahali et al., 2016</td>
<td>103</td>
<td>PVS, CDI, STA1c, RSES, PedsQL-C</td>
<td>No differences found between study and control groups for peer victimisation, depression, state and trait anxiety, self-esteem or QoL</td>
</tr>
<tr>
<td>Bez et al., 2013</td>
<td>146</td>
<td>MOCQ, SF-36, HADS</td>
<td>Study group OCD symptoms checking, slowness, rumination greater than control. Study group physical function, physical role, general health perception, vitality, emotional role worse than control</td>
</tr>
<tr>
<td>Bowe et al., 2011</td>
<td>52</td>
<td>BIDQ, Skindex-16, MBSRQ-AS, CES-D, FNE</td>
<td>A higher percentage of participants with severe acne were more affected emotionally and experienced greater social/occupational impact than those with mild acne; more than half had body image concerns</td>
</tr>
<tr>
<td>Chernyshov et al., 2018</td>
<td>150</td>
<td>DLQI, CADI</td>
<td>People with acne who sought treatment for their condition reported moderate HRQoL impairment compared to people with acne who didn’t consult with a dermatologist</td>
</tr>
<tr>
<td>Duman et al., 2016</td>
<td>125</td>
<td>AQOL, FDLQI, HADS Turkish versions</td>
<td>There was no difference between acne group and healthy controls for anxiety and depression (HADS). When HRQoL decreased, risk of anxiety and depression increased. Family members HRQoL was negatively affected</td>
</tr>
<tr>
<td>Durai &amp; Nair 2015</td>
<td>140</td>
<td>DLQI, CADI</td>
<td>Age, occupation, marital status, family and treatment history was a factor for HRQoL. Greater acne severity correlated with greater impact on HRQoL</td>
</tr>
<tr>
<td>El-Khateeb et al., 2014</td>
<td>2,068</td>
<td>Self-designed questionnaire plus DLQI &amp; CADI</td>
<td>Worse acne severity and scarring resulted in worse HRQoL</td>
</tr>
<tr>
<td>Gorelick et al., 2015</td>
<td>312</td>
<td>Acne-QoL, PHQ</td>
<td>Acne affected self-perception and social and emotional functioning. There were ethnic differences with Hispanic and Asians more impacted than Caucasian and darker skinned participants</td>
</tr>
<tr>
<td>Gupta et al., 2016</td>
<td>100</td>
<td>CADI Hindi version</td>
<td>Males HRQoL was more severely affected than females, particularly males who drank alcohol more than twice per week and who smoked</td>
</tr>
<tr>
<td>Halvorsen et al., 2011</td>
<td>3,775</td>
<td>SDQ, HSCL-90 modified</td>
<td>Suicidal ideation increased with increasing severity; substantial acne more likely to report mental health problems</td>
</tr>
<tr>
<td>Author, year</td>
<td>Sample size (n)</td>
<td>Instrument used</td>
<td>Findings</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>----------</td>
</tr>
<tr>
<td>Hanstock &amp; O’Mahony, 2002</td>
<td>Numbers not given</td>
<td>Acne-QoL, GHQ</td>
<td>High level of perfectionism was associated with greater tendency to be concerned about acne, especially appearance</td>
</tr>
<tr>
<td>Hosthota et al., 2016</td>
<td>200</td>
<td>DLQI, CADI, WHQOL-BREF</td>
<td>Medium to high impact on HRQoL in more than half of people with acne. The more severe the acne, the higher HRQoL impairment. People with acne were more psychologically affected than those without skin conditions</td>
</tr>
<tr>
<td>Ismail &amp; Mohammed-Ali, 2012</td>
<td>510</td>
<td>CADI</td>
<td>Females HRQol was worse than males. Worse acne severity correlated to worse HRQoL</td>
</tr>
<tr>
<td>Jankovic et al., 2012</td>
<td>465</td>
<td>CDLQI, CADI (Serbian versions)</td>
<td>Girls had higher CADI scores (worse HRQoL) than boys, and CDLQI was higher in those with skin conditions other than acne. Emotions (embarrassment, feeling upset or sad and self-consciousness) were a problem for children with acne</td>
</tr>
<tr>
<td>Kilkenny et al., 1997</td>
<td>2,028</td>
<td>CIS-R</td>
<td>Students with moderate acne were more likely to report a higher level of psychiatric symptoms and were in the later stages of puberty</td>
</tr>
<tr>
<td>Kokandi, 2010</td>
<td>112</td>
<td>CADI</td>
<td>Clinical severity and duration of acne did not correlate with worse CADI scores and mild acne does not necessarily mean little effect on HRQoL</td>
</tr>
<tr>
<td>Magin et al., 2006</td>
<td>26</td>
<td>Semi-structured interviews</td>
<td>Considerable psychological morbidity, embarrassment, impaired self-image, low self-esteem, self-consciousness, frustration and anger due to facial acne</td>
</tr>
<tr>
<td>Magin et al., 2008</td>
<td>26</td>
<td>Semi-structured interviews</td>
<td>Experiences of taunting, teasing or bullying relatively common. Hurtful experiences in a minority of participants (embarrassment, impairment of self-esteem) occurred during childhood or adolescence</td>
</tr>
<tr>
<td>Magin et al., 2010</td>
<td>244</td>
<td>GHQ-12, HAD, FSCS</td>
<td>Some correlation with introversion and greater self-assessed moderate and severe acne compared to mild acne</td>
</tr>
<tr>
<td>Mallon et al., 1999</td>
<td>111</td>
<td>DLQI, RSES, GHQ-28, SF-36</td>
<td>Acne affects mental health, social function, energy/vitality and role limitations due to emotional problems</td>
</tr>
<tr>
<td>Ogedegbe &amp; Henshaw, 2014</td>
<td>160</td>
<td>CADI</td>
<td>Mild acne correlated with mild impact of HRQoL</td>
</tr>
<tr>
<td>Pagliarello et al., 2015</td>
<td>195</td>
<td>SF-12, Skindex-29, GHQ-12</td>
<td>Severe acne had worse HRQoL</td>
</tr>
<tr>
<td>Purvis et al, 2004 &amp; 2006</td>
<td>9,398</td>
<td>RADS, ADI</td>
<td>Problem acne associated with increased frequency of depressive symptoms, anxiety and suicidal thoughts and attempts</td>
</tr>
<tr>
<td>Ramrakha et al., 2016</td>
<td>1,037</td>
<td>GHQ</td>
<td>Anxiety higher in those with acne than without acne</td>
</tr>
<tr>
<td>Author, year</td>
<td>Sample size (n)</td>
<td>Instrument used</td>
<td>Findings</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
<td>-----------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Rapp et al., 2004</td>
<td>479</td>
<td>Mood States</td>
<td>People with acne had anger associated with poorer HRQoL and dissatisfaction with treatment</td>
</tr>
<tr>
<td>Reljic et al., 2014</td>
<td>199</td>
<td>CDLQI</td>
<td>Impact on HRQoL was mild in the majority of adolescents however there were some severely affected</td>
</tr>
<tr>
<td>Salman et al., 2016</td>
<td>148</td>
<td>LSAS, HAD, DLQI</td>
<td>Social anxiety, anxiety and depression were worse in people with acne and vitiligo than healthy controls</td>
</tr>
<tr>
<td>Tanghetti et al., 2014</td>
<td>208</td>
<td>Acne-QoL, PHQ-4</td>
<td>Facial acne negatively impacted HRQoL in people with mild and moderate acne with symptoms of anxiety/depression affecting school and work</td>
</tr>
<tr>
<td>Tasoula et al., 2012</td>
<td>1,531</td>
<td>CDLQI</td>
<td>People with moderate/severe acne had greater psychosocial and emotional impairment than people with mild acne</td>
</tr>
<tr>
<td>Unal et al., 2016</td>
<td>102</td>
<td>CSPSCA, AQOL, RSES Turkish versions</td>
<td>No differences were seen in social anxiety levels and self-esteem between adolescents with acne compared to healthy controls</td>
</tr>
<tr>
<td>Vilar et al., 2015</td>
<td>317</td>
<td>CDLQI, DLQI, RSES</td>
<td>More severe acne correlated with worse HRQoL. There was no difference with self-esteem (RSES) between those with and without acne</td>
</tr>
<tr>
<td>Zaraa et al., 2013</td>
<td>82</td>
<td>CADI French version</td>
<td>Half of participants had a high impact on HRQoL particularly if onset was early and there were presence of pustules</td>
</tr>
<tr>
<td>Zauli et al., 2014</td>
<td>100</td>
<td>APSEA</td>
<td>Acne severity was a factor in worse HRQoL before intervention however post intervention, acne reduction of APSEA score did not correlate to reduction of acne severity indicating factors other than acne severity contributed to impact of HRQoL</td>
</tr>
</tbody>
</table>

Abbreviations: Acne-QoL Acne Specific Quality of Life, ADI Acne Disability Index, APSEA, AQOL Acne Quality of Life Scale, BIDQ Body Image Disturbance Questionnaire, CADI Cardiff Acne Disability Index, CDI Child Depression Inventory, CDLQI Children’s Dermatology Life Quality Index, CES-D Centre for Epidemiologic Studies Depression Scale, CIS-R Clinical Interview Schedule, CSPSCA Capa Social Phobia Scale for Children and Adolescents, DLQI Dermatology Life Quality Index, FDLQI Family Dermatology Life Quality Index, FNE Fear of Negative Evaluation Scale, FSCS Fenigstein Self-Consciousness Scale, GHQ General Health Questionnaire, HAD Hospital Anxiety Depression Scale, HSCL Hopkins Symptom Checklist, LSAS Liebowitz Social Anxiety Scale, MBSRQ-AS Multidimensional Body Self-Relations Questionnaire-Appearance Scales, MOCQ Maudsley Obsessive Compulsive Questionnaire, N number, OCD Obsessive compulsive disorder, PedsQL-C Pediatric Quality of Life Inventory Child Versions, PHQ-4 Patient Health Questionnaire, PVS Peer Victimization Scale, QoL quality of life, RADS, RSES Rosenberg Self-Esteem Scale, SF Short Form, SDQ Strengths and Difficulties Questionnaire, STAIc State-Trait Anxiety Inventories for Children, WHOQOL-BREF World Health Organization Quality of Life-BREF
Appendix 4 Survey questionnaire

Acne Quality of Life

Survey Flow

| Section 1: Participation information (2 Questions) |
| Section 2: Acne Quality of Life (20 Questions)   |
| Section 3: CAM Use (9 Questions)                 |
| Section 3: CAM Beliefs (14 Questions)            |
| Section 4: CM Treatment Preferences (6 Questions) |
| Section 5: Demographics (11 Questions)           |
| Standard: Pilot Questions (2 Questions)          |

Start of Block: Participation information

Preamble  Statement on Participation You are invited to participate in a research project surveying adolescents, young people and adults on how people feel about their acne, which medications they have used and the impact acne has on their daily life. It will also ask questions on your treatment preferences for Chinese medicine. It should take you 15–20 minutes to complete. Please read this statement carefully and be confident that you understand its contents before deciding whether to participate.

This research is being conducted by Suzi Mansu PhD Candidate and supervised by Associate Professor Anthony Zhang, Dr Meaghan Coyle and Professor Charlie Xue from RMIT University, School of Health and Biomedical Sciences. This project has been approved by RMIT’s Science, Engineering and Health College Human Ethics Advisory Network (CHEAN); The project is jointly supported by the China-Australia International Research Centre for Chinese Medicine (CAIRCCM) – a joint initiative of RMIT University, Australia and the Guangdong Provincial Academy of Chinese Medical Sciences.

Results are intended for publication in a journal article and then dissemination through a conference. It will also be in a chapter as part of the PhD thesis. We don’t anticipate any risks or benefits associated with participating in this study. Some of the questions included in the survey may be embarrassing or make you feel uncomfortable. You have the right to decline to answer particular questions, or to withdraw from the study prior to the completion of the survey by closing down your browser. Once you have completed the survey you will not be able to withdraw, as your responses will not be able to be identified. The information you provide will be confidential, and will only be available to members of the research team.

If there are any questions that make you uncomfortable or raises concerns for you, please contact one of the Investigators, Dr Meaghan Coyle, of this study on 03 9925 7678 or email meaghan.coyle@rmit.edu.au. Dr Coyle will discuss your concerns with you confidentially, and may suggest further follow up if necessary. You may also contact the RMIT Ethics Committee to discuss your concerns if you prefer to have them handled by someone outside the research team. Human Research Ethics Coordinator, Research
Consent To be eligible to do the survey, you must be 15 years and older and live in Australia. If you are under 15 years old, or do not live in Australia you are not eligible to participate in this survey. Please close your screen to withdraw from the survey. Thank you for your interest. Because of the nature of data collection, we are not obtaining written informed consent from you. Instead, we ask you to read this statement and click the “agree to participate” or “not agree to participate” check box. We also assume that you have given consent by your completion of the online questionnaire.

☐ I AGREE to participate (1)

☐ I DO NOT agree to participate (2)
Q1 *In the past WEEK, how unattractive did you feel because of your facial acne?*

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Q2 *In the past WEEK, how embarrassed did you feel because of your facial acne?*

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Q3 *In the past WEEK, how self-conscious (uneasy about oneself) did you feel about your facial acne?*

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Q4 *In the past WEEK, how upset were you about having facial acne?*

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Q5 *In the past WEEK, how annoyed did you feel at having to spend time every day cleaning and treating your face because of your facial acne?*

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Q6 *In the past WEEK, how dissatisfied with your self-appearance did you feel because of your facial acne?*

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Q7 *In the past WEEK, how concerned or worried were you about not looking your best because of your facial acne?*

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Q8 *In the past WEEK, how concerned or worried were you that your acne medication/products were working fast enough in clearing up the acne on your face?*

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Q9 *In the past WEEK, how bothered did you feel about the need to always have medication or cover-up available for the acne on your face?*

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Q10 *In the past WEEK, how much was your self-confidence (sure of yourself) negatively affected because of your facial acne?*

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Q11 *In the past WEEK, how concerned or worried were you about meeting new people because of your facial acne?*

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Q12 *In the past WEEK, how concerned or worried were you about going out in public because of your facial acne?*

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Q13 *In the past WEEK, how much was socializing with people a problem for you because of your facial acne?*

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Q14 *In the past WEEK, how much was interacting with the opposite sex (or same sex if gay or lesbian) a problem for you because of your facial acne?*

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Q15 *In the past WEEK, how many bumps did you have on your face?*

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Q16 *In the past WEEK, how many bumps full of pus did you have on your face?*

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<th>a lot (3)</th>
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Q17 *In the past WEEK, how much scabbing from your facial acne did you have?*

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Q18 *In the past WEEK, how concerned or worried were you about scarring from your facial acne?*

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Q19 *In the past WEEK, how oily was your facial skin?*

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End of Block: Acne Quality of Life

Start of Block: CAM Use

Q20 Have you used complementary/alternative medicine (CAM) for: *(check all that apply)*

- [ ] preventing illness (1)
- [ ] treating illness (2)
- [ ] promoting health (3)
- [ ] I have never used CAM (4)
- [ ] Other (5)

*Skip To: End of Block If = I have never used CAM*

*Skip To: Q20 Other If = Other*

Q20 **Other** If you have chosen “other” please specify:

________________________________________________________________
Q21 Identify the statement that best describes your healthcare practices:

- I use CAM only (1)
- I use CAM with treatments given to me by my medical doctor (2)

Q22 Which natural health products and therapies do you use or have you used in the past? (check all that apply)

- Acupuncture (1)
- Acupressure (2)
- Aromatherapy (3)
- Art therapy (4)
- Ayurveda (5)
- Bach flower remedies (6)
- Chiropractic (7)
- Colour therapy (8)
- Dance movement therapy (9)
- Spiritual healing (10)
Herbal medicine (11)

Homeopathy (12)

Hypnosis (13)

Magnetic therapy (14)

Massage (15)

Meditation (16)

Transcendental meditation (17)

Music therapy (18)

Naturopathy (19)

Osteopathy (20)

Reiki (21)

Reflexology (22)

Relaxation/breathing technique (23)
Skip To: Q22 other If Which natural health products and therapies do you use or have you used in the past? (Check all that apply) = Other

Q22 Other If you have chosen “other” please specify:

______________________________________________________________________________

______________________________________________________________________________

______________________________________________________________________________
Q23 Identify the statement that best describes your intake of natural health products. A natural health product includes *vitamins and minerals*. (check only one box)

- [ ] I do not take natural health products (1)
- [ ] I take natural health products on a daily basis (2)
- [ ] I take natural health products on a weekly basis (3)
- [ ] I take natural health products on a monthly basis (4)
- [ ] I take natural health products once a year (5)
- [ ] I take natural health products less often than once a year (6)
- [ ] Other (7)

Skip To: Q23 Other If Identify the statement that best describes your intake of natural health products. A natural heal... = Other

Q23 Other If you have chosen “other” please specify:

______________________________________________________________________
Q24 Identify the statement that best describes your level of involvement with a CAM provider. (check only one box)

- I do not see CAM providers (1)
- I see CAM providers on a daily basis (2)
- I see CAM providers on a weekly basis (3)
- I see CAM providers on a monthly basis (4)
- I see CAM providers once a year (5)
- I see CAM providers less than once a year (6)
- Other (7)

Q24 Other If you have chosen “other” please specify:

________________________________________________________________

End of Block: CAM Use

Start of Block: CAM Beliefs

Statement In this section, a young adult is an individual between the ages of 15 and 24 years. Listed below are a number of statements concerning your beliefs about CAM use? For each statement you should circle the number that corresponds most closely to your belief. Choose only one number. Please do not miss any statements.
Q25 CAM providers give good information on maintaining a healthy lifestyle

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Q26 There are less side effects when taking natural remedies

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Q27 CAM involves natural plant formulas which are more healthy than taking drugs given by the medical doctor

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Q28 Young adults would be more likely to use CAM if there were more CAM clinics

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Q29 Young adults are more empowered when using CAM because CAM providers involve them in decisions about their healthcare treatments

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Q30 Young adults believe that CAM builds up the body’s own defenses and promotes self-healing

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Q31 The more knowledge a young adult has about CAM, the more likely he/she is to use it

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Q32 Parent(s) and family can influence a young adult’s CAM use by exposing them to it

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Q33 Young adults are more likely to use CAM if their friends are using it

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<th>Strongly disagree (1)</th>
<th>Disagree (2)</th>
<th>Haven’t decided (3)</th>
<th>Agree (4)</th>
<th>Strongly agree (5)</th>
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</thead>
<tbody>
<tr>
<td>Please choose one (1)</td>
<td>O</td>
<td>O</td>
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</table>
Q34 Young adults are more likely to use CAM if coaches and teachers discuss it with them

<table>
<thead>
<tr>
<th></th>
<th>Strongly disagree (1)</th>
<th>Disagree (2)</th>
<th>Haven’t decided (3)</th>
<th>Agree (4)</th>
<th>Strongly agree (5)</th>
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<tbody>
<tr>
<td>Please choose one (1)</td>
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</table>

Q35 Young adults who believe in the physical, mental and spiritual aspects of health are more likely to use CAM

<table>
<thead>
<tr>
<th></th>
<th>Strongly disagree (1)</th>
<th>Disagree (2)</th>
<th>Haven’t decided (3)</th>
<th>Agree (4)</th>
<th>Strongly agree (5)</th>
</tr>
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<tr>
<td>Please choose one (1)</td>
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</table>

Q36 Young adults who fear the discomfort of treatments from medical doctors are more likely to use CAM

<table>
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<tr>
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<th>Strongly disagree (1)</th>
<th>Disagree (2)</th>
<th>Haven’t decided (3)</th>
<th>Agree (4)</th>
<th>Strongly agree (5)</th>
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<td>Please choose one (1)</td>
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<td></td>
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</table>
Q37 Young adults believe that taking CAM therapies is not harmful

<table>
<thead>
<tr>
<th>Please choose one (1)</th>
<th>Strongly disagree (1)</th>
<th>Disagree (2)</th>
<th>Haven’t decided (3)</th>
<th>Agree (4)</th>
<th>Strongly agree (5)</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

End of Block: CAM Beliefs

Start of Block: CM Treatment Preferences

Q38 What type of herbs would you be willing to use for your acne? (rank in order your preference from 1 - 6)

___ Cleanser (topical) (1)
___ Pills (oral) (2)
___ Tablets (oral) (3)
___ Granules (oral) (4)
___ Powders (oral) (5)
___ Liquid (oral) (6)
Q39 *What is the maximum time would you be willing to try these techniques (please choose one only)?*

- [ ] 2 weeks (1)
- [ ] 4 weeks (2)
- [ ] 8 weeks (3)
- [ ] 12 weeks (4)
- [ ] 6 months (5)
- [ ] 12 months (6)

---

Q40 *Herbs can be used at home. How often would you be prepared to use herbs (please choose one only)?*

- [ ] Weekly (1)
- [ ] Twice weekly (2)
- [ ] Every second day (3)
- [ ] Daily (4)
- [ ] Twice daily (5)
- [ ] Three times daily (6)

---
Q41 *What type of acupuncture and related manual therapies would you be willing to use for your acne? (rank in order your preference from 1–5)*

_____ Acupuncture (1)
_____ Acupressure (like massage) (2)
_____ Ear acupressure (3)
_____ Electro-acupuncture (mild current through electrodes on acupuncture points) (4)
_____ Laser acupuncture (5)

Q42 *What is the maximum time would you be willing to try these techniques (please choose one only)?*

- 2 weeks (1)
- 4 weeks (2)
- 8 weeks (3)
- 12 weeks (4)
- 6 months (5)
- 12 months (6)
Q43 Acupuncture-like treatments require visits to an acupuncturist. How often would you be prepared to use these types of acupuncture treatment (please choose one only)?

- [ ] Fortnightly (1)
- [ ] Weekly (2)
- [ ] Twice weekly (3)
- [ ] Every second day (4)
- [ ] Daily (5)

End of Block: CM Treatment Preferences

Start of Block: Demographics

Q44 What is your gender?

- [ ] Male (1)
- [ ] Female (2)
- [ ] Other (3)

Q45 What is your ethnicity?

▼ Please choose your ethnicity (1) ... Other (8)

Aboriginal / Torres Strait Islander
Caucasian
Asian
Middle Eastern
Pacific Islander
African
Other

Skip To: Q45 other If What is your Ethnicity? = Other

Q45 Other If you have chosen “other” please specify:
________________________________________________________________

Q46 What is your age?

▼ Please choose your age (1) ... 50+ (9)
15–19
20–24
25–30
31–35
36–40
41–45
46–50
50+

352
Q47 *How long have you had acne?*

▼ Please choose one (1) ... 10+ years (9)

- Less than 3 months
- 3–6 months
- 6–9 months
- Less than 1 year
- 1–2 years
- 3–4 years
- 5–9 years
- 10+ years

---

Q48 *Do you think your acne is:*

▼ Please choose one (1) ... Severe (4)

- Mild
- Moderate
- Severe
Q49 Have you previously sought medical advice for acne?

- Yes (1)
- No (2)

Q50 What medications have you taken for your acne? (Check all that apply)

- Topical antibiotics and benzoyl peroxide (such as Duac Once Daily Gel) (1)
- Oral antibiotics (2)
- Topical antibiotics and benzoyl peroxide (3)
- Isotretinoin (such as Roaccutane) (4)
- Benzoyl peroxide alone (such as bentonite) (5)
- Topical adapalene (such as Differin topical gel or cream) (6)
- Topical retinoids (such as Stieva A cream, Re-Trieve cream) (7)
- Topical retinoids and benzoyl peroxide (8)
- None of the above (9)
- Other (10)
Q50 **Other** If you have chosen “other” please specify:

________________________________________________________________

Q51 *What over-the-counter products have you used for your acne? (check all that apply)*

- [ ] Benzoyl peroxide lotions and creams (such as Proactive or Clearasil) (1)
- [ ] Azelaic acid preparation (such as Dermatologica or Ego Azclear) (2)
- [ ] Glycolic acid preparations (such as Glycolix) (3)
- [ ] Salicylic acid lotions and creams (such as Clearasil) (4)
- [ ] None of the above (5)
- [ ] Other (6)

Q51 **Other** If you have chosen “other” please specify:

________________________________________________________________

End of Block: Demographics
Start of Block: Pilot Questions

Q52 How long did it take you to fill out the questions?

________________________________________________________________

________________________________________________________________

Q53 *Were there any questions you didn’t understand or make sense to you?*

________________________________________________________________

________________________________________________________________

________________________________________________________________

________________________________________________________________

End of Block: Pilot Questions
Appendix 5 Advertising details for survey

Acne Quality of Life Survey

Is acne causing you grief? Do you want to tell someone how you feel?

Take a survey on acne to help us understand how you feel about acne and how it affects your life.

RMIT University is surveying adolescents, young people and adults 15 years and older on how acne is affecting your life. We are also interested to know what you think of Chinese medicine, and whether you would consider using this for your acne. The survey is anonymous and would not record any identifying data.

The study might be a good fit for you if you:

• Have facial acne
• Are 15 years and older
• Are living in Australia

If you want further information, you can contact the investigators:
Dr Meaghan Coyle meaghan.coyle@rmit.edu.au 03 9925 7678

Go to Facebook: AcneQoLSurvey
Web link: https://rmit.au1.qualtrics.com/jfe/form/SV_d6Jh5I7kjEwI4PGJ

Survey closes 31 August 2018
Appendix 6 Permissions for the use of the Acne-QoL survey

An agreement which is private and confidential was signed but is excluded from the thesis. Permission emails have been included in the following pages.
Hi Tara,

Thank you for the instrument and the instructions

cheers,

Suzi

On 10 August 2017 at 01:28, Robbins, Tara wrote:

Dear Suzi,

Thank you for the signed UA. Attached you will find the ACNE QOL measure you requested in English.

Kind Regards,

*Tara Robbins*

Administrative Assistant
Economic and Data Sciences (EDS)
Center for Observational and Real-World Evidence (CORE)

Dear Tara,

Thank you very much for following this up for me. Please find attached the signed agreement.

cheers,

Suzi
On 8 August 2017 at 06:45, Robbins, Tara wrote:

Dear Suzi,

Enclosed is a brief User Agreement that details the conditions of use for the Acne-QoL. Please review the agreement and if the terms of the agreement are acceptable to you, please sing and date the agreement an return to me a clean copy (pdf) via email.

Kind Regards,

Tara Robbins  
Administrative Assistant  
Economic and Data Sciences (EDS)  
Center for Observational and Real-World Evidence (CORE)

---

From: Suzi Mansu  
Sent: Thursday, August 03, 2017 9:42 PM  
To: Robbins, Tara  
Subject: Permission to use the Acne-QoL for research purposes

Dear Tara,

Would you be able to follow up on this request sent last month? I am hoping for Dr Martin’s permission to get ethics approval for my project. Thanking you in advance.  

cheers,  
Suzi

---

On 14 July 2017 at 07:29, Robbins, Tara wrote:

Hi Suzi,

Sorry about that, our computer systems were out of service until last week. They are slowly coming back up. I have forwarded this for approval.

Thank you,  

Tara Robbins  
Administrative Assistant  
Economic and Data Sciences (EDS)  
Center for Observational and Real-World Evidence (CORE)
Dear Ms Robbins,
I sent an email last week and got a bounce back from your company stating Dr Martin-Nguyen was not reachable. Do you have the authority or someone in your company have the authority to approve my application for the use of Acne-QoL? Or is there a forwarding email address for Dr Martin-Nguyen? Thanking you in advance for your assistance.

yours sincerely,
Suzi Mansu

---------- Forwarded message ----------
From: Suzi Mansu
Date: 30 June 2017 at 11:41
Subject: Permission to use the Acne-QoL for research purposes
To: "Martin Nguyen, Allison"
Cc: Meaghan Coyle, "Robbins, Tara"
Dear Dr. Nguyen,
Please find attached my application for permissions to use the Acne-QoL instrument.

I am conducting a survey to assess people with acne vulgaris' health related quality of life in Australia. I have come across your validated tool Acne-QoL questionnaire for the assessment of patient health related quality of life across a number of journal articles and would like to request permission to use the questionnaire. A health related quality of life survey has not been conducted in Australia since 1995 and using your health related quality of life tool would further the understanding of the burden of this condition in adolescents and young adults in Australia.

We would acknowledge your permission to use the questionnaire in resulting publications. Please also let me know if there is a cost involved for the use of the questionnaire.

Thank you for your consideration.

yours sincerely,
Suzi Mansu
Appendix 7 Permissions for the use of the CAM Questionnaire for Young Adults survey
On 2 July 2017 at 21:02, Christine Patterson wrote:

Hello: You can use the tool. All the best in your research.

On Thu, Jun 29, 2017 at 10:55 PM -0400, "Suzi Mansu" wrote:

Dear Dr. Patterson

My name is Suzi Mansu, I’m a PhD candidate at RMIT University, Melbourne. As part of my PhD studies, I am conducting a survey to assess health related quality of life among people in Australia with acne vulgaris and to examine their beliefs and usage of CAM.

I have come across your validated tool Complementary Alternative Medicine Questionnaire for Young Adults for the assessment of adolescent usage and decisions to use CAM across a number of journal articles and would like to request permission to use the questionnaire. A CAM beliefs survey has not been conducted in Australia since 2004 which was on pharmacy students. Using your questionnaire would further the understanding of the belief and attitudes in adolescents and young people in Australia, and would inform trial design of a CAM intervention for acne vulgaris.

The findings from this research will be published in peer-reviewed journals, and we would acknowledge your permission to use the questionnaire. Please also let me know if there is a cost involved.

Thank you for your consideration.

Yours sincerely,

Suzi Mansu
Appendix 8 CHEAN ethics approval for survey
Dear Dr Coyle

SEHAPP 55-17 Acne in adolescents, young people and adults: impact on quality of life and attitudes to Chinese medicine

Thank you for submitting your amended application for review.

I am pleased to inform you that the CHEAN has approved your application for a period of **3 Months** from the date of this letter to **30 November 2017** and your research may now proceed.

**Conditions to approval:**

1. School permissions will be provided to the CHEAN upon receipt by researchers
2. The CHEAN will be alerted to any changes to survey questions

The CHEAN would like to remind you that:

All data should be stored on University Network systems. These systems provide high levels of manageable security and data integrity, can provide secure remote access, are backed up on a regular basis and can provide Disaster Recover processes should a large scale incident occur. The use of portable devices such as CDs and memory sticks is valid for archiving; data transport where necessary and for some works in progress. The authoritative copy of all current data should reside on appropriate network systems; and the Principal Investigator is responsible for the retention and storage of the original data pertaining to the project for a minimum period of five years.
**Please Note:** Annual reports are due on the anniversary of the commencement date for all research projects that have been approved by the CHEAN. Ongoing approval is conditional upon the submission of annual reports failure to provide an annual report may result in Ethics approval being withdrawn.

Final reports are due within six months of the project expiring or as soon as possible after your research project has concluded.

The annual/final reports forms can be found at: [www.rmit.edu.au/staff/research/human-research-ethics](http://www.rmit.edu.au/staff/research/human-research-ethics)

Yours faithfully,

*Associate Professor Barbara Polus*
*Chair, Science Engineering & Health*
*College Human Ethics Advisory Network*

Cc  Student Investigator/s: Mrs Suzi Mansu, School of Health & Biomedical Sciences
Other Investigator/s: A/Prof Anthony Zhang, School of Health & Biomedical Sciences
                     Prof Charlie Xue, School of Health & Biomedical Sciences
Appendix 9 CHEAN ethics approval for survey amendment 1
15 September 2017

Dr Meaghan Coyle  
School of Health and Biomedical Sciences  
RMIT University

Dear Dr Coyle

SEHAPP 55-17 Acne in adolescents, young people and adults: impact on quality of life and attitudes to Chinese medicine

Thank you for requesting an amendment and extension to your Human Research Ethics project titled: Acne in adolescents, young people and adults: impact on quality of life and attitudes to Chinese medicine, which was originally approved by Science Engineering and Health CHEAN in 2017 for a period of 3 months.

I am pleased to inform you that the CHEAN has approved your amendment as outlined in your request and has been extended to 30 May 2018.

The CHEAN notes and thanks you for providing all documentation that incorporates these amendments. This documentation will be appended to your file for future reference and your research may now continue.

The committee would like to remind you that:

All data should be stored on University Network systems. These systems provide high levels of manageable security and data integrity, can provide secure remote access, are backed up on a regular basis and can provide Disaster Recover processes should a large scale incident occur. The use of portable devices such as CDs and memory sticks is valid for archiving; data transport where necessary and for some works in progress; The authoritative copy of all current data should reside on appropriate network systems; and the Principal Investigator is responsible for the retention and storage of the original data pertaining to the project for a minimum period of five years.

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The annual/final reports forms can be found at: www.rmit.edu.au/staff/research/human-research-ethics

Yours faithfully,

Associate Professor Barbara Polus  
Chair, Science Engineering & Health  
College Human Ethics Advisory Network

Cc  Student Investigator/s:  Mrs Suzi Mansu, School of Health & Biomedical Sciences A/Prof Anthony Zhang, School of Health & Biomedical Sciences Prof Charlie Xue, School of Health & Biomedical Sciences

Other Investigator/s:
Appendix 10 CHEAN ethics approval for survey amendment 2
13 November 2017

Dr Meaghan Coyle
School of Health and Biomedical Sciences
RMIT University

Dear Dr Coyle

SEHAPP 55-17 Acne in adolescents, young people and adults: impact on quality of life and attitudes to Chinese medicine

Thank you for requesting an amendment and extension to your Human Research Ethics project titled: Acne in adolescents, young people and adults: impact on quality of life and attitudes to Chinese medicine, which was originally approved by Science Engineering and Health CHEAN in 2017 for a period of 3 months.

I am pleased to inform you that the CHEAN has approved your amendment as outlined in your request.

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The committee would like to remind you that:

All data should be stored on University Network systems. These systems provide high levels of manageable security and data integrity, can provide secure remote access, are backed up on a regular basis and can provide Disaster Recover processes should a large scale incident occur. The use of portable devices such as CDs and memory sticks is valid for archiving; data transport where necessary and for some works in progress; The authoritative copy of all current data should reside on appropriate network systems; and the Principal Investigator is responsible for the retention and storage of the original data pertaining to the project for a minimum period of five years.
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Final reports are due within six months of the project expiring or as soon as possible after your research project has concluded.

The annual/final reports forms can be found at:  

Yours faithfully,

**Associate Professor Barbara Polus**  
Chair, Science Engineering & Health  
College Human Ethics Advisory Network

Cc  Student Investigator/s:  Mrs Suzi Mansu, School of Health & Biomedical Sciences  
A/Prof Anthony Zhang, School of Health & Biomedical Sciences  
Prof Charlie Xue, School of Health & Biomedical Sciences  

Other Investigator/s:  

Appendix 11 CHEAN ethics approval for survey amendment 3
Dear Dr Coyle

SEHAPP 55-17 Acne in adolescents, young people and adults: impact on quality of life and attitudes to Chinese medicine

Thank you for requesting an amendment and extension to your Human Research Ethics project titled: Acne in adolescents, young people and adults: impact on quality of life and attitudes to Chinese medicine, which was originally approved by Science Engineering and Health CHEAN in 2017 for a period of 3 months.

I am pleased to inform you that the CHEAN has approved your amendment as outlined in your request.

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Final reports are due within six months of the project expiring or as soon as possible after your research project has concluded.

The annual/final reports forms can be found at:
www.rmit.edu.au/staff/research/human-research-ethics

Yours faithfully,

Associate Professor Barbara Polus
Chair, Science Engineering & Health
College Human Ethics Advisory Network

Cc  Student Investigator/s:  Mrs Suzi Mansu, School of Health & Biomedical Sciences A/Prof Anthony Zhang, School of Health & Biomedical Sciences  Prof Charlie Xue, School of Health & Biomedical Sciences

Other Investigator/s:
Appendix 12 CHEAN ethics approval for survey amendment 4
21 March 2018

Dr Meaghan Coyle
School of Health and Biomedical Sciences
RMIT University

Dear Dr Coyle

SEHAPP 55-17 Acne in adolescents, young people and adults: impact on quality of life and attitudes to Chinese medicine

Thank you for requesting an amendment and extension to your Human Research Ethics project titled: Acne in adolescents, young people and adults: impact on quality of life and attitudes to Chinese medicine, which was originally approved by Science Engineering and Health CHEAN in 2017 for a period of 3 months.

I am pleased to inform you that the CHEAN has approved your amendment as outlined in your request and has been extended to 31 December 2018.

The CHEAN notes and thanks you for providing all documentation that incorporates these amendments. This documentation will be appended to your file for future reference and your research may now continue.

The committee would like to remind you that:

All data should be stored on University Network systems. These systems provide high levels of manageable security and data integrity, can provide secure remote access, are backed up on a regular basis and can provide Disaster Recover processes should a large scale incident occur. The use of portable devices such as CDs and memory sticks is valid for archiving; data transport where necessary and for some works in progress; The authoritative copy of all current data should reside on appropriate network systems; and the Principal Investigator is responsible for the retention and storage of the original data pertaining to the project for a minimum period of five years.

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Yours faithfully,

Associate Professor Barbara Polus  
Chair, Science Engineering & Health  
College Human Ethics Advisory Network

Cc  Student Investigator/s: Mrs Suzi Mansu, School of Health & Biomedical Sciences A/Prof Anthony Zhang, School of Health & Biomedical Sciences Prof Charlie Xue, School of Health & Biomedical Sciences  
Other Investigator/s:
### Appendix 13 Search terms acupuncture and CHM

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<th>Subblock</th>
<th>PubMed, Cochrane, Cinahl</th>
<th>EMBASE</th>
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<td><strong>Condition</strong></td>
<td>Acne vulgaris</td>
<td>Acne vulgaris OR acne cyst OR papulo-pustular acne OR papulopustular acne OR papulo pustular acne OR inflammatory acne OR polymorphic acne OR juvenile acne OR juvenile onset acne OR adult onset acne OR adult acne</td>
<td>Acne vulgaris OR acne cyst OR papulo-pustular acne OR papulopustular acne OR papulo pustular acne OR inflammatory acne OR polymorphic acne OR juvenile acne OR juvenile onset acne OR adult onset acne OR adult acne</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Acupuncture, moxibustion and related therapies</td>
<td>Acupuncture OR Meridians OR Electroacupuncture OR Moxibustion OR Auriculotherapy OR plum blossom OR acupressure OR ear acupuncture OR ear acupuncture OR moxa OR laser acupuncture OR seven star needle OR acupuncture analgesia OR acupuncture points OR electro-acupuncture OR electro acupuncture OR TENS OR transcutaneous nerve stimulation OR transcutaneous electric nerve stimulation OR transcutaneous electrical nerve stimulation OR electro-stimulation OR pharmacopuncture OR point injection OR catgut embedding</td>
<td>Acupuncture OR electroacupuncture OR moxibustion OR ear acupuncture OR plum blossom OR acupressure OR ear acupuncture OR moxa OR laser acupuncture OR seven star needle OR acupuncture analgesia OR acupuncture points OR electro-acupuncture OR electro acupuncture OR TENS OR transcutaneous nerve stimulation OR transcutaneous electric nerve stimulation OR transcutaneous electrical nerve stimulation OR electro-stimulation OR electro stimulation OR pharmacopuncture OR point injection OR catgut embedding</td>
</tr>
<tr>
<td><strong>Other CM therapies</strong></td>
<td>Tai Ji OR Tai chi OR Breathing exercises OR Qi gong OR Qigong OR Chi Kung OR Tuina OR anmo Tuina OR Chinese massage OR cupping OR guasha OR blood letting OR bloodletting OR diet therapy OR therapy, diet OR therapies, diet OR phlebotomy</td>
<td>Tai Chi OR Tai Ji OR Breathing exercise OR Qi gong OR Qigong OR Tuina OR anmo Tuina OR Chinese massage OR cupping OR guasha OR blood letting OR bloodletting OR Diet therapy OR diet treatment OR dietary therapy OR dietary treatment OR Phlebotomy</td>
<td></td>
</tr>
<tr>
<td><strong>CHM (Herbs)</strong></td>
<td>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 Kanpo OR TCM OR T.C.M. OR Medicine, Ayurvedic OR Phytherapy OR Herbiology OR Plants, Medicinal OR Plant Preparations OR Plant Extracts OR Plants, Medicine OR Materia Medica OR Single Prescription OR Herbs OR Chinese Medicine Herb OR Herbal Medicine</td>
<td>Chinese medicine OR medicinal plant OR Chinese drug OR plant medicinal product OR plant extract OR herb OR herbal medicine OR material medica OR traditional medicine OR ethnopharmacology OR ethnobotany OR Kampo OR Ayurveda OR alternative medicine OR phytherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Randomized controlled trial¹ (including RCT and CCT)</td>
<td>randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups</td>
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<td></td>
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<tr>
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<td>cohort studies OR case-control studies OR comparative study OR risk factors OR cohort OR compared OR groups OR case control OR multivariate OR case series</td>
<td>'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab OR 'case series':ti,ab</td>
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</table>
Appendix 14 Published review “Herbal medicine *Eriobotrya japonica* formula for acne vulgaris: a systematic review”
Review article

Herbal medicine Eriobotrya japonica formula for acne vulgaris: A systematic review

Suzi Shu Yi Mansu\textsuperscript{a}, Meaghan Coyle\textsuperscript{b}, Kaiyi Wang\textsuperscript{a}, Brian May\textsuperscript{b}, Anthony Lin Zhang\textsuperscript{b, c}\textsuperscript{*}, Charlie Chang Li Xue\textsuperscript{b, c}

\textsuperscript{a} Discipline of Chinese Medicine, School of Health and Biomedical Sciences, RMIT University, Bundoora, VIC, Australia
\textsuperscript{b} China-Australia International Research Centre for Chinese Medicine, School of Health Sciences, RMIT University, Bundoora, Melbourne, VIC, Australia
\textsuperscript{c} Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou 510120, China

A R T I C L E  I N F O

Keywords:
Acne vulgaris
Eriobotrya japonica
Chinese traditional medicine
Systematic review

A B S T R A C T

Acne vulgaris is a common inflammatory skin condition characterized by comedones. Current pharmacotherapies are effective but are associated with adverse events (AEs) such as mood disorders and antibiotic resistance. The Eriobotrya japonica Formula (EJF) contains six herbs commonly used in traditional Chinese medicine clinical practice. This paper evaluates the experimental evidence and clinical efficacy of EJF for acne vulgaris.

Searches of 11 English and Chinese databases were conducted to identify eligible randomized controlled trials (RCTs). PubMed was searched for experimental evidence of herbs included in EJF. Meta-analyses were performed to analyse the clinical effects of EJF compared to pharmacotherapies.

Ingredients in EJF were reported to have an effect on inhibiting TNF-\textalpha, PPAR-\gamma and IL-6 cytokines. Some also inhibited P. acnes and had anti-androgenic and anti-lipogenic effects. There were 15 RCTs included in the clinical review. The number of people achieving a clinical improvement based on lesion count was higher with EJF than pharmacotherapies. The effective rate of EJF was greater than antibiotics and benzoyl peroxide (2 studies, RR: 1.47 [1.23, 1.77], I\textsuperscript{2} = 0\%), and antibiotics with topical supplements (2 studies, RR: 1.77 [1.18, 2.67], I\textsuperscript{2} = 0\%).

There were 107 mild AEs reported in 7 trials, 33 in the intervention groups and 74 in the control groups. No serious AEs were reported.

There is some evidence that EJF can decrease inflammatory lesions in acne vulgaris with fewer AEs in the short-term. However, due to methodological limitations of the included trials, results on clinical efficacy should be interpreted with caution.

1. Introduction

Acne vulgaris is a common inflammatory condition of the pilosebaceous glands of the skin that begins at adolescence and can affect adults up to 50 years old. The prevalence of acne is higher in western countries (Cordain et al., 2002) with around 20\% of adolescents suffering moderate to severe acne, but acne may persist in 64\% of adults in their 20\s and 43\% in their 30\s (Bhate and Williams, 2014). The burden of the disease is high, with anxiety, depression, body image concerns, poor self-esteem, and suicidal tendencies and attempts reported in a number of studies (Bowe et al., 2011; Halvorsen et al., 2011; Hull and D’Arcy, 2005).

Comedones and inflammatory nodules are characteristic lesions in acne vulgaris that result from multifactorial pathogeneses. Infection from Propionibacterium acnes (P. acnes) and mites (Demodex folliculorum) (Bhate and Williams, 2014; Ren et al., 1997; Vos et al., 2012) stimulate innate and acquired immune responses and trigger inflammation (Dreno et al., 2015). The initiation of inflammation may be due to androgens such as testosterone and \textalpha-dihydrotestosterone with subsequent increase in sebum, enlargement of sebaceous glands and hyperkeratinization (Bialecka et al., 2005; Eichenfield et al., 2015). Genetics (Bhate and Williams, 2014), diet (Adebamowo et al., 2006, 2008; Smith et al., 2007) and neuroendocrine regulatory mechanisms (Lynn et al., 2016) can also contribute to occurrence and the severity of acne vulgaris.

Hyperkeratinization is caused by altered sebum and lipid content in sebocytes and keratinocytes (Zouboulis et al., 2014). Peroxisome proliferator-activated receptors (PPARs) increase human sebum production (Trivedi et al., 2006), and an innate immune response to pathogens such as P. acnes activates adaptive immune responses from T- and B-
cells (Dreno et al., 2015). P. acnes stimulate keratinocytes that produce cytokines causing ductal rupture (Dreno et al., 2015). They activate toll-like receptor (TLR)-2 and TLR-4 cytokines. IL-6 cytokine production caused by lipoxgenase is associated with sebaceous glands, which also increases concomitant PPAR-α and PPAR-γ (Zouboulis et al., 2014). Pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-1, IL-8 and IL-12 are produced with P. acnes infections (Dreno et al., 2015).

Treatment guidelines recommend four approaches to treatment including decreasing hyperkeratinization, microbial colonization of P. acnes and sebum production, and inhibiting inflammation (Zaenglein et al., 2016). Treatment of mild acne includes education about skin hygiene and debunking myths (Cook et al., 2010; Eichenfield et al., 2013). Topical and oral retinoids are prescribed for moderate to severe acne and topical benzoyl peroxide is combined with topical antibiotics to decrease antibiotic resistance with long-term use (Vos et al., 2012). Current conventional treatment therapies are effective but can have side effects. Retinoids are teratogenic and oral use is associated with mood changes, depression and suicidal thoughts (Costa Carolina et al., 2011). Topical retinoids and benzoyl peroxide can leave the skin dry and cause skin irritation (Eichenfield et al., 2015). The effectiveness of topical and oral antibiotics can decrease over time and increase the risk of antibiotic resistance (Vos et al., 2012).

Many people use complementary and alternative medicine for skin conditions (Fuhrmann et al., 2010; Neamsuvan et al., 2015). A recent systematic review on botanical and phytochemical treatments for acne vulgaris evaluated 23 clinical trials (Fisk et al., 2014), three of which evaluated Kampo/Chinese herbal medicine (CHM) formulations. The CHM preparations showed improvement for mild to moderate acne. Limitations of these clinical trials included lack of acne grading methods, and lack of a control or placebo group.

Eriobotrya japonica Formula (EJF) known as Pi Pa Qing Fei Yin is a common CHM formula which has been used clinically to treat mild to moderate inflammatory comedones in acne vulgaris (Shen et al., 1995; Xu, 2004). This formula contains six herbs that have anti-inflammatory, anti-lipogenic and antibacterial effects on P. acnes (Nam et al., 2003; Yang et al., 2014). There are no reviews on CHM for acne vulgaris to date. This review evaluates the efficacy and safety of CHM formula EJF alone or in combination with other CHM in the treatment of acne vulgaris.

1.1. Objectives

This systematic review aims to 1) describe the experimental evidence of the six EJF ingredients in reference to the current pharmaceutical treatment targets for acne including effects on P. acnes and inflammation as well as effects on hyperkeratinization, androgen and sebum production; 2) conduct a systematic review and meta-analysis to evaluate the clinical efficacy and safety of EJF for acne. The systematic review will include randomized controlled trials (RCTs) of people with acne, which compare EJF with no treatment, placebo or conventional pharmacotherapy and which report on clinically relevant outcomes.

2. Methods

2.1. Experimental evidence

A search of electronic database PubMed was performed from inception to August 2016. The six ingredients of EJF were used as key words. The pharmaceutical; species; English and pin yin names for Eriobotrya japonica Thunb. Lindl. leaf (pi pa ye); Morus alba L. root bark (sang bai pi); Coptis chinensis Franch. or Coptis teeta Wall. or Coptis deltoidea C.Y. Cheng & Hsiao stem; (huang lian); Phellodendron amurense Rupr. or Phellodendron chinense Schneid. cortex (huang bai); Panax ginseng C.A. Mey. root (ren shen) and Glycyrrhiza glabra L. P or Glycyrrhiza uralensis Fisch. or Glycyrrhiza inflata BAT. stem (gan cao) were used as search terms. These terms were combined with terms P. acnes; anti-inflammatory; sebum; androgen and hyperkeratinization. Articles were limited to English.

2.2. Clinical evidence

An electronic search of five English (PubMed, Embase, Allied and Complementary Medicine Database, the Cumulative Index to Nursing and Allied Health Literature and Cochrane Library) and six Chinese language databases (Chinese National Knowledge Infrastructure, Chongqing VIP Information Company, Wanfang Data, Chinese Biomedical Literature Database, China’s Conference Papers Database and China Dissertation database) was conducted from inception to May 2013 (and updated in February 2015) to identify RCTs of EJF. There were no language restrictions. Search terms were categorized according to intervention (CHM, traditional Chinese herbs, Chinese drugs and variants), condition (acne vulgaris, acne and variants) and trial design (RCT and variants) (see Supplementary file 1).

The title and abstracts were assessed to identify potential RCTs. Full text was retrieved for eligible studies and when eligibility could not be determined from the title and abstract. RCTs in people with acne vulgaris using EJF formula alone or combined with other CHM (oral or topical) compared with no treatment, placebo, or conventional pharmacotherapy were included in the review. Modified EJF formula was defined as using the original formula with addition, removal or replacement of one or more herbs. No age, gender or ethnicity limitations were applied. Trials that used other Chinese medicine techniques such as acupuncture or CHM as controls were excluded.

The primary outcomes for this review included change in the lesion count (measured with the Pillsbury scale (Pillsbury, 1956), Investigator’s Global Assessment or Global Acne Grading System (Doshi et al., 1997), overall grading (physician’s assessment or self-reporting), length of time between recurrence of symptoms, and the effective rate defined in guidelines. There is no published consensus guideline on western medicine outcome measures for acne although there are current efforts to standardize them (Tan et al., 2012). Chinese clinical practice guidelines (Zheng, 2002) recommend reporting the effective rate based on lesion count alone or a combination of lesion count, impacted areas, symptoms and laboratory tests (named as “comprehensive outcome evaluation”). In this guideline, clinical effectiveness is considered to be an improvement of at least 50%. For analysis, we followed the Chinese guideline and considered a 50% or greater improvement to be clinically effective. Where it was not possible to determine how many participants achieved at least 50% improvement, data were excluded from the analysis. For example, if the study reported the number of people achieving 30–60% improvement and ≥60% improvement, only the data for those who achieved ≥60% were analysed. Secondary outcomes included recurrence, acne severity measured with Leeds Revised Acne Grading System (Burke and Cunliffe, 1984), quality of life improvements such as Cardiff Acne Disability Index (Motley and Finlay, 1992), Acne Disability Index (Gupta et al., 1998), Acne-Specific Quality of Life (Fehnel et al., 2002) and Skindex (Chren et al., 1996), and adverse events (AEs) reports.

Data was extracted into a predefined file including participant characteristics, details of the intervention and comparator, outcome measures and results. If there was missing data, the reviewer attempted to contact the authors to try to obtain the data. Verification of data was conducted by an independent researcher (IZ).

Methodological quality was assessed independently by two researchers (SM and KW) using the Cochrane Collaboration’s Risk of Bias Tool (Higgins and Green, 2011). Trials were judged as either low, unclear or high risk of bias for the domains of sequence generation, allocation concealment, blinding of participants, blinding of personnel and outcome assessors, incomplete outcome data, selective reporting and other forms of bias such as conflicts of interest. A third assessor was consulted if disagreement existed that could not be resolved through
discussion (AZ).

Statistical analyses were performed using Revman 5.2.4 (The Cochrane Collaboration, 2012). Dichotomous data were presented as risk ratios (RR) and continuous data as mean difference, with 95% confidence interval (CI). Data were analysed for available cases and for dichotomous data, additional analysis was performed using the number randomized to account for missing data. A random effects model was used. Substantial heterogeneity was defined as I² greater than 50%. The authors planned to explore publication bias if more than ten studies were included in a meta-analysis and to perform a subgroup analysis according to intervention (EJF alone or in combination with other CHM). We also planned to perform sensitivity analysis with studies assessed as low risk of bias for sequence generation. Due to the number of trials included and methodological quality, not all planned analyses could be performed.

3. Results

3.1. Experimental evidence

Sebocytes and keratinocytes are both important components of the pilosebaceous glands that react to infection with *P. acnes* and stimulate inflammation (Kurokawa et al., 2009). Androgens testosterone and 5α-dihydrotestosterone stimulate sebocytes and increase lipid droplets by increasing lipogenesis (Kurokawa et al., 2009). Follicular keratinocytes are under androgen control (Gollnick, 2015). A combination of these factors cause hyperkeratinization of cells, contributing to the production of comedones and pustules seen in acne vulgaris. Relevant to the pathogenesis of acne vulgaris, the six botanicals in EJF were found to have anti-inflammatory, anti-androgenic, antibacterial to *P. acnes* and anti-adipogenic and anti-lipogenic effects. Key experimental evidence of herbs identified from the PubMed search is categorized based on the key pathogenesis described in the American Academy of Dermatology 2016 and is presented below.

3.1.1. Microbial colonization with *P. acnes*

Three of the ingredients have antimicrobial actions. *Glycyrrhiza glabra*, *Glycyrrhiza uralensis*, *Phellodendron amurense* and *Coptis chinensis* have been found to have anti-microbial actions. The whole herb extract of *Glycyrrhiza glabra* and *Glycyrrhiza uralensis* had greater antibacterial potency than erythromycin with no resistance issues (Nam et al., 2003). Berberine chloride, found in *Phellodendron amurense* and *Coptis chinensis*, decreased inflammation by inhibiting IL-6 and IL-8 but not TNF-α (Allijn et al., 2016). However, the whole herb extract of *Coptis chinensis* inhibited TNF-α in human keratinocytes (Eink et al., 2007). The whole herb extract of *Phellodendron amurense* significantly suppressed the expression of iNOS and COX-2 (Choi et al., 2014; Jeong et al., 2009; Park et al., 2007) and decreased nuclear NF-κB and phosphorylated IkBα levels (Choi et al., 2014). In addition, the whole herb extract inhibited IL-6, IL-1β and MCP-1 in vitro and in vivo (Choi et al., 2014; Jeong et al., 2009; Jeong et al., 2009). Berberine may also down-regulate the cell-mediated inflammatory response by directly inhibiting T-cell activation (Park et al., 2007). Berberine inhibited LPS-induced PPAR-γ overexpression and phosphorylation (Feng et al., 2012). It reduces pro-inflammatory cytokines such as TNF-α, IL-6, C-reactive protein (CRP) and haptoglobin (HP); and reducing the expression of LPL (lipoprotein lipase) can be induced by berberine from *Phellodendron amurense* (Choi et al., 2006).

The whole herb extract of *Morus alba* inhibited NO production in LPS-activated RAW264.7 macrophages, decreased the production of TNF-α (Choi and Hwang, 2005) and inhibited NF-κB and ERK1/2 activation (Eo et al., 2014).

3.1.2. Inflammation

All six ingredients of EJF have anti-inflammatory effects. The whole herb extract of *Eriobotrya japonica* decreased inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in LPS stimulated RAW264.7 cytokine (Uto et al., 2010). The whole leaf extract of *Eriobotrya japonica* inhibited LPS-induced IL-8, TNF-α and IL-1β in human lung epithelial cells (Lee et al., 2008), and regulated the production of TNF-α, IL-6 and IL-8 in mast cells by inhibiting nuclear factor (NF)-κB, p38 mitogen activated protein kinase and extracellular signal-regulated kinase (ERK) (Kim and Shin, 2009). Tormentic acid from *Eriobotrya japonica* decreased iNOS and COX-2 in the oedematous paw by increasing the activities of catalase, superoxide dismutase and glutathione peroxidase in the liver of male ICR mice (Chang et al., 2011).

Ginsenosides from *Panax ginseng* inhibited the expression and production of inflammatory cytokine TNF-α (Gao et al., 2013). Ginsenoside activated PPAR-γ nuclear receptor by directly increasing expressions of PPAR-γ2 and its targeting genes. In addition, ginsenoside sensitized insulin action and promoted the uptake and disposal of glucose by adipocytes (Gao et al., 2013; Wang et al., 2013a). Glabridin from *Glycyrrhiza glabra* activated PPAR-γ and binds to it. It also regulated the PPAR-γ gene expression in hepatoma cells (Rebhun et al., 2015). Berberine from *Phellodendron amurense* inhibited LPS-induced PPAR-γ overexpression and phosphorylation (Feng et al., 2012).

Glycyrrhizin from *Glycyrrhizae radix* suppressed the production of cytokines through the inhibition of lipid raft accumulation and LPS-induced TLR-4 signalling, as well as suppressing LPS-induced NF-kB and IRF3 activation (Fu et al., 2014). Glycyrrhizic acid and 18β-glycyrrhizic acid have an anti-inflammatory effect. They can inhibit the production of nitrous oxide (NO), prostaglandin E2 (PGE2), TNF-α, IL-6, IL-1β and reactive oxygen species (ROS). They reduced expression of pro-inflammatory genes (iNOS and COX-2) and significantly blocked transcription factors NF-κB and phosphoinositide-3-kinase, p110α and p110γ (Wang et al., 2011).

Liquiritigenin from *Glycyrrhizae radix* blocked the induction of iNOS protein and its mRNA at the transcriptional level and significantly inhibited LPS-induced TNF-α, IL-1β and IL-6 secretions (Kim et al., 2008). In this study, inhibition effect was greater on TNF-α, a secondary cytokine (Kim et al., 2008). Liquiritigenin inhibited NF-κB activation in macrophages, due to its inhibition of IκBα phosphorylation (Kim et al., 2008). Whole herb extract of *Glycyrrhiza glabra* inhibited LPS-induced NO and ROS production and expression of cytokines, iNOS, COX-2, TNF-α, IL-1β and IL-6; and protected macrophages from cell death caused by NO and TNF-α (Li et al., 2015).

Berberine chloride, found in *Phellodendron amurense* and *Coptis chinensis*, decreased inflammation by inhibiting IL-6 and IL-8 but not TNF-α (Allijn et al., 2016). However, the whole herb extract of *Coptis chinensis* inhibited TNF-α in human keratinocytes (Eink et al., 2007). The whole herb extract of *Phellodendron amurense* significantly suppressed the expression of iNOS and COX-2 (Choi et al., 2014; Jeong et al., 2009; Park et al., 2007) and decreased nuclear NF-κB and phosphorylated IκBα levels (Choi et al., 2014). In addition, the whole herb extract inhibited IL-6, IL-1β and MCP-1 in vitro and in vivo (Choi et al., 2014; Jeong et al., 2009; Jeong et al., 2009). Berberine may also down-regulate the cell-mediated inflammatory response by directly inhibiting T-cell activation (Park et al., 2007). Berberine inhibited LPS-induced PPAR-γ overexpression and phosphorylation (Feng et al., 2012). It reduces pro-inflammatory cytokines such as TNF-α, IL-6, C-reactive protein (CRP) and haptoglobin (HP); and reducing the expression of LPL (lipoprotein lipase) can be induced by berberine from *Phellodendron amurense* (Choi et al., 2006).

The whole herb extract of *Morus alba* inhibited NO production in LPS-activated RAW264.7 macrophages, decreased the production of TNF-α (Choi and Hwang, 2005) and inhibited NF-κB and ERK1/2 activation (Eo et al., 2014).

3.1.3. Follicular hyperkeratinization

Three ingredients have an effect on adipogenesis, lipogenesis and decreasing serum testosterone levels. *Glycyrrhiza glabra*, *Glycyrrhiza uralensis* and *Phellodendron amurense* have been found to have anti-adipogenic and lipolytic actions. Glycyrrhizic acid from *Glycyrrhiza glabra* and *Glycyrrhiza uralensis* produced short-term decreases in total serum testosterone and 5α-dihydrotestosterone in human studies (Armanini et al., 2004). 18β-Glycyrrhetinic acid decreases fat mass by affecting adipogenesis in maturing preadipocytes and lipolysis in mature adipocyte in 3T3-L1 cells (Moon et al., 2012). Berberine, an alkaloid of *Phellodendron amurense* and *Coptis chinensis* reduced secretion of leptin and glycerol in 3T3-L1 adipocytes and may reduce the mRNA expression of adipocyte-secreted inflammatory molecules (Choi et al., 2006).

3.1.4. Sebum production, anti-lipogenic and anti-adipogenic effects

Two of the ingredients have an effect on sebum. *Coptis chinensis* and *Eriobotrya japonica* have anti-lipogenic and anti-adipogenic effects. *Coptis chinensis* whole herb extract had a greater effect on lipogenesis suppression than 0.01% retinoic acid in hamster skin (Nam et al., 2003). *Eriobotrya japonica* inhibited lipid accumulation and adipocyte
lipid-binding protein (aP2) (Sharma et al., 2015). The whole leaf extract of Eriobotrya japonica had potent inhibition of 11β-HSD1, an enzyme in adipose tissue (Gumy et al., 2009).

3.2. Clinical evidence

3.2.1. Characteristics of clinical studies

The original search (to May 2013) yielded 27,476 records, with one additional record identified through other sources. A targeted update search for studies of Eriobotrya japonica Formula (Pi Pa Qing Fei Yin) to February 2015 identified a further 143 studies (Fig. 1). In total, 15 studies, all in Chinese, met the inclusion criteria, with 13 included in quantitative analysis. No RCTs were found in English.

Fifteen RCTs included 1782 participants (Chen and Zhou, 2011; Han, 2006; Liang and Wang, 2009; Liu, 1997; Liu, 2010; Liu et al., 2012; Ma, 2013; Ou and Tao, 2012; Shi et al., 2005, 2008; Wang et al., 2013b; Wang et al., 2014; Yan and Li, 2005; Zhang, 2006; Zhang and Huang, 2011) (Table 1). The mean number of participants was 119 with a sample size ranging from 60 to 228. Fourteen trials included both males and females and one trial included only female participants. Participants’ age ranged from 14 to 39 years old (median age 24). The inclusion criteria for all apart from two trials (Shi et al., 2008; Wang et al., 2014) was acne patients, with few studies reporting additional criteria. All trials were conducted in China between 1997 and 2014. Treatment duration varied from 2 to 8 weeks. Three trials reported a follow-up period which ranged from 3 months (Zhang and Huang, 2011) to 1 year (Ma, 2013). The diagnostic tool used in the trials include the Pillsbury scale (Chen and Zhou, 2011; Liu, 2010; Ou and Tao, 2012), Gollnick scale (Shi et al., 2008), and dermatological textbooks (Liang and Wang, 2009; Liu et al., 2012; Ma, 2013; Wang et al., 2013b; Wang et al., 2014; Yan and Li, 2005; Zhang and Huang, 2011). Diagnostic tool was not specified in four studies (Han, 2006; Liu, 1997; Shi et al., 2005; Zhang, 2006).

All trials used the oral herbal formula EJF as a base formula for the main intervention (Table 2). Three trials combined oral EJF with topical herbs (Liu et al., 2012; Liu, 2010; Ou and Tao, 2012). Two trials used EJF in combination with other oral herbal formulae (Liu, 2010; Shi et al., 2005). Comparators included pharmacotherapy such as topical and oral antibiotics, topical retinoids and topical benzoyl peroxide. Topical agents vitamin E, vitamin B6 and sulphur creams were added in three trials (Liang and Wang, 2009; Ma, 2013; Shi et al., 2005). Three trials used viaminate as a comparator (Chen and Zhou, 2011; Zhang,
<table>
<thead>
<tr>
<th>First author, publication year, country, setting</th>
<th>Study design, blinding, number of arms</th>
<th>Eligibility Criteria</th>
<th>Treatment duration, follow-up duration</th>
<th>Stage, severity and duration of condition</th>
<th>No. of participants randomized/assessed</th>
<th>Age (mean (SD) or range); gender (M/F)</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen LJ, 2011, China, Out patients</td>
<td>RCT non-blinded 2 arms</td>
<td>Acne patients, Dec 2008 – Dec 2009</td>
<td>4 weeks, 0 weeks</td>
<td>NS, Pillsbury: I–IV, I: 2 (1.44) years, I: 53/53</td>
<td>I: 24.3 (3.3), 27/26</td>
<td>C: 25 (2.0), 24/23</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral)</td>
</tr>
<tr>
<td>Han SX, 2006, China, Out patients</td>
<td>RCT, non-blinded 2 arms</td>
<td>Acne vulgaris patients</td>
<td>15 days, 0 weeks</td>
<td>NS, C: 52/52</td>
<td>I: 38/38</td>
<td>C: NS, NS</td>
<td>Pi Pa Qing Fei Yin (oral) + Mask (topical)</td>
</tr>
<tr>
<td>Liang XS, 2009, China, Out patients</td>
<td>RCT, non-blinded 2 arms</td>
<td>Acne patients</td>
<td>30 days, 0 weeks</td>
<td>NS, NS, 1 week-6 years, C: 28/28</td>
<td>I: 32/32</td>
<td>C: 24.5 (NS), 18/10</td>
<td>Pi Pa Qing Fei Yin Jia Wei (oral)</td>
</tr>
<tr>
<td>Liu H, 1997, China, Out patients</td>
<td>RCT, non-blinded 3 arms</td>
<td>Patients with acne vulgaris</td>
<td>2 weeks, 0 weeks</td>
<td>NS, NS, 2 weeks –3 years, I: 24 (3.3), 27/26</td>
<td>I: 22.5 (NS), NS</td>
<td>C: 22.5 (NS), NS</td>
<td>I: Jiawei Pi Pa Qing Fei Yin (oral)</td>
</tr>
<tr>
<td>Han SX, 2006, China, Out patients</td>
<td>RCT, non-blinded 2 arms</td>
<td>Acne vulgaris patients</td>
<td>15 days, 0 weeks</td>
<td>NS, NS</td>
<td>I: 38/38</td>
<td>C: NS, NS</td>
<td>Pi Pa Qing Fei Yin + Wu Wei Xiao Du Yin Jia Jian (oral)</td>
</tr>
<tr>
<td>Liang XS, 2009, China, Out patients</td>
<td>RCT, non-blinded 2 arms</td>
<td>Acne patients</td>
<td>30 days, 0 weeks</td>
<td>NS, NS</td>
<td>I: 28/28</td>
<td>C: 24.5 (NS), 18/10</td>
<td>Pi Pa Qing Fei Yin Jia Wei (oral)</td>
</tr>
<tr>
<td>Liu Y, 2010, China, Out patients</td>
<td>RCT, non-blinded 2 arms</td>
<td>Acne patients</td>
<td>4 weeks, 0 weeks</td>
<td>NS, NS, 2 weeks –3 years, I: 24 (3.3), 27/26</td>
<td>I: 22.5 (NS), NS</td>
<td>C: 22.5 (NS), NS</td>
<td>I: Jiawei Pi Pa Qing Fei Yin (oral)</td>
</tr>
<tr>
<td>Ma TL, 2013, China, Out patients</td>
<td>RCT, non-blinded 3 arms</td>
<td>Acne patients, 2002 – 2012</td>
<td>4 weeks, 0 weeks</td>
<td>NS, NS, 7 days –5 years, I: 42/42</td>
<td>C: 42/42</td>
<td>C: 24.84 (NS), 27/15</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral)</td>
</tr>
<tr>
<td>Ou HB, 2012, China, Out patients</td>
<td>RCT, non-blinded 2 arms</td>
<td>Acne patients</td>
<td>3 weeks, 0 weeks</td>
<td>NS, Pillsbury: I–IV, 2 (1.5) years</td>
<td>I: 40/40</td>
<td>C: 29.12 (3.48), 19/21</td>
<td>Pi Pa Qing Fei Yin (oral) + Dian Dao San (topical)</td>
</tr>
<tr>
<td>Shi X, 2005, China, Out patients</td>
<td>RCT, non-blinded 2 arms</td>
<td>Acne patients</td>
<td>2 weeks, 0 weeks</td>
<td>NS, Moderate –severe (Lesion: II–III), C: 82/79</td>
<td>C: 21.2 (2.4), 18/12</td>
<td>Pi Pa Qing Fei Yin (oral) + Bian Hua Fang</td>
<td></td>
</tr>
<tr>
<td>Shi X, 2008, China, Out patients</td>
<td>RCT, non-blinded 2 arms</td>
<td>Acne patients</td>
<td>8 weeks, 0 weeks</td>
<td>NS, Gollnick: I–II, I: 39/39 (all dropouts are included as &quot;no improvement&quot;)</td>
<td>C: 20.87 (8.67), 34/46</td>
<td>C: 21.2 (2.4), 18/12</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral)</td>
</tr>
<tr>
<td>Wang S, 2013, China, NS</td>
<td>RCT, non-blinded 2 arms</td>
<td>Female acne patients</td>
<td>1 month, 0 weeks</td>
<td>NS, slight-severe, NS</td>
<td>I: 12–30; NS</td>
<td>C12–30, NS</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral)</td>
</tr>
<tr>
<td>Wang X, 2014, China, Out patients</td>
<td>RCT, non-blinded 3 arms</td>
<td>Acne patients in outpatients department; 15 -45 yo; no topical treatments in the past 7 days; no acne oral medication in the past 30 days;</td>
<td>1 month, 0 weeks</td>
<td>NS, C: 60/60</td>
<td>I: 61/61</td>
<td>C: 60/60</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral)</td>
</tr>
<tr>
<td>Yan Y, 2005, China, Out patients</td>
<td>RCT, non-blinded 2 arms</td>
<td>Acne patients</td>
<td>3 weeks, 6 months</td>
<td>NS, light-severe, 560 days</td>
<td>I: 12/14/14</td>
<td>C: 17/60 (NS), 49/65</td>
<td>Bai Di She Xi Ji + Cuo Chuang Ling + Pi Pa Qing Fei Yin Jia Jian (oral)</td>
</tr>
<tr>
<td>Zhang LL, 2006, China, Out patients</td>
<td>RCT, non-blinded 2 arms</td>
<td>Acne patients with CM diagnosis (damp-heat in Lung and Stomach)</td>
<td>4 weeks, 0 weeks</td>
<td>NS, NS, I: 2 months – 7 years, C: 5 months – 6 years</td>
<td>I: 60/60</td>
<td>C: 60/60</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral)</td>
</tr>
</tbody>
</table>
Viaminate is a non-conventional oral retinoid derivative that is approved in China for clinical treatment of acne. One trial used a combination of viaminate and an antibiotic (Shi et al., 2005) which is not a common prescribing practice outside of China. None of the trials used placebo control.

Eight trials reported effective rate based on lesion count (Liu, 1997; Liu et al., 2012; Shi et al., 2005, 2008; Wang et al., 2013b; Wang et al., 2014; Zhang, 2006; Zhang and Huang, 2011), six reported effective rate based on both lesion count and severity (Chen and Zhou, 2011; Liang and Wang, 2009; Liu, 2010; Ma, 2013; Ou and Tao, 2012; Yan and Li, 2005) and one study did not report details on how the effective rate was calculated (Han, 2006). Four trials (Liu et al., 2012; Ma, 2013; Shi et al., 2008; Yan and Li, 2005) reported on recurrence rate. None of the trials reported on the length of time between recurrences or acne severity and only one paper (Wang et al., 2014) reported on the health-related quality of life (HRQoL) measure Dermatology Life Quality Index (DLQI).

3.2.2. Risk of bias

Overall, methodological quality of included trials was low to moderate (Fig. 2). Two trials (Ou and Tao, 2012; Zhang, 2006) were assessed to have low risk of bias in sequence generation as they used random number generators. Two trials (Chen and Zhou, 2011; Wang et al., 2014) were assessed as high risk, as Chen and Zhou used hospital record numbers (2011) and Wang et al. used sequence of visit order (2014). There was insufficient information reported on blinding of participants in 14 papers and these were assessed as unclear. One paper (Wang et al., 2014) was assessed to have high risk in blinding of participants based on the inclusion of a subjective quality of life (DLQI) outcome measure. As there was insufficient information reported on allocation concealment and blinding of personnel and outcome assessors, all studies were assessed as unclear risk for these domains. All trials were assessed as low risk for incomplete outcome data and selective reporting. One paper was assessed as high risk for other biases due to baseline imbalance of participants (Zhang and Huang, 2011) with no explanation provided. No other biases such as large differences in sample size between groups, or potential conflict of interests were observed in the other 14 trials.

3.2.3. Effective rate

Two studies (Han, 2006; Zhang, 2006) were excluded from the meta-analysis as they did not report the standard effective rate of 50% as outlined in Zheng (2002). The quality of the evidence was low (see Supplementary file 2). The effective rate was higher in those who received EJF compared to pharmacotherapy (13 studies, RR: 1.30 [1.13, 1.49], I² = 70%) although substantial heterogeneity was detected (Fig. 3). Analysis to account for missing data did not alter this result (13 studies, RR: 1.30 [1.13, 1.49], I² = 70%). Sensitivity analysis excluding two studies assessed as high risk for incomplete outcome data and selective reporting. One paper was assessed as high risk for other biases due to baseline imbalance of participants (Zhang and Huang, 2011) with no explanation provided. No other biases such as large differences in sample size between groups, or potential conflict of interests were observed in the other 14 trials.

Heterogeneity was explored through subgroup analysis by interventions and comparators. When EJF was used alone the effective rate was similar to the overall pool (10 studies, RR: 1.31 [1.21, 1.58]). EJF alone compared to antibiotics with topical supplements
<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Chinese herbal medicine formula and ingredients</th>
<th>Preparation type and dosage</th>
<th>Co-intervention/Control</th>
<th>Dosage and administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen LJ, 2011</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral): Pi Pa Ye, Zao Jiao Ci, Zhe Bei, Mu Dan Pi, Bai Xin Pi; Sang Bai Pi, Huang Qin, Zhi Zi, Ye Ju Hua, Jin Yin Hua; Bai Zao Xiu, Huang Lian, Lu Hui, Gan Cao. Syndrome differentiation: Bai Jiang Cao, Bai Hua She She Cao, Bai Zhi (cysts); Dang Gui, Bai Shao, Yi Mu Cao (irregular menstruation); Chan Tui, Wu She (itch); Shi Gao, Tian Hua Fen (dry); Yi Yi Ren, Bai Zhi (oily)</td>
<td>Decoction 150 ml tid</td>
<td>Viaminate capsules (oral); Benzoyl Peroxide gel (topical)</td>
<td>Viaminate Capsules 25 mg tid po.; Benzoyl Peroxide gel tid. topical.</td>
</tr>
<tr>
<td>Han SX, 2006</td>
<td>Pi Pa Qing Fei Yin (oral) &amp; Mask (ext) NS Metronidazole (oral) &amp; Roxithromycin (oral) &amp; Viaminate &amp; Vit E (ext)</td>
<td>Metronidazole (oral) &amp; Roxithromycin (oral) &amp; Viaminate &amp; Vit E (ext)</td>
<td>Metronidazole 0.2 g tid po.; Roxithromycin 150 mg bid po.;</td>
<td>Metronidazole 0.2 g tid po. Roxithromycin 150 mg bid po. Viaminate &amp; Vit E ext Erythromycin 0.2 g bid po. Sulphur cream qd ext. Zinc Sulfate 0.2 g bid po.</td>
</tr>
<tr>
<td>Liang XS, 2009</td>
<td>Pi Pa Qing Fei Yin Jia Wei: Pi Pa Ye, Huang Bai, Huang Lian, Ren Shen, Gan Cao, Sang Bai Pi, Lian Qiao, Bai Zhi, Chuan Bei, Dang Gui, Da Huang, Xia Ku Cao, Mu Li, Shan Zha, Yi Yi Ren. Syndrome differentiation: Chai Hu, Huang Qin (dry and bitter taste); Long Dan Cao (hypochondriac pain and irascibility); Su An Zao Ren, Zi Lin Xin (insomnia); Da Huang (constipation)</td>
<td>Decoction 1 bid po.</td>
<td>Erythromycin (oral) &amp; Sulphur cream (ext) &amp; Zinc Sulfate (oral)</td>
<td>Erythromycin 0.2 g bid po. Sulphur cream qd ext. Zinc Sulfate 0.2 g bid po.</td>
</tr>
<tr>
<td>Liu H, 1997</td>
<td>I1: Jia Wei Pi Pa Qing Fei Yin – Pi Pa Ye, Sang Bai Pi, Huang Lian, Huang Bai Plus Huang Qin, Da Huang, Dan Shen, Sheng Di, Zi Cao, She She Cao, Ye Ju Hua, Sheng Shan Zha, Shen Qu, Gan Cao (Topical &amp; Oral). I2: Pi Pa Qing Fei Yin (Ext &amp; Oral): Pi Pa Ye, Sang Bai Pi, Ren Shen, Huang Lian, Huang Bai</td>
<td>Decoction 1 qd po.</td>
<td>Metronidazole (topical &amp; oral)</td>
<td>0.2 g tid po, 5%tid topical</td>
</tr>
<tr>
<td>Liu HS., 2012</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral): Pi Pa Ye, Sang Bai Pi, Bai Mao Gen, Lian Qiao, Ye Ju Hua, Huang Qin, Zhi Zi, Bai Hua She She Cao, Chai Hu, Mu Dan Pi, Dan Shen, Yi Yi Ren, Cang Zhu, Gan Cao &amp; Dian Dao San (topical): Da Huang, Liu Huang, Bai Zhi</td>
<td>Decoction 200 ml bid po.; Dian Dao San qd ext.</td>
<td>Adapalene cream &amp; Erythromycin capsules (oral)</td>
<td>Adapalene cream bid topical; Erythromycin capsules 0.5 g bid po.</td>
</tr>
<tr>
<td>Liu Y, 2010</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral): Pi Pa Ye, Huang Lian, Sang Bai Pi, Lian Qiao, Bai Zhi, Ye Ju Hua, Xia Ku Cao, Zi Hu Di Ding, Jin Yin Hua, Pu Gong Ying, Bai Hua She She Cao, Zao Jiao Ci, Dan Shen, Mu Dan Pi, Jiaang, Shi Da Huang. Syndrome differentiation: Change Shu Da Huang to Sheng Da Huang (constipation); Zhe Bei, Mu Li, Kun Bu, Hai Zao (nodules, cysts); Hua Shi, Ze Xie (yellowish or reddish urine); Long Dan Cao, Yin Chen (heat of Liver); Chai Hu, Bai Shao (irregular menstruation)</td>
<td>Decoction 1 tid po. Decoction bid. topical.</td>
<td>Viaminate capsules &amp; Roxithromycin (oral) &amp; Adapalene cream &amp; Roxithromycin (oral) &amp; Adapalene cream bid topical.</td>
<td>Viaminate Capsules 25 mg tid po. Roxithromycin 150 mg tid po. Adapalene cream &amp; Roxithromycin (oral) &amp; Adapalene cream bid topical.</td>
</tr>
<tr>
<td>Ma TL, 2013</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral): Pi Pa Ye, Sang Bai Pi, Gan Cao, Huang Bai, Huang Lian, Sang Bai Pi. Syndrome differentiation: Jin Yin Hua, Bai Hua She She Cao (wind and Heat of Lung); minus Ren Shen, plus Yin Chen 15 g, Mu Dan Pi (stagnation of heat and damp); minus Huang Lian, plus Zhi Ban Xia, Bai Zhu (Stagnation of phlegm and damp)</td>
<td>Decoction 200 ml bid po.</td>
<td>Vit C (oral) &amp; Roxithromycin (oral) &amp; Vit B6 cream</td>
<td>Vit C 0.2 g tid po.; Roxithromycin 75 mg tid po.; Vit B6 cream tid. topical.</td>
</tr>
<tr>
<td>Ou HK, 2012</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral): Pi Pa Ye, Huang Bai, Huang Lian, Gan Cao, Sang Bai Pi, Bai Zhi, Fang Feng, Fu Ling, Dang Gui, Chai Hu, Chan Tui. Syndrome differentiation: Lian Qiao, Pu Gong Ying, Zi Cao (nodules, fester); Huang Qin (chronic); Mu Li, Ze Bei (white head); Tao Ren, E Zha (chromatosis); Da Huang (Constipation); Xiang Fu (irritability); Dan Shen, Sheng Di, Gu Zhi, Shi Chang Pu (pain and itch) Dian Dao San (ext): Da Huang, Liu Huang</td>
<td>Pi Pa Qing Fei Yin Jia Jian: Decoction 1 bid po.; Dian Dao San qd topical.</td>
<td>Benzyol Peroxide (topical) &amp; Minocycline Hydrochloride capsules (oral)</td>
<td>Benzyol Peroxide tid ext.; Minocycline Hydrochloride capsules: 50 mg bid po.</td>
</tr>
<tr>
<td>Shi XB, 2005</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral): Pi Pa Ye, Sang Bai Pi, Huang Qin, Zhi Zi, Pu Gong Ying, Dan Shen, Sheng Shan Zha, Bai Hua She She Cao. Syndrome differentiation: Lian Qiao, Pu Gong Ying, Zi Cao (nodules, fester); Huang Qin (chronic); Mu Li, Ze Bei (white head); Tao Ren, E Zha (chromatosis); Da Huang (Constipation); Xiang Fu (irritability); Dan Shen, Sheng Di, Gu Zhi, Shi Chang Pu (pain and itch) Dian Dao San (ext): Da Huang, Liu Huang</td>
<td>Decoction 100 ml bid po.</td>
<td>Achromycin (oral antibiotic) &amp; Viaminate &amp; Vit E cream (topical)</td>
<td>Achromycin: 0.5 g tid. (first course) po. 0.25 g tid. (second course); Viaminate &amp; Vit E cream qd topical.</td>
</tr>
<tr>
<td>Shi XB, 2008</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral): Pi Pa Ye, Sang Bai Pi, Huang Qin, Zhi Zi, Sheng Shan Zha, Pu Gong Ying, Dan Shen, Bai Hua She She Cao. Decoction 100 ml qd po. Tretinoin cream (ext) and if there is inflammation will add Clindamycin (topical)</td>
<td>Tretinoin cream (ext) and if there is inflammation will add Clindamycin (topical)</td>
<td>Tretinoin cream: qd ext.; Clindamycin bid topical</td>
<td>(continued on next page)</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Chinese herbal medicine formula and ingredients</td>
<td>Preparation type and dosage</td>
<td>Co-intervention/Control</td>
<td>Dosage and administration</td>
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<td>-------------------------------</td>
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</tr>
<tr>
<td>Wang X, 2014</td>
<td>Pi Pa Qing Fei Yin (oral): Pi Pa Ye, Huang Lian, Huang Qin, Sang Bai Pi, Jin Yin Hua, Mu Dan Pi, Gan Cao</td>
<td>Decoction 50 ml bid.po.</td>
<td>Doxycycline Hyclate tablets</td>
<td>0.1 g bid. po.</td>
</tr>
<tr>
<td>Yan LY, 2005</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral) (No Details): Bai Di She Xi Ji (ext): She Chuang Zi, Bai Fan, Di Pu Zi, Bai Ji Li; Cuo Chuang Ling (Ext): Xin Yi, Hu Po, Bai Zhu, Bai Ji, Hong Hua, Chuan Xiong, Huang Qin, Shui Zhi, Zhen Zhu Fen, San Qi Fen, Bing Pian.</td>
<td>Bai Di She Xi Ji: Decoction 1 bid. topical.; Cuo Chuang Ling: Cream qd. ext.; Pi Pa Qing Fei Yin Jia Jian (oral): Decoction 1 bid.po.</td>
<td>Benzoyl Peroxide (topical) &amp; Achromycin (oral antibiotic) &amp; Zinc Gluconate (oral)</td>
<td>Benzoyl Peroxide (topical): NS; Achromycin (oral antibiotic): 0.5 g qid.po.; Zinc Gluconate: 1 bid.po.</td>
</tr>
<tr>
<td>Zhang LL, 2006</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral): Pi Pa Ye 10 g, Sang Bai Pi 15 g, Huang Qin 10 g, Zhi Zi 10 g, Huang Lian 10 g, Da Huang 10 g, Mu Dan Pi 15 g, Jin Yin Hua 15 g, Lian Qiao 15 g, Pu Gong Ying 30 g, Yi Yi Ren 30 g, Che Qian Zi 15 g.</td>
<td>Decoction 1 bid.po.</td>
<td>Viaminate Capsules</td>
<td>25 mg bid.po.</td>
</tr>
<tr>
<td>Zhang Y, 2011</td>
<td>Pi Pa Qing Fei Yin Jia Jian (oral): Pi Pa Ye, Bai Hua She She Cao, Jin Yin Hua, Dan Shen, Sang Bai Pi, Lian Qiao, Xia Ku Cao, Huang Qin, Zhi Zi, Ren Shen, Shan Zha, Gan Cao, Huang Lian, Da Huang. Syndrome differentiation: Pu Gong Ying, Di Ding (red pimple); Xuan Shen, Hua Fen (dry); Chai Hu, Xiang Fu (irregular menstruation); Chen Pi, Ban Xia (cysts); Chi Shao, Dan Pi (blood stasis); Tao Ren, Hong Hua (rosacea); Mang Xiao, Hua Ma Ren (constipation).</td>
<td>Decoction 1 bid.po.</td>
<td>Viaminate capsules (oral)</td>
<td>25 mg bid. po.</td>
</tr>
</tbody>
</table>

bid: twice daily; ext: external; ml: milliliters; NS: Not stated; po: per oral; qd: one time daily; tid: three times daily; vit: vitamin.
which recurrence rate was assessed (Ma, 2013; Yan and Li, 2005) while two did not (Liu et al., 2012; Shi et al., 2008). Results from single studies showed lower recurrence rate with EJF (RR: 1.37 [1.18, 1.59] (Yan and Li, 2005), RR: 1.63 [1.23, 2.14] (Ma, 2013)) while two showed no statistical significant benefit (RR: 1.19 [1.00, 1.41] (Liu et al., 2012), RR: 1.19 [0.99, 1.42] (Shi et al., 2008)).

3.2.4. Recurrence rate

Four studies reported on recurrence rate (Liu et al., 2012; Ma, 2013; Shi et al., 2008; Yan and Li, 2005). Two specified the time point at which recurrence rate was assessed (Ma, 2013; Yan and Li, 2005) while two did not (Liu et al., 2012; Shi et al., 2008). Results from single studies showed lower recurrence rate with EJF (RR: 1.37 [1.18, 1.59] (Yan and Li, 2005), RR: 1.63 [1.23, 2.14] (Ma, 2013)) while two showed no statistical significant benefit (RR: 1.19 [1.00, 1.41] (Liu et al., 2012), RR: 1.19 [0.99, 1.42] (Shi et al., 2008)).

3.2.5. Quality of life

Only one study reported on HRQoL, using DLQI (Wang et al., 2014). The quality of evidence was moderate (see Supplementary file 2). DLQI scores after 1 month of treatment with EJF were higher, indicating poorer HRQoL, than with doxycycline (MD: 3.07 [2.42, 3.72]).

3.2.6. Adverse events

There were 107 mild AEs reported in seven of the 15 trials (Liang and Wang, 2009; Liu, 1997; Liu et al., 2012; Ou and Tao, 2012; Shi et al., 2005, 2008; Yan and Li, 2005) with 33 events in the intervention groups and 74 in the control groups. There were no serious AEs reported in the trials. In the intervention group, AEs included nausea, vomiting or stomach discomfort (29 cases), itch (2), diarrhoea (1) and burning sensation (1). In the control group, AEs included nausea or stomach discomfort (28), scaling (11), dry mouth (10), itching (9), burning sensation (8), erythema (7), nausea or vertigo (3) and erythema, itching or scaling (3).

4. Discussion

The experimental evidence showed that all ingredients in EJF exhibited at least one mechanism of action relevant to acne pathogenesis with the majority showing evidence of decreasing inflammation. In clinical studies, EJF used alone produced greater improvement in symptoms compared with pharmacotherapies. The clinical findings should be considered in light of low to moderate methodological quality.

EJF is a common CHM formula recommended clinically for acne vulgaris in textbooks (Shen et al., 1995; Xu, 2004). All six ingredients of EJF may have an effect in decreasing inflammation, sebum production and hyperkeratinization. They may also have an inhibitory effect on *P. acnes* as well as preventing *P. acnes* from adhering to host cells. Panax *ginseng* and glycyrrhizic acid from Glycyrrhiza glabra and Glycyrrhiza uralensis decrease serum testosterone (Armanini et al., 2004) and encourage lipolysis in mature adipocytes (Moon et al., 2012). Glycyrrhiza glabra, Panax ginseng, Phellodendron amurense and Coptis chinensis all inhibit *P. acnes* growth (Higaki et al., 1996; Nam et al., 2003; Wang et al., 2013a).

Four of the six ingredients Glycyrrhiza glabra, Coptis cottidis, Eriobotrya japonica and Panax ginseng inhibit PPAR-γ. Phellodendron amurense, Eriobotrya japonica, Panax ginseng, liquiritigenin from Glycyrrhiza glabra and the whole herb extract of Coptis chinensis all inhibit TNF-α. NF-κB is activated in comedones and strongly expresses IL-1α which increases hyperkeratinization (Zouboulis et al., 2014). Three of the ingredients, Phellodendron amurense, Morus alba and Eriobotrya japonica, inhibit NF-κB cytokines. Three of the ingredients, Glycyrrhiza glabra, Phellodendron amurense and Eriobotrya japonica, inhibited IL-1β not IL-1α (Choi et al., 2014; Lee et al., 2008; Wang et al., 2011).

The clinical evidence showed that the results of the pooled studies of EJF was more effective in reducing lesion count, and the effect of the intervention was greatest when EJF was used alone compared to pharmacotherapy though there was considerable heterogeneity. The effect of EJF varied according to the comparator type, with the highest effect seen when compared with antibiotics plus topical supplements. There were conflicting findings when EJF was compared with antibiotics alone and in combination with other medications. The reasons for this are unclear. Each of the studies varied the ingredients in their studies. Future research should use identical herbs to evaluate the effect on acne.
The combination of EJF with other herbal formulae appears to introduce statistical heterogeneity which may reflect clinical heterogeneity. Some studies included in this review used only two of the six above ingredients, while others used four or more ingredients. Many studies added extensively to the base formula. While this is reflective of clinical practice, variations in the formula across studies may have produced different clinical effects. Other factors that could have contributed to statistical heterogeneity included variations in the severity of disease (mild to severe) across the 15 studies. Statistical heterogeneity was also detected in several subgroup analyses which were not able to be explored due to small numbers of studies. Therefore, the effect of EJF compared with some drugs and drug combinations remains uncertain.

Acne treatment varies dependent on acne severity and cost. For mild to moderate acne in primary care, the combination of antibiotics with topical medications are first line therapy (Archer et al., 2012; Cook et al., 2010). Oral antibiotics are prescribed for up to 6 months with 20% improvement within 2 months and 80% within 6 months (Archer et al., 2012). Second line therapy includes topical or oral retinoids. This review included studies using either the first or second line therapies.

Several studies reported severity ranging from mild to severe acne. This may have introduced clinical heterogeneity and impacted on the potential effect of EJF. Pharmacotherapies such as antibiotics and isotretinoin require 4 to 6 months of treatment in order to see clinical benefit (Archer et al., 2012).

The prescribing western medicine practices for treating acne in China at times differed to practices in Europe, Australia and the US (Archer et al., 2012; Cook et al., 2010; Dermatological Society Acne Treatment Guidelines Working Group, 2008). One trial combined both oral antibiotics with topical antibiotics (Liu, 1997). The combination of oral and topical antibiotics is no longer a common prescribing practice due to antibiotic resistance issues (Archer et al., 2012). Four trials used an unconventional retinoid derivative (viaminate) (Chen and Zhou, 2011; Liu, 2010; Zhang, 2006; Zhang and Huang, 2011) that is not recommended by international guidelines for acne vulgaris (Archer et al., 2012; Cook et al., 2010; Nast et al., 2016; Zaenglein et al., 2016).

The number of AEs was lower among those who received EJF than those in the control group. Few studies reported causality assessment of AEs. Monitoring of safe use of herbal products is important for public safety (Kalaiselvan et al., 2015). Many of the comparators used have known side effects, such as skin irritation and dryness with topical benzoyl peroxide (Eichenfield et al., 2013) and burning, pruritus, scaling and erythema with topical tretinoin and adapalene (Ellis et al., 1998). Based on the studies included, the formula was well tolerated by people with acne vulgaris.

There is one published review (Fisk et al., 2014) on botanical and phytochemical treatments for acne reporting on three Kampo/CHM formulations, none of which were EJF. Due to differing scales used in assessing disease severity it was not possible to explore the effect of EJF on severity subgroups, therefore we were unable to compare directly to the findings reported in the Fisk et al. (Fisk et al., 2014) review. Similar limitations such as reporting issues and non-validated outcome measures were also seen in the trials included in this review.

The studies included in this review had largely low to moderate methodological quality with inadequate sequence generation and description of blinding procedures which may cause bias. There were no sample size calculations, and sample size in all trials was generally small. The variability in the interventions and comparators contributed to considerable heterogeneity. The reporting of effective rate was not consistent among trials. All trials reported on lesion count but not all
reported on severity of lesions. Although not a validated outcome, reporting of lesion count and severity is widely used (Barratt et al., 2009). There is a need to establish the criteria for assessing lesion count.

Few studies reported on recurrence rate and follow up, with a lack of descriptions of withdrawals and drop-outs. None of the studies reported on intention-to-treat analyses to account for missing data. There was also large variability in comparators and the use of unconventional retinoid derivatives introduced considerable statistical heterogeneity in this review. Considering the low to moderate methodological quality in study design for most of the trials included in this review, the results should be interpreted with caution.

5. Conclusions

The six ingredients of EJF have anti-inflammatory, antibacterial, anti-lipogenic, anti-adipogenic and anti-androgenic effects. These actions may contribute to the effects seen in clinical studies. The number of people achieving a reduction in lesion count was higher with EJF compared with various pharmacotherapies, although statistical heterogeneity was detected in several meta-analyses. No serious AEs were reported in clinical trials, suggesting that EJF was well-tolerated by people with acne. Rigorously designed studies that describe original formula ingredients, grade the severity of acne and report on clinically relevant outcomes such as HRQoL are needed.

Contributions of authors

SM and KW performed searches of English (SM) and Chinese (KW) databases. KW performed data extraction. SM and KW drafted the manuscript. MC, BM and AZ contributed to the interpretation of results and reviewed the manuscript for critical contents. CX provided critical comments and revised the manuscript. All authors read and approved the final version.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhermed.2017.09.001.

References

Dermatological Society Acne Treatment Guidelines Working Group, C.M.D., 2008. Guidelines for acne treatment guidelines 2008/2009: a joint initiative of RMIT University, Australia and the Guangdong Provincial Academy of Chinese Medical Sciences, China. We also thank Dr. Wenyu (Iris) Zhou for data validation and assistance with data extraction.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhermed.2017.09.001.

References

S.S.Y. Mansu et al.  


Appendix 15 published review “Evidenced-based complementary and alternative medicine”
**Acupuncture for Acne Vulgaris: A Systematic Review and Meta-Analysis**

Suzi S. Y. Mansu, Haiying Liang, Shefton Parker, Meaghan E. Coyle, Kaiyi Wang, Anthony L. Zhang, Xinfeng Guo, and Charlie C. L. Xue

1. Introduction

Acne vulgaris (acne) is a chronic and self-limiting condition that begins in adolescence and can last over 10 years [1]. Acne is characterized by inflamed and noninflamed comedones, oily skin, and cysts [2]. The mechanisms for the initial development of comedones are not fully understood [3]. Four factors have been identified which contribute to acne lesions and are the main targets of treatment. These factors include follicular keratinization, sebum production, Propionibacterium acnes (P. acnes), and inflammatory mediator release [4]. Acne lesions may involve cellular inflammation causing hyperkeratinization of follicular ducts [5]. P. acnes can induce keratinocytes to produce cytokines which rupture ducts, causing comedones [3]. Genetics [6] and androgen imbalances [7] can influence sebaceous gland lipid synthesis. Exacerbation can result from single or multiple factors such as P. acnes, menstruation, occupation, personal sweating, diet, or stress [2, 8].

Treatment of acne includes topical benzoyl peroxide and topical retinoids or antibiotics for mild to moderate acne and oral antibiotics combined with either topical benzoyl peroxide or topical or oral retinoids for severe acne [4]. Acupuncture is an umbrella term for traditional Chinese medicine techniques that stimulate acupuncture points. Techniques include acupuncture (insertion of fine needles at specific loci typically for a period of 20 to 30 minutes), auricular acupuncture (insertion of needles in specific loci of the auricle), auricular acupressure (placement of blunt instruments such as small metallic ball bearings at specific...
loci of the auricle), electroacupuncture (mild electric stimulation of acupuncture needles) [9], and moxibustion (burning of Artemisia argyi Lev. et Vant or Artemisia vulgaris leaf in a processed form) [10]. Several studies have suggested a potential role of acupuncture techniques in acne. Auricular acupressure and surrounding needle (where two to four needles are inserted superficially around the acne lesion) have been shown to reduce serum excretion rate (SER) and testosterone [11]. When acupuncture was combined with benzoyl peroxide, SER in women was reduced compared to benzoyl peroxide alone [12]. In animal studies, auricular acupuncture, auricular electroacupuncture, body acupuncture, and electro-acupuncture have been shown to decrease inflammation [13–16]. Auricular acupuncture may reduce acne inflammation through peripheral muscarinic receptors [13] and innate and adaptive immune responses [14, 17, 18], thereby possibly reducing acne inflammation.

Several reviews have examined the potential benefits of acupuncture techniques in clinical studies. A Cochrane review on complementary therapies for acne [19] evaluated efficacy of herbal medicine, acupuncture, cupping therapy, dietary modifications, purified bee venom, and tea tree oil. The review found there was a lack of evidence to support the use of herbal medicine and acupuncture. Two systematic reviews of acupuncture for acne have been published, one in English [20] and one in Chinese [21]. Cao et al. [20] included trials which used acupuncture, cupping, and other herbal medicines. While the number of “cured” cases increased when acupuncture was combined with cupping, or oral or topical herbal medicines, no benefit was found when acupuncture was compared with pharmacotherapy. The reviewers described the methodological quality of the papers as poor. Li et al. [21] included trials of manual acupuncture compared to routine conventional medicine (isotretinoin and antibiotics) or multiple Chinese medicine therapies. The authors were unable to provide conclusions due to the poor quality of the included trials.

These reviews included herbal medicines and techniques not commonly used outside of China. Acupuncture is commonly used in clinical practice for skin conditions, yet a gap exists in the evaluation of efficacy and safety of acupuncture for acne vulgaris. This review will analyze acupuncture compared to pharmacotherapies, no treatment, and sham or placebo acupuncture to evaluate the efficacy and safety of acupuncture and acupressure for acne vulgaris.

2. Methods

Eleven databases were searched from inception to May 2013, with an update in May 2016. Five English (PubMed, Embase, Allied and Complementary Medicine Database (AMED), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Cochrane Central Register of Controlled Trials (CENTRAL)) and six Chinese databases (Chinese National Knowledge Infrastructure (CNKI), Chongqing VIP Information Company (CQVIP), Wanfang Data, Chinese Biomedical Literature Database (CBM)) as well as China's Conference Papers Database and China Dissertation database were searched. There were no language restrictions.

Search terms included acne vulgaris, papulo-pustular acne, acupuncture, acupressure, moxibustion, auricular acupuncture and auricular acupressure, electro-acupuncture, electro-stimulation, and variants. Moxibustion and acupressure were included as they are commonly used techniques to directly stimulate acupuncture points. Moxibustion in particular is commonly combined with acupuncture, and the Chinese term for acupuncture “zhen jiu” literally means acupuncture and moxibustion. Search terms for study design included randomized controlled trials, controlled clinical trials, drug therapy, placebo, and variants.

Titles and abstracts of identified citations were scanned to identify potentially eligible randomized controlled trials (RCTs). Full text was retrieved when eligibility could not be ascertained from the title and abstract. RCTs of acupuncture, acupressure, auricular acupuncture, moxibustion, and electroacupuncture compared to no treatment, sham acupuncture, placebo, or conventional pharmacotherapy for acne vulgaris were included in the review. No age, gender, ethnicity, or language limitations were applied. Trials that included other modalities, as cointervention, such as pharmacotherapy or Chinese medicine techniques other than those specified above were excluded.

The primary outcome was the change in lesion count measured by therapeutic effective rate (TER). Chinese medicine guidelines recommend reporting the TER ≥50% based on lesion count alone or a combination of lesion count and severity [22]. Many of the studies used a TER of ≥30% as an improvement based on Chinese medicine guidelines from 1994 [23]. The criteria for therapeutic effective rate from the 1994 guideline were based on a change in lesion count and associated symptoms. For analysis, we included data for people who achieved 30% or greater on lesion count, irrespective of the minimum threshold used by the study for effectiveness. Secondary outcomes included severity grading, physician’s overall grading (physician’s assessment or self-reporting), photographic grading, quality of life instruments, and adverse events (AE) reports.

Data extracted included patient demographics, sample size, dropout rate, details of the intervention and comparator, outcome measures, results, and adverse events. Authors were contacted if there was missing data. Verification of data was conducted by an independent researcher (IZ).

Two researchers (KW, IZ) independently assessed methodological quality using Cochrane Collaboration’s risk of bias tool [24]. Trials were judged as low, unclear, or high risk of bias for the domains of sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data, selective reporting, and other forms of bias such as conflicts of interest. For acupuncture studies, it is not feasible to blind personnel (practitioner) [25]. Disagreements in judgments were resolved by consulting another reviewer (TZ).

Statistical analyses were performed using Review Manager 5.3.5 [26]. Dichotomous data are presented as risk ratio (RR) and continuous data as mean difference, with 95% confidence intervals (CIs). Data were analyzed for available cases. A random effects model was used. Statistical heterogeneity
3. Results

3.1. Search Results. A total of 15,306 records with one additional record sourced elsewhere were identified from database searches. After removal of duplicates, screening of titles and abstracts excluded 7,673 papers, and 2,485 full texts were reviewed (Figure 1).

3.2. Characteristics of Studies. Twelve RCTs involving 1,026 participants met the inclusion criteria [27–38]. Ten RCTs with 975 participants were included in the meta-analysis. The data presented from two trials could not be reanalyzed due to data not being available for individual groups; these were excluded from quantitative analysis [37, 38]. The authors were contacted for additional information; however this was unsuccessful. All trials recruited male and female participants except K. S. Kim and Y.-B. Kim [37] who recruited only male
Subjects. Participant age ranged from 13 to 37 with a median of mean age of 23.1 years. Details of trial location, treatment times, follow-up periods, and participant stage and duration of condition are presented in Table 1.

The intervention most frequently used was acupuncture (six trials) [27, 28, 31–33, 35] followed by auricular acupuncture (two trials) [29, 30]. One trial used electroacupuncture [36] and one trial used acupuncture combined with moxibustion [34]. The comparators are described in Table 2. K. S. Kim and Y.-B. Kim 2012 [37] included three treatment arms, one of acupuncture alone, one of herbal medicine alone, and one where herbal medicine was combined with acupuncture. These three groups were compared with a wait list control. Only the data for the acupuncture arm was included in this analysis. McKee et al. 2004 [38] included two treatment arms, auricular acupuncture and auricular electroacupuncture which were compared to placebo control groups, sham auricular acupuncture, and sham auricular electroacupuncture, respectively.

There was large variation in acupuncture points used (Table 2). Three studies [27, 28, 34] used CV13 Shangwan, CV12 Zhongwan, CV4 Guanyuan, CV6 Qihai, ST24 Huaroumen, ST26 Wailing, Shang Feng Shi Dian (an abdominal point 0.5 cun lateral to ST 24 Huaroumen), and KI13 Qixue. Most of the studies used a standardized set of acupuncture points with one study using a semistandardized approach [30]. Four studies used Ashi points [28, 29, 33, 34] where the location was not specified and two used needles around acne lesions (surrounding acupuncture [29, 33]).

One trial [29] reported on therapeutic effective rate based on lesion count and severity and also reported on serum testosterone and recurrence rate. Four trials [27, 31, 34, 35] reported on therapeutic effective rate according to the 2002 Chinese medicine research guidelines [22]. One trial [33] used the Chinese medicine research guidelines from 1997 [39] and three trials [28, 32, 36] used the 1994 Chinese medicine research guidelines [23]. One trial did not refer to a guideline for judgment of therapeutic effective rate but indicated an improvement of lesion of 95% was a cure and 60% was a significant improvement; these data were included in the meta-analysis [30]. The criteria for determining clinical effect are described in Supplementary Table 1. Only one trial reported measuring quality of life, using Skindex 29 [37].

3.3. Risk of Bias. Methodological quality of the trials was generally low (Figure 2). Four trials [28, 29, 32, 35] were assessed as high risk of bias in the domain of sequence generation as they used sequence of visit for randomization. Five trials [27, 31, 34, 36, 37] were assessed as low risk as random number generators were used. Three trials were assessed as unclear as there was insufficient information [30, 33, 38]. All trials were assessed as unclear risk in blinding of participants. Two trials were assessed as low risk for blinding of outcome assessors [37, 38] and ten were at unclear risk due to insufficient information. One trial was assessed as unclear risk for incomplete data [31] as they did not report dropout data. One trial, Zhang et al. [36], reported on dropout but data was reported only for those who completed the trial and thus was assessed as high risk for incomplete outcome data. Ten trials were assessed as low risk for incomplete data. Two trials were assessed as high risk for selective outcome reporting. McKee et al. [38] stated they would include data on adverse events but no data were presented. K. S. Kim and Y.-B. Kim 2011 indicated in their protocol [40] the use of VAS scale but no data was reported. The remaining ten trials were assessed as unclear as there were no trial protocols published or trial registrations identified [27–36].

3.4. Primary Outcome: Therapeutic Effective Rate. Figure 3 presents the forest plot for TER $\geq$30% change in symptoms. In the meta-analysis of the trials that defined the TER $\geq$30% as improvement, the chance of achieving a 30% or greater change in lesion count in the acupuncture group was not different to the combined pharmacotherapy group (retinoids, antibiotics, and other supplements) (four studies, RR: 1.07 [95% CI 0.98, 1.17] and $I^2 = 8\%$) [28, 32, 33, 36] with low heterogeneity. Subgroup analysis of studies where the comparator was antibiotics plus other supplements showed the chance of a 30% or greater change in lesion count was not
### Table 1: Characteristics of studies.

<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Trial location</th>
<th>Treatment duration, follow-up duration</th>
<th>Stage, severity, and duration of condition</th>
<th>Number of participants randomized/assessed; dropouts or withdrawals</th>
<th>Age (mean (SD) or range); gender (M/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han; 2010 [27]</td>
<td>China, hospital, outpatients</td>
<td>8 w, 1 m</td>
<td>Stage: NS, Severity: Pillsbury I, II Duration: I: 2.35 ± 0.86; C: 2.15 ± 0.82</td>
<td>I: 50/46; 4 C: 50/47; 3</td>
<td>I: 25.83 ± 5.25; 18/28 C: 24.68 ± 4.36; 14/33</td>
</tr>
<tr>
<td>He; 2009 [28]</td>
<td>China, hospital, outpatients</td>
<td>3 w, NS</td>
<td>Stage: NS, Severity: slight to severe Duration: I: 20 d to 16 y; C: 1 m to 17 y</td>
<td>I: 24/24; 0 C: 22/22; 0</td>
<td>I: 25.2; NS C: 23.6; NS</td>
</tr>
<tr>
<td>Li; 2002 [29]</td>
<td>NS</td>
<td>6 d, 1 m</td>
<td>Stage: NS, Severity: Samuelson 1–9 Duration: I: 14 d–15 y, I2: 7 d–13 y; C: 4 d–14 y</td>
<td>II: 200/200; 0 I2: 60/60; 0 C: 60/60; 0</td>
<td>II: 13–37; NS I2: 14–35; NS C: 14–33; NS</td>
</tr>
<tr>
<td>Liu; 2011 [30]</td>
<td>NS</td>
<td>2 w, 6 m</td>
<td>Stage: NS, Severity: NS Duration: I: 1 w–14 y; C: 1 w–10 y</td>
<td>I: 40/40; 0 C: 40/40; 0</td>
<td>I: 14–41; 6/34 C: 13–30; 7/33</td>
</tr>
<tr>
<td>Mo; 2005 [32]</td>
<td>NS</td>
<td>2 w, NS</td>
<td>Stage: NS, Severity: NS Duration: NS</td>
<td>I: 42/42; 0 C: 38/38; 0</td>
<td>NS C: NS</td>
</tr>
<tr>
<td>Tang; 2011 [33]</td>
<td>NS</td>
<td>10 d, NS</td>
<td>Stage: NS, Severity: NS Duration: I: 1 w–9 y</td>
<td>I: 42/42; 0 C: 42/42; 0</td>
<td>NS I1/31 NS 7/35</td>
</tr>
<tr>
<td>Wu; 2011 [34]</td>
<td>NS</td>
<td>8 w, 2 m</td>
<td>Stage: NS, Severity: NS Duration: I: II 92 ± 8.93; C: 12.77 ± 9.58</td>
<td>I: 40/36; 4 C: 40/35; 5</td>
<td>I: 24.31 ± 4.08; 13/23 C: 23.91 ± 3.83; 13/22</td>
</tr>
<tr>
<td>Liu; 2015 [31]</td>
<td>NS</td>
<td>8 w, NS</td>
<td>Stage: NS, Severity: NS Duration: I: 6.5 m; C: 6.1 m</td>
<td>I: 60/50; 10 C: 58/50; 8</td>
<td>I: 23.2; 27/33 C: 24; 27/31</td>
</tr>
<tr>
<td>Zhang; 2014 [36]</td>
<td>NS</td>
<td>4 w, NS</td>
<td>Stage: NS, Severity: NS Duration: I: 6 m–5 y; C: 6 m–4.5 y</td>
<td>I: 20/19; 1 C: 20/20; 0</td>
<td>I: 18–23; 2/17 C: 18–24; 5/15</td>
</tr>
<tr>
<td>You; 2014 [35]</td>
<td>NS</td>
<td>30 d, NS</td>
<td>Stage: NS, Severity: NS Duration: I: 23.36 m; C: 22.81 m</td>
<td>I: 30/30; 0 C: 30/30; 0</td>
<td>I: 25 ± 5; 17/13 C: 25 ± 5; 15/14</td>
</tr>
<tr>
<td>McKee; 2004 [38]</td>
<td>USA, outpatient clinic</td>
<td>20 w, NS</td>
<td>Stage: NS, Severity: grade I &amp; II mild-to-moderate nonscarring facial by dermatologist; photographs grading by Cook 1979 and lesion count Duration: NS</td>
<td>II: 6/6; 2 I2: 11/11; 6 C1: 6/6; 1 C2: 6/6; 0</td>
<td>II: F16 (2.1) M15 (0.7); NS I2: F21 (3.4) M16 (3.6); NS C1: F19 (4.2) M17 (1.9); NS C2: F21 (1.5) M15 (1.2); NS</td>
</tr>
<tr>
<td>Kim; 2012 [37]</td>
<td>Korea, outpatient clinic</td>
<td>4 w, NS</td>
<td>Stage: NS, Severity: Korean Acne Grading System grades 2–4 (&gt;10 papules, &lt;20 nodules on face); Duration: &gt;3 months (chronic stage)</td>
<td>I: II/II, 3 C: II/II, 2</td>
<td>I: M 21.5 (3.6); NS C: M 23.3 (4.1); NS</td>
</tr>
</tbody>
</table>

NS: not stated; I: intervention; C: control; F: female; M: male; d: days; w: weeks; m: months; y: years.
<table>
<thead>
<tr>
<th>First author, publication year</th>
<th>Intervention type</th>
<th>Acupuncture points</th>
<th>Intervention treatment frequency</th>
<th>Control details</th>
<th>Control treatment frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han, 2010 [27]</td>
<td>Acupuncture</td>
<td>CV13 Shangwan, CV12 Zhongwan, CV4 Guanyuan, CV6 Qihai; ST24 Huaroumen, ST26 Wailing; Shangfeng Shidian (abdominal point 0.5 cm lateral and superior to ST24); KI13 Qixue, M-CA-23 Sanniaoju (Qipang)</td>
<td>30 mins, 3 times per week</td>
<td>Isotretinoin capsules (oral)</td>
<td>10 mg b.i.d. (first month); 10 mg q.d. (second month)</td>
</tr>
<tr>
<td>He, 2009 [28]</td>
<td>Acupuncture</td>
<td>CV13 Shangwan, CV12 Zhongwan, CV4 Guanyuan, CV6 Qihai; ST24 Huaroumen, ST26 Wailing; Shangfeng Shidian (abdominal point 0.5 cm lateral and superior to ST24); KI13 Qixue, M-CA-23 Sanniaoju (Qipang), M-HN-3 Yintang, SI18 Quanliao, ST4 Dicang, M-HN-9 Taiyang, Ashi points</td>
<td>30 mins: body points; 15–20 mins: head points Ashi points q.d. (first week), every 2 days (2nd and 3rd weeks)</td>
<td>Metronidazole (topical)</td>
<td>b.i.d.</td>
</tr>
<tr>
<td>Li, 2002 [29]</td>
<td>I1 AA + SA</td>
<td>SA: Ashi points, AA: endocrine, lung, sympathetic, stomach, large intestine, ear Shen Men, internal genitals</td>
<td>SA: 30 min q.d.; AA: 3–5 min, b.i.d.</td>
<td>Tetracycline (oral)</td>
<td>0.5g, q.i.d.</td>
</tr>
<tr>
<td>Liu, 2011 [30]</td>
<td>AA</td>
<td>Lung, endocrine, adrenal gland, ear Shen Men, subcortex, cheek; large intestine (wind and heat in lung meridian); spleen, stomach, large intestine (heat and damp in spleen and stomach); liver, kidney (penetrating and conception meridian disharmony)</td>
<td>AA: 5–10 min, t.i.d.</td>
<td>Benzamycin (oral)</td>
<td>b.i.d.</td>
</tr>
<tr>
<td>Mo, 2005 [32]</td>
<td>Acupuncture</td>
<td>Governor meridian</td>
<td>4-5 hrs/treatment, 5 times per week</td>
<td>Viaminate capsules, Vit B6 (oral)</td>
<td>Viaminate 0.25 mg t.i.d.; Vit B6, 2 pills t.i.d.</td>
</tr>
<tr>
<td>Tang, 2011 [33]</td>
<td>Acupuncture + SA</td>
<td>Manual: ST36 Zusanli, ST40 Fenglong, ST45 Lidui, LI11 Quchi, LI10 Shoushani, LI4 Hegu; SA: Ashi points</td>
<td>30 min q.d.</td>
<td>Erythromycin, zinc sulfate (oral); sulphur (topical)</td>
<td>Erythromycin 0.2 g b.i.d.; zinc sulfate 0.2 g b.i.d.; sulphur (topical) q.d.</td>
</tr>
<tr>
<td>Wu, 2011 [34]</td>
<td>Acupuncture + moxibustion</td>
<td>Acupuncture: CV17 Shangwan, CV12 Zhongwan, CV4 Guanyuan, CV6 Qihai; ST24 Huaroumen, ST26 Wailing; Shangfeng Shidian (abdominal point 0.5 cm lateral and superior to ST24); KI13 Qixue; Moxa: CV4 Guanyuan, CV6 Qihai</td>
<td>Acupuncture and moxibustion: 3 times per week</td>
<td>Isotretinoin capsules (oral)</td>
<td>10 mg b.i.d.</td>
</tr>
<tr>
<td>Liu, 2015 [35]</td>
<td>Acupuncture</td>
<td>GB4 Yangbai, SI18 Quanliao, GV4 Dazhui, LI4 Hegu, LI11 Quchi, ST44 Neiting</td>
<td>q.d. (total of 56 treatments)</td>
<td>Isotretinoin (oral)</td>
<td>10 mg b.i.d.-t.i.d.</td>
</tr>
<tr>
<td>Zhang, 2014 [36]</td>
<td>EA</td>
<td>Governor meridians, Jiaji and bladder through the first lateral line, lung, large intestine, stomach</td>
<td>Twice per week (total of 15 treatments)</td>
<td>Tretinoin (topical)</td>
<td>b.i.d.</td>
</tr>
<tr>
<td>First author, publication year</td>
<td>Intervention type</td>
<td>Acupuncture points</td>
<td>Intervention treatment frequency</td>
<td>Control details</td>
<td>Control treatment frequency</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>------------------------------------------------------------------------------------</td>
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<td>-----------------------------</td>
</tr>
<tr>
<td>McKee, 2004 [38]</td>
<td>Auricular acupuncture and EA</td>
<td>I1: Oleson’s Shen Men, allergy point, skin disorder point F, point zero, lungs 1 and 2, endocrine point, genital control point, face point bilateral ears; I2: points as I1 plus EA 8–16 sec on 5–80 Hz</td>
<td>20 min weekly</td>
<td>Cl: 9 sham points on helix auricular ridge C2: 9 sham points on helix auricular ridge as Cl plus EA 8–16 sec, 10–40 Hz</td>
<td>20 min weekly</td>
</tr>
<tr>
<td>Kim, 2012 [37]</td>
<td>Acupuncture</td>
<td>ST2 Sibai, ST6 Jiache, ST36 Zusani, LI120 Yingxiong, LI11 Quchi, PC6 Neiguan, H18 Shaofu, SP3 Taibai, SP6 Sanyinjiao, SP10 Xuehai, LR3 Taichong, and/or Ashi points randomly selected at papules and nodules on the face by acupuncture practitioner</td>
<td>Twice weekly for 4 weeks</td>
<td>Waitlist (no treatment)</td>
<td></td>
</tr>
</tbody>
</table>

I: intervention; C: control; EA: electroacupuncture; q.d.: one time per day; b.i.d.: twice daily; t.i.d.: three times daily; q.i.d.: four times daily; q.n.: once nightly; AA: auricular acupressure; SA: surround needle; sec: seconds; Hz: hertz.
different between acupuncture and topical/oral antibiotics and supplements group (two studies, RR: 1.03 [95% CI 0.91, 1.16] and I² = 14%) [28,33] with low heterogeneity. In a subgroup analysis of the chance of a change of 30% or greater in lesion count acupuncture was as effective as the retinoids groups (vitamin A and tretinoin) (two studies, RR: 1.07 [95% CI 0.86, 1.31]) [27,31,34,35]; however there was moderate-to-substantial heterogeneity. In a subgroup analysis, the chance of a 50% or greater change in lesion count in the acupuncture group was not different to the pharmacotherapy group (isotretinoin and antibiotics) (six studies, RR: 1.07 [95% CI 0.98, 1.17] and I² = 50%) [27,29–31,34,35]; however there was moderate-to-substantial heterogeneity. In a subgroup analysis, the chance of a 50% or greater change in lesion count in the acupuncture group was not different to the retinoids group (isotretinoin and topical tretinoin) in four studies (four studies, RR: 1.05 [95% CI 0.93, 1.17] and I² = 59%) with moderate-to-substantial heterogeneity [27,31,34,35]. Two auricular acupuncture trials were not combined due to differences in comparator types (one comparator was an oral pharmaceutical and the other was a topical preparation). Auricular acupuncture was more effective compared to oral tetracycline for TER ≥50% (one study, RR: 1.15 [95% CI 1.02, 1.31]) [29]; however there were four times more participants in the intervention group compared to the comparator group with no reasons provided. Another study of auricular acupuncture found no benefit compared to topical benzamycin (one study, RR: 1.12 [95% CI 0.88, 1.43]) [30].

3.5. Secondary Outcomes. The paper by K. S. Kim and Y.-B. Kim [37] was the only trial to report on quality of life using Skindex 29 score. The data were not presented in a way that permitted reanalysis, so the effects remain unclear. The study authors concluded that the use of acupuncture and Chinese herbal medicine Keigai-renyou-to could be used for inflammatory acne lesions but further research was required.

A total of 127 adverse events were reported in three trials [27,33,34]. The other nine did not mention any adverse events. There were more adverse events in the control group (98 in the control group and 29 in the intervention group). Adverse events in the intervention group included painful sensation (11 cases), ecchymosis (nine cases), flushing (five cases), and itchy sensation after needle withdrawal (four cases) which are common adverse events seen after needle penetration and acupuncture [41,42]. In the control group, adverse events that included dry mouth (75 cases), dry skin and desquamation (17 cases), and gastrointestinal discomfort (six cases) are also common adverse events following topical benzoyl peroxide and retinoid treatment [4,43]. No serious adverse events were reported in the included trials.

4. Discussion

This systematic review showed that the chance of ≥30% and ≥50% improvement in acne symptoms with body acupuncture, electroacupuncture, and auricular acupuncture was not statistically different from that of pharmaceuticals for acne vulgaris. Interestingly, the magnitude of the treatment effect and the 95% CIs were the same for the primary meta-analyses, regardless of which criteria were used to measure clinical change. There were more adverse events in the pharmacotherapy/control group than in the acupuncture/intervention group. Based on the included studies, acupuncture was well tolerated by participants with acne vulgaris.
While not validated, TER is a common measure of effect in Chinese medicine trials. The TER for acne vulgaris is a subjective outcome that includes a change in lesion count or severity. The Chinese research guidelines for acne from 2002 [22] suggest a ≥50% change in lesion count or severity whereas the 1994 guidelines [23] suggested ≥30% change in lesion count and symptoms. In this review, acupuncture was as effective as antibiotics in trials that used the TER criteria of a ≥30% improvement in symptoms. In the trials that used a ≥50% improvement in symptoms, auricular acupressure was as effective as antibiotics and acupuncture was as effective as topical and oral retinoids. There is currently no consensus on outcome measures for acne though there are efforts underway to standardize them [44]. There was only one trial that reported on quality of life measure Skindex 29 even though there is mounting evidence that suffers of acne vulgaris may experience considerable psychological and emotional burden [45].

All trials in the quantitative analysis used retinoids or antibiotics as the comparator. Retinoids and antibiotics have demonstrated efficacy for acne [4]; however long term antibiotic use can contribute to antibiotic resistance [46]. Retinoids have severe adverse effects such as teratogenicity and should be used with caution in people of childbearing age [46]. Acupuncture and auricular acupressure were shown in this analysis not to be statistically different to guideline recommended treatments but with fewer side effects and may be an option for those wanting an alternative treatment to pharmaceuticals. Treatment times varied considerably across the trials. Such variations of treatment times could introduce clinical heterogeneity. The typical treatment duration for body acupuncture is 20 to 30 minutes for each treatment and treatment frequency may vary from one to five times per week depending on the local clinical practice environment. Fibromyalgia and tension headache studies have found 20- to 30-minute needle retention, repeated stimulation on acupuncture points (de-qi sensation), and daily or twice weekly treatment to have better clinical outcomes compared to less needle retention time and once-per-week treatment [47, 48].

The findings of this review are similar to previous reviews [20, 21]; however previous reviews included trials that compared Chinese medicine interventions against each other such as acupuncture compared to herbal medicines. This review faced the same limitations as others in terms of the methodological quality of included trials. Methodological quality of included studies was low, with four of the twelve studies assessed as high risk of bias and three unclear in the domain of sequence generation. There was also insufficient information on blinding of outcome assessors and participants.

Sample sizes were small, and none of the included studies reported sample size calculations. Not all trials reported on the severity of lesions. There were no follow-up assessments.
in the included trials. Statistical heterogeneity was also detected in several subgroup analyses which were not able to be explored due to small numbers of studies. Detailed reporting of trial information was lacking; none of the trials addressed all items from Consolidated Standard of Reporting Trials (CONSORT) [49] or Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [50] standard reporting conventions. The STRICTA guidelines are important to improve transparency of intervention reporting in acupuncture clinical trials. For studies included in this review, several items were reported well in all trials: the type of acupuncture used, standard acupuncture name and/or locations of acupuncture points, the number and duration of treatment sessions, and the precise descriptions of the controls or comparators (Supplementary Table 2). The trials conducted in China did not provide information about practitioners, the setting and context of treatment, instructions to practitioners, and information and explanations to the patients. This can pose an issue with reproducibility of studies and may be a source of bias. Reporting of such details would enhance accurate analysis and interpretation of data and improve research reliability in acupuncture interventions [51].

5. Conclusions

There was no statistical difference in the efficacy of acupuncture compared to pharmacotherapies for acne vulgaris; however, acupuncture interventions reported less adverse effects. Poor methodological quality of trial design and lack of consistent reporting of outcome measures from some trials were found in this review; therefore results should be interpreted with caution. Future trials should include rigorous methodological design and reporting should follow standard reporting conventions such as CONSORT and STRICTA. Quality of life measures and further understanding of the mechanisms of acupuncture on acne should also be considered for future studies.

Conflicts of Interest

The authors report no conflicts of interest.

Acknowledgments

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Supplementary Materials

Supplementary Table 1: therapeutic effective rate criteria and secondary outcomes. Supplementary Table 2: assessment of reporting of STRICTA items. (Supplementary Materials)

References


Evidence-Based Complementary and Alternative Medicine

11


B. Han, A clinical study on abdominal acupuncture for acne by conditioning Liver and Kidney, Guangzhou University of Chinese Medicine, 2010.


# Appendix 16 Assessment of Reporting of STRICTA items for acupuncture studies

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>1. Acupuncture rationale</td>
<td>1a) Style of acupuncture (e.g. Traditional Chinese Medicine, Japanese, Korean, Western medical, Five Element, ear acupuncture, etc)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>1c) Extent to which treatment was varied</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>2. Details of needling</td>
<td>2a) Number of needle insertions per subject per session (mean and range where relevant)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>NA (auricular)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>NA (plum blossom needle)</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>2b) Names (or location if no standard name) of points used (uni/bilateral)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>2c) Depth of insertion, based on a specified unit of measurement, or on a particular tissue level</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>NA</td>
<td>N</td>
<td>Auricular</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>2d) Response sought (e.g. de qi or muscle twitch response)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>NA</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>Auricular</td>
<td>N</td>
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</tr>
<tr>
<td>2c) Needle stimulation (e.g. manual, electrical)</td>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>NA</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>2f) Needle retention time</td>
<td></td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>2g) Needle type (diameter, length, and manufacturer or material)</td>
<td></td>
<td>Y</td>
<td>Partial</td>
<td>Partial</td>
<td>NA</td>
<td>Partial</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
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<td>Y</td>
</tr>
<tr>
<td>3. Treatment regimen</td>
<td>3a) Number of treatment sessions</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>Y</td>
</tr>
<tr>
<td></td>
<td>3b) Frequency and duration of treatment sessions</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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</tr>
<tr>
<td>4. Other components of treatment</td>
<td>4a) Details of other interventions administered to the acupuncture group (e.g. moxibustion, cupping, herbs, exercises, lifestyle advice)</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>NA</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>4b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients</td>
<td>NA</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>NA</td>
<td>NA</td>
<td>N</td>
<td>NA</td>
<td>N</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>5. Practitioner background</td>
<td>5) Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
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<td>-----------------------------------------------------------</td>
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<td>----------</td>
</tr>
<tr>
<td>6. Control or comparator interventions</td>
<td>6a) Rationale for the control or comparator in the context of the research question, with sources that justify this choice</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>6b) Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for Items 1 to 3 above.</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

Abbreviations: Y Yes, N No, NA Not applicable
Appendix 17 Assessment of *P. acnes*

| Specify location (location must be the same each visit) | Count at baseline (week 0) | Count at end of treatment (week 8) | Count at follow-up (week 12) |
### Appendix 18 SPIRIT statement

**SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents**

<table>
<thead>
<tr>
<th>Section/item</th>
<th>Item No</th>
<th>Description</th>
<th>Addressed on page number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Descriptive title identifying the study design, population, interventions,</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and, if applicable, trial acronym</td>
<td></td>
</tr>
<tr>
<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>registry</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
<td>N/A</td>
</tr>
<tr>
<td>Protocol version</td>
<td>3</td>
<td>Date and version identifier</td>
<td>N/A</td>
</tr>
<tr>
<td>Funding</td>
<td>4</td>
<td>Sources and types of financial, material, and other support</td>
<td>N/A</td>
</tr>
<tr>
<td>Roles and responsibilities</td>
<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection,</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>management, analysis, and interpretation of data; writing of the report, and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>the decision to submit the report for publication, including whether they</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>will have ultimate authority over any of these activities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5d</td>
<td>Composition, roles, and responsibilities of the coordinating centre,</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>steering committee, endpoint adjudication committee, data management team,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>and other individuals or groups overseeing the trial, if applicable (see</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Item 21a for data monitoring committee)</td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background and rationale</td>
<td>6a</td>
<td>Description of research question and justification for undertaking the trial,</td>
<td>228-239</td>
</tr>
<tr>
<td></td>
<td></td>
<td>including summary of relevant studies (published and unpublished) examining</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>benefits and harms for each intervention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>Explanation for choice of comparators</td>
<td>237-239</td>
</tr>
<tr>
<td>Objectives</td>
<td>7</td>
<td>Specific objectives or hypotheses</td>
<td>215</td>
</tr>
<tr>
<td>Trial design</td>
<td>8</td>
<td>Description of trial design including type of trial (eg, parallel group,</td>
<td>228</td>
</tr>
<tr>
<td></td>
<td></td>
<td>crossover, factorial, single group), allocation ratio, and framework</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(eg, superiority, equivalence, noninferiority, exploratory)</td>
<td></td>
</tr>
<tr>
<td>Methods: Participants, interventions, and outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study setting</td>
<td>9</td>
<td>Description of study settings (eg, community clinic, academic hospital) and</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>list of countries where data will be collected. Reference to where list of</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>study sites can be obtained</td>
<td></td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>10</td>
<td>Inclusion and exclusion criteria for participants. If applicable, eligibility</td>
<td>229-232, 258</td>
</tr>
<tr>
<td></td>
<td></td>
<td>criteria for study centres and individuals who will perform the interventions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(eg, surgeons, psychotherapists)</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered</td>
<td>233-237</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)</td>
<td>233-237, 246-247, 255-259, 264</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)</td>
<td>258-259, 261-262, 264</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11d Relevant concomitant care and interventions that are permitted or prohibited during the trial</td>
<td>258-259</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended</td>
<td>240-248</td>
<td></td>
</tr>
<tr>
<td>Participant timeline</td>
<td>13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)</td>
<td>248-255</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations</td>
<td>260-261</td>
<td></td>
</tr>
<tr>
<td>Recruitment</td>
<td>15 Strategies for achieving adequate participant enrolment to reach target sample size</td>
<td>261-262</td>
<td></td>
</tr>
</tbody>
</table>

**Methods: Assignment of interventions (for controlled trials)**

**Allocation:**

| Sequence generation | 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 252-253 |
| Allocation concealment mechanism | 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 252-253 |
| Implementation | 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 252-253 |
| Blinding (masking) | 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 253 |
|               | 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial | 248, 253, 264 |

**Methods: Data collection, management, and analysis**
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 240-248, 259 |
| Data management | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 258-259, 262 |
| 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 259 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 263-264 |
| 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | Nil |
| 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 263 |

**Methods: Monitoring**

| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 263-264 |
| 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 263-264 |

**Harms**

| 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 246-248, 264 |

**Auditing**

| 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 235-237, 251 |

**Ethics and dissemination**

| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 252 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 264-265 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 230-231, 248-251 |
| 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | N/A |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 259 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | N/A |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 259 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | 246-248, 264 |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 264 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | N/A |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | N/A |
| Appendices | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | N/A |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | 244-248, 250-251 |

* It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.