Chinese Medicine for Herpes Zoster

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

Doctor of Philosophy

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March 2017
Declaration

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

Kaiyi Wang __________________

Date __________________
Acknowledgements

First of all, I would like to express my sincere gratitude to my parents Mrs Yuping Wang and Mr Ruilin Wang, for encouraging and supporting me to undertake this research degree in RMIT University, Australia.

I would also like to express my appreciation to my supervisors, Associate Professor Anthony Lin Zhang, Dr Meaghan E. Coyle and Professor Charlie Changli Xue, for their continuous guidance, patience and invaluable support during my Ph.D candidature.

I would like to sincerely thank Dr Jason Jingjie Yu, for his assistance in the systematic reviews of this research; Dr Haiying Liang, for her help in Chinese databases search and classical literature research in this thesis; Dr Suzi Mansu, for her assistance in English databases search; Dr Brian May, for his professional advice on safety of the herbal ingredients in this research; Dr Iris Wenyu Zhou, for her help in assessing the methodological quality in the systematic reviews in this project; Dr Claire Shuiqing Zhang, for her guidance in data coding and data mining in classical literature research; Dr Neil Owens, for his editorial work for this thesis. I would like to acknowledge the help from all staff and other HDR students of China-Australia International Research Centre for Chinese Medicine of RMIT University and Guangdong Provincial Academy of Chinese Medical Sciences.

To my dearest friends Dr Jingyang Liu, Mr Wuyu Li, Dr Malcom Lingzhou Ma, Mr Tony Cheung, Mr Bowei Li, Mr Sam Huansen Fan, and Dr Brian Huiming Liang, thank you for
listening to me and helping me with infinite patience during my research life in Melbourne. I am lucky and grateful to have you all.
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Publications

Thesis related:


3. Wang KY, Coyle ME, Liang HY, Zhang AL, Xue CCL. Data mining and cluster analysis of herpes zoster symptoms of classical literature. (Due for submission in March 2017)


Conference papers:

Additional papers:


Conference:

## Abbreviations

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMED</td>
<td>Allied and Complementary Medicine Database</td>
</tr>
<tr>
<td>API</td>
<td>Activator protein 1</td>
</tr>
<tr>
<td>CAIRCCM</td>
<td>China-Australia International Research Centre for Chinese Medicine</td>
</tr>
<tr>
<td>CAM</td>
<td>Complementary and alternative medicine</td>
</tr>
<tr>
<td>CCTs</td>
<td>Non-randomised controlled clinical trials</td>
</tr>
<tr>
<td>CBM</td>
<td>China Biomedical Literature</td>
</tr>
<tr>
<td>CNKI</td>
<td>China National Knowledge Infrastructure</td>
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<tr>
<td>CHM</td>
<td>Chinese herbal medicine</td>
</tr>
<tr>
<td>CMBA</td>
<td>Chinese Medicine Board of Australia</td>
</tr>
<tr>
<td>CQVIP</td>
<td>Chongqing VIP</td>
</tr>
<tr>
<td>CIs</td>
<td>Confidence intervals</td>
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<tr>
<td>CM</td>
<td>Chinese medicine</td>
</tr>
<tr>
<td>CMI</td>
<td>Cell-mediated immunity</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>Cox-2</td>
<td>Cyclooxygenase-2</td>
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<tr>
<td>CRF</td>
<td>Case report form</td>
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<tr>
<td>CRG</td>
<td>Cranial root ganglia</td>
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<tr>
<td>CSWLT</td>
<td>Chu shi wei ling tang 除湿胃苓汤</td>
</tr>
<tr>
<td>CINAHL</td>
<td>Cumulative Index of Nursing and Allied Health Literature</td>
</tr>
<tr>
<td>DRG</td>
<td>Dorsal root ganglia</td>
</tr>
<tr>
<td>EA</td>
<td>Electro-acupuncture</td>
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</table>
EQ-5D         Euroqol-5 Dimensions
GL           Glycyrrhizin
GPRN         General Practice Resource Network
HLA-DR+      Human leukocyte antigen-antigen D related
HRQoL        Health related quality of life
HSV-2        Herpes simplex type 2
HZ           Herpes zoster
HZO          Herpes zoster ophthalmicus
IDO          Indoleamine 2, 3-dioxygenase
IFN-γ        Interferon-gamma
IL           Interleukin
iNOS         Nitric oxide synthase
JC           Jaccard coefficient
LDXGT        Long dan xie gan tang 龙胆泻肝汤
LPS          Lipopolysaccharide
MAPK         Phosphorylated mitogen activated protein kinases
MDs          Mean differences
mRNA         Messenger ribonucleic acid
NF-κB        Nuclear factor-κb
NHMRC        Australian National Health and Medical Research Council
NO           Nitric oxide
NSAIDs       Nonsteroidal anti-inflammatory drugs
PBMC         Peripheral blood mononuclear cells
PGE2         Prostaglandin E2

XXI
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>PHN</td>
<td>Postherpetic neuralgia</td>
</tr>
<tr>
<td>PICF</td>
<td>Participant information and consent forms</td>
</tr>
<tr>
<td>PY</td>
<td>Person-years</td>
</tr>
<tr>
<td>RCTs</td>
<td>Randomised controlled trials</td>
</tr>
<tr>
<td>RGP</td>
<td><em>Rehmannia glutinosa</em> polysaccharides</td>
</tr>
<tr>
<td>RR</td>
<td>Risk ratios</td>
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<tr>
<td>sCAPs</td>
<td>Selenizing Chinese angelica polysaccharides</td>
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<tr>
<td>SF 36</td>
<td>Medical Outcomes Study Short-Form 36</td>
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<tr>
<td>SM</td>
<td>Sneath and Sokal Measurement</td>
</tr>
<tr>
<td>SOPs</td>
<td>Standard operating procedures</td>
</tr>
<tr>
<td>SRs</td>
<td>Systematic reviews</td>
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<tr>
<td>TCAs</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>TER</td>
<td>Therapeutic effective rate</td>
</tr>
<tr>
<td>TI</td>
<td>Therapeutic index</td>
</tr>
<tr>
<td>TNFα</td>
<td>Tumour necrosis factor</td>
</tr>
<tr>
<td>TSQM</td>
<td>Treatment Satisfaction Questionnaire for Medication</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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<tr>
<td>VZV</td>
<td>Varicella zoster virus</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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<tr>
<td>ZBPI</td>
<td>Zoster Brief Pain Inventory</td>
</tr>
<tr>
<td>ZHYD</td>
<td><em>Zhong Hua Yi Dian</em> 中华医典</td>
</tr>
<tr>
<td>ZIQ</td>
<td>Zoster Impact Questionnaire</td>
</tr>
<tr>
<td>ZYFJDCD</td>
<td><em>Zhong Yi Fang Ji Da Ci Dian</em> 中医方剂大辞典</td>
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Summary

Background

Herpes zoster (HZ) is a neurocutaneous disease caused by reactivation of the varicella zoster virus. The characteristic clinical manifestations of HZ include grouped blistering vesicles erupting on a red base of skin, and burning or stabbing pain with a unilateral dermatome distribution. The pain of HZ is associated with significant reduction on patients’ health related quality of life (HRQoL). Conventional treatments include antiviral therapies and pain management. These therapeutic approaches have not been able to provide effective relief of these symptoms for all patients.

Hence other therapies such as Chinese medicine (CM) have been used to treat symptoms of HZ, either alone or as add-on therapy to conventional approaches. Over the long history of Chinese medicine development, valuable information on clinical manifestations, diagnosis, and treatment for HZ have been described and explained in-depth in the classical literature, which continues to be included in the contemporary guidelines and textbooks for CM practice. Currently the classical literature evidence for HZ has not been systematically evaluated.

Chinese herbal medicine (CHM) and acupuncture are the two main CM therapies for HZ included in contemporary CM textbooks and guidelines. The clinical evidence based on several systematic reviews (SRs) of CM indicated that they are beneficial for pain control and cutaneous outcomes. However, the quality of current evidence is limited by the databases searched, study inclusion criteria, and statistical analyses. To address this gap, SRs based on a more comprehensive search of databases and strict inclusion criteria are needed.
Objectives

Guided by the “Whole Evidence” approach, this thesis aims to:

1. Examine the evidence of Chinese medicine classical literature for HZ.
2. Evaluate the current clinical trial evidence of CHM and acupuncture for HZ.
3. Review the current experimental evidence of CHM treatment for HZ.
4. Design a rigorous trial protocol on a CHM formula for HZ.

Methods

Classical literature evidence research

The comprehensive classical literature search was conducted using the Zhong Hua Yi Dian 中华医典 (ZHYD). Citations identified by search terms were extracted for further analysis. Descriptive statistical analyses were performed to identify the frequency of each search term, signs and symptoms and treatment. Cluster analyses were performed to discover the potential relationships of the HZ symptoms in the data set which were judged to be most likely HZ citations.

Modern literature evidence research

Nine English and Chinese databases were searched for evidence from randomised controlled trials (RCTs). Overviews of CHM and acupuncture therapies were conducted to summarise and discuss the characteristics of included studies. Two specific interventions were selected as the foci for the SRs: a CHM formula Long dan xie gan tang 龙胆泻肝汤 (LDXGT), and acupuncture combined with moxibustion. The general methods for the SRs followed the
methods of Cochrane Handbook for Systematic Reviews and Interventions. Data were extracted and risk of bias was assessed. All statistical analyses were carried out in RevMan 5.3.

A literature search for experimental evidence of the most frequently used herbs in the included CHM studies was conduct in PubMed. In vivo and in vitro studies which described mechanisms relevant to HZ were included for a general review.

**Trial protocol design**

According to the classical and modern literature evidence in this research, LDXGT formula was the most commonly cited CHM intervention. Clinical evidence showed LDXGT was a well-tolerated and effective treatment. However the evidence was limited by the methodological limitations. A rigorous trial protocol using LDXGT integrated with antiviral therapy was developed to generate new clinical evidence data.

**Results**

**Classical literature evidence**

Ninety-six (96) classical citations were included. *Chan yao* 缠腰 and *huo dan* 火丹 were the most common terms in included citations. The symptoms and CHM treatments described in classical literature are consistent with contemporary conventional medicine and CM textbooks. The most frequently reported formula was LDXGT. A hypothetical symptom structure for HZ has been proposed based on cluster analysis, with a key symptoms classification of heat disease in CM theory highlighted in further inferential analysis.
Clinical trial evidence

Ninety-four (94) RCTs were included for the overview of CHM for HZ. A variety of CHM formulae, single herbs and chemical compounds were evaluated. Findings show that LDXGT was the most commonly used formula. Twenty-six (26) studies were included for the SR of LDXGT for HZ. Modified LDXGT formula was found to shorten the time to alleviate pain and reduce postherpetic neuralgia (PHN) incidence compared with pharmacotherapies. Mild adverse events such as gastrointestinal discomfort were reported from one study.

Experimental evidence of the most commonly used herbs in the included CHM clinical trials found that many of the constituents isolated from these herbs have shown anti-inflammatory actions. Inhibition of inflammatory cytokines and pro-inflammatory enzymes have been reported, which may contribute to relieving the acute inflammatory response of HZ.

Twenty-seven (27) RCTs were included for the overview of acupuncture therapies for HZ. Acupuncture approaches and acupuncture points selection were consistent with the contemporary acupuncture guideline. Nine studies were included for the SR of acupuncture plus moxibustion for HZ. Key findings showed promising benefit from acupuncture and moxibustion in reducing pain, improving rash healing, and reducing the incidence of PHN, with few mild adverse events such as haematoma and bleeding reported.

Trial protocol design

Guided by the findings from the reviews, a randomised, double-blinded, placebo controlled trial protocol using LDXGT integrated with antiviral therapy in the management of HZ was developed. The participants are expected to be immunocompetent patients aged ≥50 years with acute stage HZ; and CM syndrome of Stagnant heat in the Liver meridian. Both the
intervention and control group will receive antiviral therapy. Participants in the intervention group will also receive LDXGT granules and those in the control group will receive placebo granules. The primary outcome will be evaluation of pain, and secondary outcomes will be HRQoL assessment and adverse events.

**Conclusion**

This research applied a systematic approach to summarise the whole evidence of CM therapies in the management of HZ. Data mining results from the classical literature demonstrated that the inflammation symptoms cluster was one of the components of the HZ symptoms structure. Modern literature research showed CM therapies of both CHM and acupuncture plus moxibustion were well tolerated with promising benefit in hastening pain relief, improving cutaneous outcomes, and decreasing the incidence of PHN. The anti-inflammatory effects of the most commonly used herbs from the experimental studies help to elucidate the potential mechanism of actions of these herbs for HZ. To further determine the benefit of LDXGT formula as an add-on therapy to antiviral drugs, a rigorous RCT has been proposed to be undertaken.
Chapter 1. General introduction

1.1 Background

Herpes zoster (HZ), or shingles, is a distinctive neurocutaneous disease resulting from reactivation of the varicella zoster virus (VZV). The preceding infection of VZV (commonly known as chickenpox) occurs during childhood, and the virus remains dormant in the sensory ganglia for decades [1]. When the immune system of the virus carrier weakens due to the aging process, immune suppression or immunodeficiency, the VZV reactivates, causing HZ [2]. Postherpetic neuralgia (PHN) may develop after resolution of the rash, inducing chronic pain without any visual lesion [1].

The global median incidence rate of HZ is 4 - 4.5 per 1,000 person-years, based on data from the United States, Canada, South America, Europe, Asia and Australia [3]. The pain that HZ causes results in considerable impact on four aspects of health related quality of life: physical health, psychological wellbeing, social functioning and activities of daily living [4-6]. Accordingly, pain relief is the primary goal of pharmacological management [7]. The economic burden of HZ is considerable, and the high cost of caring for elderly patients has also raised a particular concern amongst countries [8, 9]. An epidemiological study from Spain estimated the cost of hospitalization due to HZ was USD 10 million [10]. The cost of vaccination against VZV is relatively high, at approximately USD 197 per dose [11].

The development of lesions is preceded by non-specific clinical symptoms including tiredness, headache, low grade fever, and an itchy and tight sensation of the skin [1, 7]. Groups of small to medium tight walled vesicles containing clear fluid develop above a red macular base, with a unilateral and asymmetric distribution. Itching, tightening, and painful
sensation also occur with the cutaneous symptoms [9, 12]. Diagnosis is usually based on clinical presentation, although polymerase chain reaction (PCR) may be used to confirm the diagnosis [13].

Pharmaceutical treatments in treatment guidelines aim to relieve the acute pain, limit the course and the spread of lesions and prevent PHN and other complications [1, 7]. Whilst tolerable, side effects caused by both antiviral (nausea and headache) and pain control therapies (vomiting, constipation, drowsiness and dizziness) have been reported [14]. Research by Gater et al. [15] found that patients were most satisfied with side effects of treatment, but least satisfied by the perceived effectiveness of treatment. The authors highlight this as an unmet need for people with HZ.

Chinese medicine (CM) has been used to treat HZ for many years in China, and may provide an alternative treatment to conventional management. Various treatment approaches have been practiced in the management of HZ, including Chinese herbal medicine (CHM), acupuncture, moxibustion and other CM therapies. Over thousands of years, valuable information on diagnosis, symptoms, and treatment for HZ have been described and explained in depth in the classical literature. This continues to guide the contemporary guidelines and textbooks for CM practice. Currently, the classical literature evidence has not been evaluated systematically.

According to contemporary CM textbooks [16-18] and the current clinical practice guideline [12], CHM and acupuncture therapies are the two main CM treatments recommended for HZ. The clinical evidence for these CM treatments has been evaluated by several systematic reviews (SRs) [19-28], showing benefits for pain control and improving cutaneous outcomes.
However, the evidence is limited by the databases searched, study inclusion criteria, and review methods. To address this gap, SRs prepared with a comprehensive search of databases and more strict inclusion criteria are needed. This thesis directly addresses this knowledge gap.

1.2 Research questions

The aim of this thesis is to evaluate the classical and modern literature evidence for CM treatment of HZ. The research questions of this project are:

• What is the evidence of classical CM literature for HZ?
• What is the current clinical trial evidence of CHM and acupuncture for HZ?
• What is the current experimental evidence for commonly used CM treatments for HZ?
• Is CHM formula *Long dan xie gan tang* (LDXGT) effective for people with HZ? Will it be safe to use for HZ?

1.3 Scope of thesis

This thesis addresses the above questions focusing on CHM treatments (for example, oral and topical CHMs) and acupuncture-related approaches (for example, manual acupuncture, electro-acupuncture, moxibustion, acupressure, and ear acupuncture) only. These CM therapies are widely used for treating HZ in clinical CM practice and are recommended in contemporary CM textbooks and guidelines (see detailed inclusion criteria in Chapter 5) [12, 16-18]. Other CM therapies are not commonly used outside of China and may not be
permitted in some countries (for example, bloodletting, point injection and catgut embedding). These therapies are excluded from the research scope of this research.

1.4 Organisation of the thesis

Chapter One and Two are the introductory chapters of this thesis. **Chapter One** briefly introduces the background of this research. The objectives and research questions are proposed.

**Chapter Two** reviews the definition, epidemiology, aetiology, pathophysiology, diagnostic criteria, clinical manifestations, and current management for HZ in conventional medicine. This chapter highlights the unmet need to address the effectiveness of conventional medication for treating people with HZ. The latter section of this chapter reviews CM for HZ, including definition, aetiology, pathophysiology, syndrome differentiation and CM therapies drawn from contemporary CM textbooks and guidelines. A summary of current clinical evidence of CM for HZ from systematic reviews is provided. This chapter generally reviews the background knowledge of HZ from conventional medicine and CM viewpoints.

Chapter Three and Four demonstrate the research on classical CM literature for HZ in this thesis. These two chapters describe CM knowledge in the classical literature, which contributes to the “whole evidence” of CM for HZ.

**Chapter Three** details the methods for the data mining and cluster analysis of classical literature are provided; the methods of citation identification, data collection, coding and sorting of classical CM literature of HZ are presented in the former section of the chapter. Statistical analysis methods, including descriptive analysis and cluster analysis is presented in the latter section.
**Chapter Four** presents the results of data mining and cluster analysis of classical CM literature. The descriptive analysis section systematically evaluates CM interventions used for HZ in classical literature. Search terms, publication dynasty, symptoms in the ‘possible’ and ‘most likely’ to be HZ citations are analysed. The potential relationships of the HZ symptoms from most likely to be HZ citations are explored through cluster analysis. Hypothetical symptom structures of HZ and *huo dan* 火丹 skin conditions are proposed based on these findings research.

Chapter Five to Eight present the research in modern literature of CM for HZ in this thesis. Two systematic reviews on CHM and acupuncture therapies are demonstrated, and laboratory research on the most frequently used herbs for HZ are reviewed. These chapters provide the modern literature evidence to the “whole evidence” of CM for HZ.

**Chapter Five** introduces the methods used for systematic reviews of modern literature. The general methods for the systematic reviews used in this thesis is followed by the methods of Cochrane Handbook for Systematic Reviews and Interventions. Details of study inclusion criteria, identification of studies and data analysis methods are presented.

**Chapter Six** systematically reviews CHM for HZ. The first section provides a general overview of CHM treatments in the included randomised controlled trials (RCTs). The second section presents the findings of the systematic review for efficacy and safety of LDXGT formula.

**Chapter Seven** systematically reviews acupuncture therapies for HZ. Following the approach used in Chapter six, the first section provides a general overview of acupuncture therapies in the included studies. The second section presents the resulting evaluation of efficacy and safety of acupuncture plus moxibustion in the management of HZ. Benefits of the combination of acupuncture and moxibustion are provided as well as adverse events.

**Chapter Eight** provides an overview of the experimental evidence of the most frequently
used herbs for HZ identified in modern literature research. *In vivo* or *in vitro* studies that described mechanisms relevant to HZ were included.

Based on the findings from the classical and modern literature evidence CM for HZ from this thesis, a rigorous RCT has been proposed to inform future research. **Chapter Nine** details the protocol for a randomised, double-blinded, placebo controlled trial using LDXGT integrated with antiviral therapy in the management of HZ.

**Chapter Ten** summarises and discusses the findings from this research. A discussion of limitations of this research has also been discussed in this chapter.

**Appendix 1 to 9** present the tabulations of data presented in the above chapters.
Chapter 2. Herpes zoster

2.1 Conventional medicine

2.1.1 Definition

Herpes zoster (HZ), or shingles from the Latin word cingulum, which means belt, is a type of neurocutaneous disease caused by reactivation of the varicella zoster virus (VZV) [29]. Typical distinctive clinical symptoms include grouped blistering eruption on a red base of skin, burning or stabbing pain with a unilateral dermatome distribution [1].

The preliminary infection of varicella (commonly known as chickenpox) usually occurs during childhood, either as infection with the VZV, or through weakened VZV in the varicella vaccine [3]. The virus persists dormant in sensory ganglia neurons for up to several decades [1]. When the immune system of the virus carrier weakens for reasons such as the aging process, immune suppression or immunodeficiency resulting from Acquired Immunodeficiency Syndrome (AIDS) [2], the VZV re-activates, causing HZ.

A common chronic sequelae of HZ is postherpetic neuralgia (PHN), which may develop after the acute stage of visible lesions has subsided. There is no consensus on the definition of PHN, with definitions as chronic pain lasting ranging from one month to three months after the resolution of rash [1, 7, 9]. The generally accepted definition is three months. HZ and PHN both impact greatly on patients’ daily life.
2.1.2 Epidemiology

2.1.2.1 Prevalence

A global epidemiology review on HZ indicates that the median incidence is 4 to 4.5 per 1,000 person-years (PY), which is based on studies conducted in the United States, Canada, South America, Europe, Asia and Australia [3]. The statistical data indicated an increasing trend of the age-adjusted incidence among the global epidemiology research. As the studies demonstrated, the incidence rates of HZ were between 1 and 5 per 1,000 PY under the age of 18. The trends of the incidence rates increased gradually to a range of 4 to 6 per 1,000 PY by the age of 50. After 50 years, the incidence rates increased distinctively, peaking at around 10 to 16 per 1,000 PY by the age of 90 years [3].

Epidemiological studies show comparable annual incidence rate across countries. Data from the USA reported incidence rate of 4.47 per 1,000 PY in 2011 (95% confidence interval PY: 4.45, 4.5) with higher prevalence with older adults [30]. Incidence rates in Germany were slightly higher (5.3 to 5.5 per 1000 PY) from 2006 to 2009 [31], while data from Sweden reported lower incidence of 3.15 per 1,000 PY [32]. In China, the average annual incidence rate was 3.43 per 1,000 people aged more than 50 years old in the years 2010 to 2012, based on a retrospective cohort study [33]. Findings from MacIntyre et al. in Australia [34], Li et al. in China [33] and Hillebrand et al. in Germany [31] support those of Johnson in the US [30], showing age and gender differences, with older adults and females having a higher incidence rate [30, 31].

In Australia, research from 2007 reports that the HZ annual incidence rate is between 4.7 to 4.9 per 1,000 patients, which is consistent with that of the USA and Europe [35]. The incidence appears to be rising, with recent data showing incidence rate of 5.6 per 1,000 PY.
from October 2006 to March 2013 [34].

The incidence of PHN is estimated to be 10 to 20% in all HZ patients and increases with age [36]. A study based on German Pharmacoepidemiological Research Databases covering all geography regions of Germany indicated that the PHN proportions among HZ cases increased from 11.5% in 2005 to 14.9% in 2009 [31]. Eighty per cent of PHN cases occur in HZ patients older than 50 years old [3].

Vaccination against varicella has been shown to reduce the incidence of HZ in children [37]. Data from the National Health Insurance Research Database in Taiwan found the incidence rate of HZ in children with previous VZV vaccination was 93.3 per 100,000 PY, compared with 262.1 per 100,000 PY in those who had not received the vaccination [37].

2.1.2.2 Impact

2.1.2.2.1 Herpes zoster related mortality

Data from individual epidemiology studies and the World Health Organisation (WHO) shows HZ associated mortality varied among countries, with a median mortality of 0.039 per 100,000 [38]. HZ associated mortality significantly increases with age [39, 40]. In younger age groups, the mortality rate was higher in males [38]. Conversely, in older groups, mortality was greater in females [38].

2.1.2.2.2 Impact of herpes zoster on health-related quality of life

The pain with acute HZ and PHN is always the most significant concern of patients, and can remarkably reduce the quality of life of patients. HZ or PHN patients with higher levels of pain reported the greatest impact on health-related quality of life (HRQoL) [15]. Impacts can
be seen in four aspects of their life: physical health, psychological wellbeing, social functioning and activities of daily living (Table 2.1) [4-6].

Table 2.1 Impact of herpes zoster or postherpetic neuralgia on patient quality of life

<table>
<thead>
<tr>
<th>Physical Health</th>
<th>Psychological Wellbeing</th>
<th>Social Functioning</th>
<th>Activities of Daily Living</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia, tiredness, anorexia, loss of weight, reduced mobility and physical inactivity</td>
<td>Depression, anxiety, emotional distress, difficulty concentrating and fear</td>
<td>Withdrawal, isolation, reduced social interaction, increasing dependence and social role changes</td>
<td>Cooking and eating meals, wearing clothes, doing housework, traveling and shopping</td>
</tr>
</tbody>
</table>

A UK study on the impact of HZ on quality of life found people with HZ had significantly lower quality of life than age-matched norms on two quality of life measures (Medical Outcomes Study Short-Form 36 (SF 36), and the EuroQol-5 Dimensions (EQ-5D) [15]. The main domains where poorer quality of life was seen were “Vitality”, “Social-functioning”, “Role-emotional”, “Mental health” and the “Mental Component Summary”. A European review on the health burden of HZ indicated that HZ and PHN greatly impacts on patient’s mood, mental well-being, family and social relations [41]. In a single-cohort study in Taiwan, HZ was found to have significant impact on HRQoL assessed by EQ-5D, with poorer quality of life up to 60 days after rash onset [42].

2.1.2.2.3 Economic burden

The economic burden of HZ is considerable, and the high cost of caring for elderly patients has also raised a particular concern [8, 9]. An epidemiological study from Spain estimated the cost of hospitalization due to HZ was USD 10 million [10]. The average annual hospital costs in the management for HZ was estimated to be GBP 13.0 million in England in the year 2013 to 2014 [43]. The cost for management of PHN was higher than HZ [41, 44]. Particularly, the
direct economic burden of HZ for older patients is higher in terms of visiting the general practitioner (GP) or specialist, medication costs and hospitalisations, while the indirect burden is higher for younger patients due to absenteeism [41]. An increase in costs for the management for HZ and PHN was observed from 1997 to 2014 in Canada, and the primary reason might be the increasing use of anticonvulsants (for example, gabapentin) as analgesic therapy [45]. Vaccination against VZV is considered relatively high, with cost of USD 197 per dose [11].

In Australia, the pain from HZ and PHN also impacts the community significantly and prolongedly. Primary care data from the General Practice Resource Network (GPRN) and Bettering the Evaluation and Care of Health (BEACH) databases indicate that more than 10% of the HZ patients have pain lasting longer than 1 month, 92% of whom require continuous use of prescription treatment [46]. An increasing trend of antiviral prescriptions specific for HZ was observed, with an increase of 4.2% per year between July 2002 and 2012 [34]. In the population aged 50 years or older, the total annual cost to the health care system was estimated at approximately AUD 33 million in the management of HZ and PHN [47].

2.1.3 Aetiology and pathophysiology

The VZV can cause two distinctive cutaneous diseases, chickenpox, and herpes zoster. The connection between these two diseases has been known for many years based on two main findings: that VZV is transported up the peripheral nerve and remains dormant in sensory ganglion neurons for decades after acute infection of the virus, and sufficient VZV-specific cell-mediated immunity (CMI) helps to maintain the dormancy. When the immune system of the virus carrier weakens through progressing age, or immune suppression or deficiency, the virus reactivates, transports down the peripheral nerve and induces HZ [48].
2.1.3.1 Infection of varicella zoster virus

People who develop HZ are usually infected with VZV in their early age. The virus is highly infectious, and is contracted via the respiratory tract. The VZV spreads from the pharyngeal lymphoid tissue to the circulating T lymphocytes [48]. Two VZV transmission mechanisms have been found in current research: within the superficial epidermis (cell-free), and outside the suprabasal epidermis (cell-to-cell contact) [48].

After an incubation of one to three weeks period, the virus reaches the skin and causes the typical cutaneous symptoms of vesicular rash, called varicella (chickenpox). At this point, a lifelong immunity against VZV is established, and the majority of people will not have a second episode of varicella during their lifetime [49]. Three main components are involved in the immune response: innate immunity, humoral immunity and CMI [48]. CMI is considered as the essential component for the cell-associated characteristic of VZV, and its T-cell-mediated immunity response feature [50].

2.1.3.2 Latency

Two hypotheses have been proposed as to how the virus gets access to the dorsal and cranial root ganglia (DRG and CRG, respectively) and maintains latency. First, cell-free VZV which originate in the epidermis travel via the axons of sensory neurons to the cell bodies; second, the VZV is carried by T-cells to the DRG/CRG and infects the neuronal cell bodies [51-53]. Latency is established and maintained by VZV-specified CMI, unless T-cell immunity weakens [48].
2.1.3.3 Reactivation

After the reactivation of VZV, the virus begins replication and transports to infect epithelial cells via sensory axons of the sensory neurons, usually without inducing viraemia. The infection usually causes inflammation and necrosis of all the cells within the affected ganglion, resulting in a dermatome rash, characteristic vesicles and pain symptoms by an individual sensory nerve. Thoracic, trigeminal, and cervical sensory nerves are the most commonly involved in HZ during clinical observation [48].

2.1.3.3.1 Risk factors

Various risk factors have been shown to have a potential impact on weakening CMI, decreasing latency of VZV and causing HZ. Worldwide epidemiology studies indicate that older age and female gender are risk factors for developing HZ [30, 31, 34]. Other risk factors are as below.

Cell-mediated immunity dysfunction immunosuppressed individuals

Reduced CMI, HIV-positive patients, and transplant recipients can have up to ten times the risk of getting HZ compared with the general population [48].

Diabetes

People with diabetes mellitus are more likely to get infectious diseases due to the impaired cell-mediated immunity [54]. A population-based case control study showed that individuals with diabetes had a higher risk of HZ [55].

Genetic susceptibility

Individual studies suggested that the risk of HZ might be related to some genetic factors: haplotype of human histocompatibility leukocyte antigen (HLA) [56], polymorphism of the interleukin 10 (IL-10) gene [57], and family history of HZ [58].
Mechanical trauma

Mechanical trauma was found to be a risk of inducing HZ in case reports and case series studies. Stimulation by trauma of the sensory nerve may activate the VZV latent in the ganglion and cause HZ [59].

Recent psychological stress

A case-control study indicated that recent stressful events were found significantly more commonly in HZ patients [60]. In contrast, a recent study indicated that there was no evidence supporting that psychological stress triggers HZ based on the data from 2002 to 2011 in the USA [61]. Currently, the link between psychological stress and HZ is unclear.

Ethnicity

Racial differences in the incidence of HZ were found in epidemiology studies. The survey was conducted in a community-dwelling sample of persons > 64 years old in North Carolina, USA over three time periods: 1986 to 1987, 1989 to 1990, and 1992 to 1994. Results suggested that Caucasians had a significantly higher risk of developing HZ than African Americans. [62, 63].

2.1.3.4 Pathophysiology of herpes zoster in postherpetic neuralgia stage

After the resolution of cutaneous symptoms in acute stage HZ, the paroxysmal or constant pain may persist for more than 3 months. This complication is named as PHN [9]. PHN is a heterogeneous disorder that involves both peripheral and central processes [64]. For the peripheral processes, an increased expression of messenger ribonucleic acid (mRNA) for voltage-gated sodium channels were shown in primary afferent neurons after nerve injury, which may contribute to an increased responsiveness of primary nociceptors [64]. The central process involves secondary changes in the spinal cord dorsal horn atrophy, affected sensory
neuronal cell bodies and axon degeneration, dorsal root ganglion scarring, and epidermal innervation loss [64, 65]. Another study showed the unilateral PHN might be associated with bilateral sensory neuron damage [66].

Increasing age [36], high severity of pain and lesion in the acute stage [67], facial and sacral locations of HZ [68], female gender, psychological distress [69] and viremia all have a close association with the risk of PHN [70].

2.1.4 Diagnosis

*Herpes zoster characteristic clinical symptoms*

According to current guidelines [7, 14, 71], The diagnosis of HZ is usually confirmed by its characteristic clinical symptoms: grouped vesicles rash with asymmetrical dermatomal distribution, most commonly located in thoracic dermatome, limited by midline of body, prodromal symptoms and HZ-associated segmental pain. Local clinical manifestation may include pruritus, paraesthesia, dysesthesia or anaesthesia [71]. The most common anatomic location is the thoracic dermatome [7, 71]. The diagnosis based on clinical symptoms of classical unilateral HZ that occurred on the thoracic or lumbar dermatomes is strongly recommended by the most recent European Academy of Dermatology and Venereology (EADV) guideline [71].

*Laboratory diagnostic techniques*

Further evidence of infection of VZV where the symptoms are not obvious can be provided by laboratory examination techniques. For suspected infection of newborn infants, pregnant women, immune-deficient patients and central nervous system (CNS) involvement, laboratory diagnosis must be used to confirm the infection [7, 14, 71]. Currently, the VZV
polymerase chain reaction (PCR), specific VZV antigens and antibodies detection, and viral culture through cell cultures are recommended by guidelines for the above special circumstances [7, 71].

2.1.5 Clinical characteristics

In the acute stage, the VZV spreads via sensory nerves to the skin and causes prodromal pain with papulovesicular rash. Small to moderate size papules with tense wall and clear fluid distribute unilaterally in dermatomes as a result of the inflammatory response and necrosis of the infected nerve [7, 14]. HZ can occur in any part of the skin, and the thoracic region is the most frequently infected area [72]. The time course of HZ is typically divided into 3 phases: (1) prodromal phase, (2) vesicular and (3) encrustation phase, and PHN phase.

2.1.5.1 Prodromal phase

The prodromal phase lasts 3 to 5 days. Clinical symptoms are non-specific, and may include tiredness, low grade fever, headache, photophobia, burning pain and unusual sensation such as itchy or tight feeling of the skin [7, 9, 12].

2.1.5.2 Vesicular and encrustation phase

In the vesicular phase, groups of papules appear which are small to moderate in size. Tight wall vesicles with clear fluid develop above a red macular base. The rash will have a unilateral and asymmetric distribution, with some itching, tingling and painful abnormal sensation of the skin. It usually takes 10 days from the appearance to disappearance of the lesion. However, for some immunocompromised patients, the duration of this period may be up to several months [9, 12].
2.1.5.3 Postherpetic neuralgia

PHN is defined as an intractable, chronic, neuropathic pain continuing after the recovery from acute infection [9]. No consensus on the time course of PHN has yet been reached among various guidelines and reviews, with definitions of chronic pain ranging from one month to three months after the resolution of acute rash [1, 7, 9]. The most recognised definition is three months.

2.1.5.3 Herpes zoster pain

Up to 90% of HZ patients report that pain is commonly the predominant symptom through either acute or PHN [73]. Due to the inflammatory response and necrosis of the VZV infected sensory nerve in the acute phase of HZ, most patients suffer from moderate to the severe dermatomal pain of the affected area [74]. Patients ranked the acute HZ pain as more severe than labour or post-surgical pain [75]. The symptoms of allodynia, numbness and tingling sensation had an adverse effect on quality of life in 70% of people with PHN, with these symptoms described as ‘debilitating’ and ‘depressing’ [76].

2.1.5.4 Other types of herpes zoster

Reactivation of VZV can occur in any location. When affecting certain nerves, the consequences can be more severe and are diagnosed as sub-types of HZ. In this thesis, the sub-types of HZ are all excluded for analysis.

2.1.5.4.1 Zoster ocular diseases

The second most commonly affected area is the ophthalmic division of the trigeminal nerve,
which may result in HZ ophthalmicus (HZO) [14]. *Hutchinson’s sign*, which means the skin lesion involves the tip, side or root of the nose, is a strong predictor of the ocular and corneal inflammation in HZO [77]. A series of ocular diseases and complications are related to the involvement of ocular infection due to the inflammatory and immune response to the VZV: episcleritis, scleritis, iridocyclitis, acute retinal necrosis, choroiditis, glaucoma, and keratitis [78]. The basic management of HZO is the same as HZ. For viral epithelial keratitis, local virostatic agents, acyclovir eye ointment for example, must be prescribed to patients [7]. Therapies are emerging which re-establish corneal aesthesia destroyed by the inflammation, including substance P and thymosin beta 4 eye drops, and the use of artificial cornea [78].

2.1.5.4.2 Herpes zoster oticus

Another commonly affected area is the ganglial cells of the VII and VIII cranial nerve, which usually results in facial paralysis (Ramsay Hunt Syndrome) [14]. The cranial nerve lesion is quite often associated with an acute peripheral facial nerve paresis, leading to a cluster of neurological damage disorders: facial muscle paralysis, hypofunction of hearing and balance function, disturbances of taste, lacrimal and nasal secretion [79]. First line recommendation for HZ oticus is initiating combined antiviral-corticosteroid therapy as early as possible, with adequate analgesic therapy [79].

2.1.5.4.3 Zoster encephalitis and meningitis

In some cases, the virus will travel through liquor and cause severe complications such as zoster encephalitis and meningitis [80, 81]. Immunocompromised and CNS involved patients have a higher risk of getting encephalitis and meningitis [14]. Acute or subacute delirium are the most common clinical symptoms, with other clinical observation of headache, fever, ataxia, meningismus, and seizures [82]. High-dose intravenous acyclovir therapy is
recommended by guidelines [7, 14].

2.1.5.4.4 Zoster sine herpete

In some case reports, HZ may also occur in the absence of skin lesions (zoster sine herpete) [83, 84]. Laboratory techniques of PCR or specific VZV antibodies detection can be used to confirm diagnosis of the infection [7].

2.1.6 Current management

2.1.6.1 Prevention

From 2006, a vaccine against VZV has been available to reduce the incidence of HZ and PHN. In a randomised placebo-controlled trial, zoster vaccine significantly reduced the burden of illness of HZ by 61.1%, and reduced the incidence rate of HZ and PHN by 51.3% and 66.5% respectively [85].

2.1.6.2 Conventional therapies

The aim for HZ management is to relieve the acute pain, to limit the spread and time course of lesions, and to prevent or relieve PHN and other complications [1, 7]. Current pharmaceutical management includes antivirals, corticosteroids, analgesics (nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and anticonvulsants) therapies. They are all recommended by EADV guideline 2016 [86], German Dermatology Society (DDG) guideline 2003 [7], European review 2005 [9], and American guideline 2007 [14]. Table 2.2 (Therapies recommended in clinical guidelines) highlights the therapies used in both acute HZ and PHN as recommended by clinical management guidelines.
## Table 2.2 Therapies recommended in clinical guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Antiviral Therapies</th>
<th>CS</th>
<th>Analgesics</th>
<th>Anti-convulsants</th>
<th>Patient Education</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dworkin et al. 2007 [14]</td>
<td>HZ</td>
<td>HZ</td>
<td>HZ/PHN</td>
<td>HZ</td>
<td>HZ</td>
<td>Neural, blockade, TENS</td>
</tr>
<tr>
<td>Werner et al. 2016 [86]</td>
<td>HZ</td>
<td>HZ</td>
<td>HZ</td>
<td>HZ</td>
<td>NS</td>
<td>Local therapies: antiseptics and zinc oxide</td>
</tr>
</tbody>
</table>

CS: corticosteroid; HZ: acute stage herpes zoster; PHN: postherpetic neuralgia; TENS: transcutaneous electrical nerve stimulation; NS: not specified

For patients presenting with acute HZ, risk factors for PHN need to be assessed. If the patient has any of the following risk factors, antiviral therapy should be prescribed for 7 days:

- Severe acute pain
- Age >50 years
- Severe rash
- Significant prodromal symptoms.

If no risk factors are present, analgesics should be prescribed (see Figure 2. Stepped care in the management of neuralgia of HZ). The American guideline also emphasizes patient education as a routine treatment for people with HZ, which can be beneficial to patients’ well-being [14]. Review at 3-4 weeks is recommended [9] to assess for ongoing significant pain or allodynia. If pain persists, medications such as those suggested in steps 2 and 3 of Figure 2.1 may be considered [7, 86].
**Step 1:** Non-steroidal analgesics (for example paracetamol 1.5-5g daily).

**Step 2:** additional low-potency opioid analgesics (for example tramadol 200-400 mg per day, codeine 120 mg per day), if necessary, combined preparations.

**Step 3:** in addition to a ‘peripheral’ analgesic, administration of a high-potency central opioid (for example buprenorphine 1.5-1.6 mg per day; oral morphine 30-360 mg per day) is indicated. This refers to patients who fail to respond the more measured treatment approaches.

*Figure 2.1 Stepped care in the management of neuralgia of herpes zoster*

**2.1.6.2.1 Antiviral therapy**

HZ is a self-limiting neurocutaneous disease. It usually heals without any complications when it occurs on the trunk or extremities of young individuals without risk factors, even if no specific antiviral therapy is prescribed to them [7]. When HZ develops beyond the age of 50 years, and for people with other risk factors, antivirals are recommended as first-line pharmacotherapy [7, 9] (Table 2.3). The use of antiviral treatment has been shown to shorten the healing process, limit the duration of viral replication and further damage to the infected neuron, and reduce the incidence, duration, and severity of PHN [7, 9]. Topical therapy is not usually recommended, as there is limited evidence [14].
Table 2.3 Indications for antiviral therapy in the management of herpes zoster

<table>
<thead>
<tr>
<th>Urgent Indications</th>
<th>Non-urgent Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoster of any localization in patients beyond the age of 50;</td>
<td>Zoster on the trunk/on the extremities in patients younger than 50 years old</td>
</tr>
<tr>
<td>Zoster in the head/neck area of patients at any age;</td>
<td></td>
</tr>
<tr>
<td>Severe zoster on the trunk/extremities;</td>
<td></td>
</tr>
<tr>
<td>Zoster in immunodeficient patients;</td>
<td></td>
</tr>
<tr>
<td>Zoster in patients with severe atopic dermatitis and severe eczemas</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Gross et al. [43]

Available clinical practice guidelines and review for the management of acute stage HZ recommend antiviral therapy, including acyclovir, valacyclovir (a pro-drug of acyclovir), famciclovir, and brivudin [7, 9, 14]. Brivudin is not approved by Food and Drug Administration in the USA [7, 14], although the reasons for this are unclear. Commencement of therapy is needed as soon as the diagnosis of HZ is made, as the damage to sensory neurons is likely to have been occurring for several days before presentation to a General Practitioner or emergency department [7, 9]. Clinical trials have initiated antiviral therapy within 72 hours of onset of the rash, although Dworkin et al. [14] describe this as an “arbitrary inclusion criterion that does not necessarily reflect the cessation of viral replication”. In practice, this is unlikely to occur as patients may not present until after this time. The effect of antiviral therapy after 72 hours has not been evaluated systematically, therefore the effect of later initiation of antiviral therapy is unclear [14]. The dosage of these antiviral agents is described in German Dermatology Society guideline 2003 [7], European review 2005 [9], American guideline 2007 [14] (see Table 2.4. Antiviral therapy for herpes zoster for dosage by guidelines and review).
Table 2.4 Antiviral therapy for herpes zoster

<table>
<thead>
<tr>
<th>Medication</th>
<th>Prescription Type</th>
<th>Dosage</th>
<th>Duration of Treatment Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valacyclovir</td>
<td>Oral</td>
<td>1000 mg $^{1,2,3}$</td>
<td>3 times daily for 7 days</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Oral</td>
<td>800 mg $^{1,2,3}$</td>
<td>5 times daily for 7 days</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Intravenous</td>
<td>5-7.5 mg $^{2}$</td>
<td>3 times daily for 7 days</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Intravenous (immunodeficient patients)</td>
<td>8-10 mg $^{2}$</td>
<td>3 times daily for 7 to 10 days</td>
</tr>
<tr>
<td>Famiclovir</td>
<td>Oral</td>
<td>250 mg (UK) $^{1,2,3}$</td>
<td>3 times daily for 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg (North America) $^{1,3}$</td>
<td></td>
</tr>
<tr>
<td>Brivudin</td>
<td>Oral</td>
<td>125 mg $^{1,2,3}$</td>
<td>1 times daily for 7 days</td>
</tr>
</tbody>
</table>

$^{1}$ Dworkin et al. 2007 [14]; $^{2}$ Gross et al. 2003 [7]; $^{3}$ Volpi et al. 2005 [9]

Valacyclovir and famciclovir have been the most commonly used oral antiviral management of uncomplicated acute stage herpes zoster [87]. Both of these drugs have better bioavailability than acyclovir with fewer administration times for patients. Benefits with valacyclovir are also seen in shortening the time to resolution of pain compared to acyclovir [88]. Brivudin has the highest antiviral potency among these antiviral substances, requiring only one dose daily. However, this drug is not recommended for children, pregnant or lactating women, immunosuppressed patients and patients taking 5-fluoropyrimidines [7].

2.1.6.2.2 Corticosteroids

Combining corticosteroids with antiviral therapy is recommended by the DDG [7]. The typical dosage for this treatment is prednisone, 60 mg daily for seven days, then reduce the dosage for the next two weeks [1]. These drugs should be prescribed with caution due to known adverse effects.
2.1.6.2.3 Analgesics therapy for neuralgia

A stepped-care approach has been recommended by the DDG to manage neuralgia of HZ and PHN [7]. First line therapy are NSAIDs (Figure 2). Although there has been no systematic evaluation of the effects of NSAIDs on acute pain of HZ, it has been hypothesised that using analgesics in combination with antiviral therapy may reduce the risk of PHN [14] due to severe acute pain being a risk factor for PHN. Opioid analgesics (either peripheral or high potency central) may be added or substituted if pain relief is insufficient.

Other analgesics options are anticonvulsants and tricyclic antidepressants (TCAs) when moderate to severe pain has not been resolved rapidly by opioid treatment [7]. Although there is little evidence for use of TCAs in acute stage HZ, they have been shown to be effective in providing moderate to excellent pain relief of PHN, and may be beneficial for acute pain [14]. In addition to this, TCAs can benefit through improving patients’ mood and sleep [87]. The most widely used TCA for PHN is amitriptyline [14, 87]. A placebo-controlled trial suggested that the use of amitriptyline with a dosage of 25 mg once daily for three months reduced the incidence of PHN by more than 50% six months after the acute stage [89].

Anticonvulsants can be selected to reduce lancing pain in severe neuralgia cases [7]. Gabapentin or pregabalin are the two recommended by guidelines, which inhibit the alpha-2 delta (α2-δ) subunit to reduce relevant neurotransmitter release [90]. Randomised controlled trials showed both gabapentin and pregabalin had demonstrated their efficacy in the pain management of PHN [91, 92]. There is no standard dosage recommendation for these anticonvulsant medications. From individual clinical trials, gabapentin can be initiated from 900 mg/day to 1800 mg/day (7 to 10 days) based on the condition of patients [93], while pregabalin is usually prescribed at 150 to 600 mg/ day in flexible-dose studies with an
acceptable safety profile [87, 94]. Other treatments such as local anaesthetic neural blockade, transcutaneous electric nerve stimulation, and neurosurgery can be applied to the patients when necessary [7].

2.1.6.2.4 Safety profile and limitations of pharmaceutical therapies

Although the management for HZ and PHN has proved to be beneficial, side effects are often associated with antiviral and analgesic therapy, and must be considered when determining treatment (Table 2.5). Nausea and headache are the two most common side effects of antiviral therapy [14]. Patients may suffer from vomiting, constipation, drowsiness and dizziness when taking analgesics [14]. With antidepressant use, drowsiness, dry mouth, blurred vision, weight gain and urinary retention may occur. More side effects such as gastrointestinal distress, oedema, and weight gain would appear when anticonvulsants and corticosteroids are used [14].

Table 2.5 Adverse events of pharmaceutical therapies

<table>
<thead>
<tr>
<th>Medication</th>
<th>Common Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiviral therapy (including valacyclovir, acyclovir, famciclovir, and brivudin)</td>
<td>Nausea, headache</td>
</tr>
<tr>
<td>Oxycodone (opioid analgesic)</td>
<td>Nausea/vomiting, constipation, sedation, dizziness</td>
</tr>
<tr>
<td>Tramadol (opioid-like analgesics)</td>
<td>Nausea/vomiting, constipation, sedation, dizziness, seizures, postural hypotension</td>
</tr>
<tr>
<td>Prednisone (oral corticosteroid)</td>
<td>Gastrointestinal distress, nausea, changes in mood, oedema</td>
</tr>
<tr>
<td>Anticonvulsants (gabapentin and pregabalin)</td>
<td>Sedation, dizziness, peripheral oedema</td>
</tr>
<tr>
<td>Tricyclic antidepressants (especially nortriptyline)</td>
<td>Sedation, dry mouth, blurred vision, weight gain, urinary retention</td>
</tr>
</tbody>
</table>

In addition, Gater et al. [15] evaluated patient satisfaction with antiviral and analgesic treatment for HZ using the Treatment Satisfaction Questionnaire for Medication (TSQM,
version II [95]). Patient satisfaction was highest on the ‘side effects’ domain and lowest on the ‘effectiveness’ domain of the TSQM. The authors highlight this as an unmet need for people with HZ.

2.2 Chinese medicine for herpes zoster

2.2.1 Introduction of Chinese medicine

Chinese medicine (CM) has been practised for thousands of years in China, with its earliest medical treatise *Huang Di Nei Jing* (The Yellow Emperor’s Classic of Internal Medicine) dating back to Warring States Period and from the Spring and Autumn period (770-221 BC) [96]. Various treatment methods have been developed by CM practitioners to prevent and manage diseases, including acupuncture, Chinese herbal medicine (CHM), and other CM therapies (Chinese therapeutic massage, moxibustion, cupping, *guasha*, *qigong*, and *tai chi*). The scope of this thesis is limited to CHM and acupuncture therapies.

The unique concepts of *qi*, *yin* and *yang*, and the five elements taken from the ancient Chinese naturalistic philosophy are the foundations of the CM theory [97]. The basic principles of CM include “concept of holism” (that is, recognising the human body as an organic whole and human beings interrelated with nature), and “treatment according to syndrome differentiation” (that is, individualised treatment based on grouped, related symptoms which facilitate diagnosis) [98]. With its unique theory and approach to diagnosis and treatment, CM contributes to the conventional management for diseases as an important complementary medicine with its encouraging clinical effect.

In a national survey of Australia in 2005, 68.9% of the 1,067 interviewees used at least one kind of complementary and alternative medicine (CAM) in the previous year [99]. These
included CM therapies such as acupuncture (9.2%), CHM (7.0%), qigong, martial art and tai chi (6.0% in total), Chinese therapeutic massage (5.1%) and CM dietary therapy (2.3%) [99].

### 2.2.2 Definition of herpes zoster in Chinese medicine

CM has been used for treating HZ for a long time, with one of the earliest recognised citations of HZ from the *Zu Bing Yuan Hou Lun* 诸病源候论 (610 AD) [100]. In this classical CM literature, HZ was described as “a skin disease encircles the waist” (Original text: 甑带疮者，绕腰生) [100]. The location of the rash described in this citation is consistent with that in conventional medicine and contemporary CM textbooks [7, 16, 17].

In contemporary CM, HZ is commonly called *she chuan chuang* 蛇串疮, *chan yao* 缠腰, or *huo dan* 火丹. In Chinese language, the Chinese characters describe the symptoms as lesions grouped in a snake-like belt together on unilateral side of the body, with burning pain [16]. Consistent with conventional medicine, the diagnosis principles of HZ in CM textbooks are based on its characteristic symptoms [16, 17].

### 2.2.3 Aetiology and pathophysiology in Chinese medicine

According to CM theory, HZ can be caused by both internal and external pathogens [16]. Stagnated heat generated by emotional injuries and retention of damp by improper diet are the two main internal pathogenic factors that may lodge in the skin and cause HZ. The external toxin pathogens can also directly attack the skin and induce cutaneous inflammation [16-18]. After the resolution of the acute infection, elderly people with HZ may suffer from long-lasting chronic pain (similar to the definition of PHN, consistent with clinical medicine) by qi stagnation and Blood stasis generated by the aging process [16-18]. Figure 2.2
summarises the possible aetiologies and pathogeneses of HZ according to CM.

Figure 2.2 Chinese medicine aetiology and pathogenesis of herpes zoster [16]

2.2.4 Syndrome differentiations

Based on current CM textbooks, there are four main syndromes in acute stage HZ: Stagnant heat in the Liver meridian, Spleen deficiency with damp, damp and fire toxin, and qi stagnation and Blood stasis. After the resolution of acute lesions, qi stagnation and Blood stasis is also the common syndrome that people have for PHN [16-18].

Stagnant heat in the Liver meridian is a syndrome mainly dominated by heat pathogens. The symptoms in the syndrome of damp and fire toxin are similar to Stagnant heat in the Liver meridian. Spleen deficiency with damp retention is another syndrome of HZ, which is mainly dominated by damp pathogens. Syndrome of qi stagnation and Blood stasis can arise from
residual toxin obstructing meridians, or may result from accumulation of damp. A summary of key symptoms for the syndrome differentiations is shown in Table 2.6.

Table 2.6 Syndrome differentiations of herpes zoster

<table>
<thead>
<tr>
<th>Syndrome Differentiations</th>
<th>Lesion</th>
<th>Accompanying Symptoms</th>
<th>Tongue</th>
<th>Pulse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stagnant heat in the Liver meridian</td>
<td>Red lesion, tense blister walls, burning heat, pricking pain</td>
<td>Irritability, dry throat and bitter taste in mouth, dry stools with yellow urine</td>
<td>Red tongue with thin or thick yellow coat</td>
<td>Rapid, rolling and string-like pulse</td>
</tr>
<tr>
<td>Damp and fire toxin</td>
<td>Numerous big lesions, red base</td>
<td>Burning heat and severe pain, headache, dry and bitter taste in mouth, yellow urine, and dry stool</td>
<td>Red tongue with dry and yellow coat</td>
<td>Rapid and rolling pulse</td>
</tr>
<tr>
<td>Spleen deficiency with damp retention</td>
<td>Light colour lesion, loose vesicular walls</td>
<td>Abdominal distension with poor appetite, loose stool</td>
<td>Pale tongue with white or greasy tongue coat</td>
<td>Deep or rolling pulse</td>
</tr>
<tr>
<td>Qi stagnation and Blood stasis</td>
<td>Long lasting pain after disappearance of the lesion</td>
<td>None specified</td>
<td>Dark tongue with white fur</td>
<td>String-like and thready pulse</td>
</tr>
</tbody>
</table>

2.2.5 Chinese medicine treatment

2.2.5.1 Oral Chinese herbal medicine

Guided by the basic principle “treatment according to syndrome differentiation”, different Chinese herbal formulae are recommended by CM textbooks based on specific syndromes [16-18]. There is no clinical practice guideline on CHM for HZ. The CHM formulae recommended by CM dermatology textbooks for use in HZ syndromes are outlined in Table 2.7. As the herbal ingredients of the formulae are not specified in the CM dermatology textbooks [16-18], the ingredients have been sources from a CM formulae textbook [101].
### Table 2.7 Oral Chinese medicine formulae recommended in Chinese medicine textbooks [16-18]

<table>
<thead>
<tr>
<th>Syndrome Differentiations</th>
<th>Formulae</th>
<th>Function of the Formulae</th>
<th>Herbal Ingredients [101]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stagnant heat in the Liver meridian</td>
<td>Long dan xie gan tang</td>
<td>Clear heat of Liver and Bladder, and resolve dampness</td>
<td>Long dan cao, huang qin, zhi zi, ze xie, mu tong, che qian zi, dang gui, chai hu, gan cao, sheng di, gan cao</td>
</tr>
<tr>
<td>Damp and fire toxin</td>
<td>Qing gan xie huo jie du tang</td>
<td>Clear heat of Liver</td>
<td>Not specified</td>
</tr>
<tr>
<td>Spleen deficiency with damp retention</td>
<td>Chu shi wei ling tang</td>
<td>Clear heat and resolve dampness</td>
<td>Cang zhu, hou po, chen pi, zuo ling, ze xie, fu ling, hua shi, fang feng, zhi zi, mu tong, rou gui, gan cao</td>
</tr>
<tr>
<td>Qi stagnation and Blood stasis</td>
<td>Chai hu shu gan san with Tao hong si wu tang</td>
<td>Regulate qi and activate blood</td>
<td>Chai hu, shu di, dang gui, bai shao, chuan xiong, tao ren, hong hua, shen di</td>
</tr>
</tbody>
</table>

#### 2.2.5.2 Topical Chinese herbal medicine

Different CHM formulae and single herbs can be applied to the acute lesions [17]. CHM bath, moist compress therapy, and topical application are the common therapies. Herbs used for topical application have the actions of clearing heat (eg. ye ju hua 野菊花, da huang 大黄), activating blood (eg. di yu 地榆, zi cao 紫草, yu jin 郁金), resolving dampness (eg. ku shen 苦参), and regulating qi (eg. ru xiang 乳香). The main function of the herbs are consistent with the treatment principles for resolving the four main syndromes of HZ. A summary of the topical CHM therapies is shown as below:
Table 2.8 Topical Chinese medicine herbs/formulae recommended in Chinese medicine textbooks [17]

<table>
<thead>
<tr>
<th>Topical Chinese Herbal Medicine Therapies</th>
<th>Before Resolution of Lesions</th>
<th>After Formation of Scars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese herbal medicine bath</td>
<td>Zi cao 紫草, ye ju hua 野菊花, da huang 大黄, di yu 地榆, ku shen 苦参</td>
<td>Yu jin 郁金, ji xue teng 鸡血藤, chi shao 赤芍, ru xiang 乳香, mo yao 没药, wei ling xian 威灵仙</td>
</tr>
<tr>
<td>Moisten compress therapy</td>
<td>Da huang 大黄, ku fan 枯矾, ku shen 苦参, zi cao 紫草, di yu 地榆, wu bei zi 五倍子</td>
<td>Not specified</td>
</tr>
<tr>
<td>Topical application</td>
<td>San huang xi ji 三黄洗剂, qin dai you 青黛油, hong tiao zi cao you 红条紫草油</td>
<td>Jing su lan ding 金素兰酊</td>
</tr>
</tbody>
</table>

2.2.5.3 Acupuncture therapies and other Chinese medicine therapies

For acupuncture and other CM therapies such as cupping, pricking to bleed and fire needle therapy, a recent acupuncture practice guideline recommends different treatment or combinations according to the course of progression of HZ (Table 2.9) [12]. Although treatment for HZ varies according to the different stage, the acupuncture point selections have similarity: *ashi* points 阿是穴 (translated as “where is the pain where is the acupuncture point for treatment”) are applying the treatment directly to the painful and lesion area; *Huatuojiaji* points 华佗夹脊穴 refer to the acupuncture points distributed parallel to the spinal column. The main function of stimulating *ashi* points 阿是穴 and *Huatuojiaji* points 华佗夹脊穴 is to regulate *qi* and have a local analgesic effect, which can be beneficial in managing the symptoms of HZ.

Some acupuncture therapies including pricking to bleed and fire needling are recommended in the Chinese acupuncture practice guideline for HZ. However, these acupuncture practices
are seldom used outside of China, and will not be included in this thesis.

Acupuncture treatment described in CM textbooks is more detailed, taking a different approach to the acupuncture practice guideline. CM textbooks recommend a group of acupuncture points for manual acupuncture selection, without reference to CM syndromes or HZ time course [16-18]. As for the main function of the acupuncture points, TE6 Zhigou 支沟, PC6 Neiguan 内关, GB34 Yanglingquan 阳陵泉 are commonly used for alleviating pain, LI4 Hegu 合谷 and LI11 Quchi 曲池 are for clearing heat, while ST36 Zusanli 足三里 and SP6 Sanyinjiao 三阴交 are both for strengthening the Spleen and revolving dampness. Moxibustion is another acupuncture therapy recommended for HZ, with ashi points 阿是穴 being recommended [17].
Table 2.9 Treatments recommendations by clinical practice guideline of acupuncture for herpes zoster [12]

<table>
<thead>
<tr>
<th>Phase</th>
<th>Treatments</th>
<th>Point Selection</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodomal phase</td>
<td>Manual acupuncture, pricking to bleed with plum blossom tapping cupping</td>
<td><em>Ashi</em> points 阿是穴 (translated as “where is the pain where is the acupuncture point for treatment”)</td>
<td>Once a day, 3-5 treatments</td>
</tr>
<tr>
<td>Vesicular phase</td>
<td>Pricking to bleed and cupping</td>
<td>Vesicles on the trunk: <em>Huatuojiaji</em> points 华佗夹脊穴 (refers to the acupuncture points distributed parallel to the spinal column); vesicles on head and facial region: GV14 <em>Dazhui</em> 大椎</td>
<td>Once a day, 6-10 treatments per course</td>
</tr>
<tr>
<td></td>
<td>Fire needling</td>
<td><em>Ashi</em> points 阿是穴 between vesicles</td>
<td>Once a day, 10 treatments per course</td>
</tr>
<tr>
<td></td>
<td>Moxibustion</td>
<td><em>Ashi</em> points 阿是穴 on vesicles</td>
<td>Once a day, 10 treatments per course</td>
</tr>
<tr>
<td></td>
<td>Surround acupuncture combined with electro-acupuncture</td>
<td><em>Ashi</em> points 阿是穴 of vesicles</td>
<td>Once a day, 10 treatments per course</td>
</tr>
<tr>
<td>Encrustation phase</td>
<td>Same as vesicular phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postherpetic neuralgia phase</td>
<td>Fire needling</td>
<td><em>Ashi</em> points 阿是穴 and <em>Huatuojiaji</em> points 华佗夹脊穴 on the affected side</td>
<td>Once a day, 2 weeks as one course</td>
</tr>
<tr>
<td></td>
<td>Surround acupuncture</td>
<td><em>Ashi</em> points 阿是穴</td>
<td>Once a day, 10 treatments per course, 2 courses in succession</td>
</tr>
<tr>
<td></td>
<td>Electro-acupuncture</td>
<td><em>Huatuojiaji</em> points 华佗夹脊穴 on the affected side</td>
<td>Once a day, 10 treatments per course, 2 courses in succession</td>
</tr>
<tr>
<td></td>
<td>Pricking to bleed and cupping</td>
<td><em>Ashi</em> points 阿是穴 and <em>Huatuojiaji</em> points 华佗夹脊穴 on the affected side</td>
<td>Once a day, 10 treatments per course, 2 courses in succession</td>
</tr>
</tbody>
</table>
2.2.6 Current evidence of Chinese medicine treatment for herpes zoster

Currently, there are no identified systematic reviews (SRs) published in English which evaluate CM treatment for HZ. Three SRs evaluating the efficacy and safety of CHM therapies in the management for HZ [19-21], and seven SRs evaluating acupuncture therapies [22-28] were identified in Chinese databases CBM (China BioMedical Literature), CNKI (China National Knowledge Infrastructure), CQVIP (Chongqing VIP) and WanFang data (Table 2.10). The comparators reported in these SRs varied, with pharmacotherapies being used alone or in combination of CHM or acupuncture. The evidence of the SRs has shown CM therapies might be beneficial in improving HZ symptoms with mild adverse events reported (Table 2.10). However, the evidence is limited by some methodological issues. A summary of the current evidence of CM for HZ is shown as below.

2.2.6.1 Chinese herbal medicine systematic reviews

Of the three SRs evaluating the clinical evidence of CHM, one study evaluated general CHM therapies (no specified formulae names provided) [19], one study evaluated formulae which included the herb Dan shen 丹参 (alone or combined with other CM or pharmacotherapies) [21], and the other one evaluated formulae used to address one treatment principle Huo xue hua yu 活血化瘀 (activate Blood and dispel stasis) formulae (Table 2.10) [20]. The CHM therapies in these studies showed benefits in shortening time to resolution of skin rash, reducing pain and PHN incidence rate compared with pharmacotherapies. Only one SR [20] evaluated the safety of Huo xue hua yu 活血化瘀 formulae (Table 2.10). Mild gastrointestinal discomfort, diarrhoea, and drowsiness were reported in several studies. The formulae were well tolerated by the participants.
2.2.6.2 Acupuncture therapies systematic reviews

Various acupuncture therapies including general acupuncture therapies, electro-acupuncture, moxibustion, and fire needling were evaluated systematically in the SRs [22-28] (Table 2.10). The evidence from SRs showed that acupuncture therapies shortened the time to resolution of pain, reduced the incidence of PHN, and improved cutaneous outcomes compared with pharmacotherapies. Only one SR evaluated the safety of fire needling [25]. Fire needling showed mild side effects among the included studies, with individual cases of drowsiness and fatigue being reported.

2.2.6.3 Limitation of the systematic reviews

Not all reviews searched the English language databases, and those that did only searched two databases (Medline and the Cochrane Library) [20-23, 27, 28]. None of the reviews searched the databases Embase, CINAHL (Cumulative Index of Nursing and Allied Health Literature), or the specialist database AMED (Allied and Complementary Medicine Database). For the Chinese databases, CBM, CNKI, CQVIP, and Wanfang Data were the key databases searched. However, only four of the SRs covered all the Chinese databases above [23-25].

One paper clearly stated an inclusion criterion of acyclovir as the comparator [28], all others included a broad range of intervention and comparator types. For example, one SR combined the results of studies of electro-acupuncture (EA) plus pricking to bleed and cupping with EA plus ear pricking to bleed. Pooling of studies with different interventions for statistical analysis may cause high heterogeneity and results in weak strength of evidence. The reason for pooling studies for statistical analysis was not clear.
None of the SRs reported the dosage of the comparators in the included studies, so the efficacy of either CHM or acupuncture remains unclear. Among these studies, only two studies evaluated the safety of the intervention, which is also a gap to evaluate CM therapies systematically.

The evidence from SRs published in Chinese language is insufficient to draw conclusions about the efficacy and safety of CM for HZ. To address this gap, SRs prepared with a more comprehensive search of both Chinese and English databases and more strict inclusion and exclusion criteria are needed.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Databases</th>
<th>No. of Trials</th>
<th>Intervention ; Comparator</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systematic review of Chinese herbal medicine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fu, 2014 [24]</td>
<td>CNKI, Wanfang</td>
<td>7</td>
<td>CHM; WM</td>
<td>X - - - - - -</td>
<td>I &gt; C</td>
</tr>
<tr>
<td>Xu, 2010 [21]</td>
<td>Cochrane, MEDLINE, CBM, CNKI, Wanfang</td>
<td>13</td>
<td>Dan shen 或 dan shen 丹参 +other CHM or WM; WM</td>
<td>X - X X -</td>
<td>X -</td>
</tr>
<tr>
<td><strong>Systematic review of acupuncture therapies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu, 2007 [26]</td>
<td>Wanfang, CNKI, CQVIP</td>
<td>10</td>
<td>General acupuncture; WM</td>
<td>X - - X - - -</td>
<td>I &gt; C</td>
</tr>
<tr>
<td>Fu, 2009 [24]</td>
<td>Wanfang, CNKI, CQVIP, CBM</td>
<td>14</td>
<td>Huatuojiaji points 华佗夹脊穴 acupuncture; WM or general acupuncture</td>
<td>X X X - - - -</td>
<td>I &gt; C</td>
</tr>
<tr>
<td>Cao, 2010 [22]</td>
<td>MEDLINE, CNKI, CQVIP,</td>
<td>12</td>
<td>General acupuncture; WM or CHM</td>
<td>X - - X - - -</td>
<td>I &gt; C</td>
</tr>
<tr>
<td>Author</td>
<td>Database</td>
<td>RCTs</td>
<td>Intervention</td>
<td>C</td>
<td>CHM</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------</td>
<td>------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---</td>
<td>-----</td>
</tr>
<tr>
<td>Chen, 2013</td>
<td>MEDLINE, Wanfang, CNKI, CQVIP, CBM</td>
<td>9</td>
<td>Electro-acupuncture; WM</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Zheng, 2011</td>
<td>MEDLINE, SCI, CNKI, CQVIP, Wanfang</td>
<td>5</td>
<td>Moxibustion; acyclovir</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Zhao, 2007</td>
<td>Cochrane, MEDLINE, CBM</td>
<td>7</td>
<td>General acupuncture; WM</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Wang, 2009</td>
<td>PubMed, CENTRAL, Business Source Premier, HSRPROJ, Clinical Trials Databases, CBM, CNKI, CQVIP, Wanfang</td>
<td>6</td>
<td>Fire needle; WM</td>
<td>X</td>
<td>-</td>
</tr>
</tbody>
</table>
2.3 Chapter summary

HZ is a distinguishing neurocutaneous disease caused by reactivation of the VZV. Global HZ incidence rate is 4 to 4.5 per 1,000 PY and has an age-adjust increasing trend of incidence [3]. Both HZ and its most common sequelae PHN have a great impact on patient’s quality of life and economic burden to individuals and the healthcare system.

Current management for HZ aims to relieve the acute pain, to limit the spread and time course of lesions and to prevent or relieve PHN and other complications. Antiviral therapy, corticosteroids, analgesics, anticonvulsants, and antidepressants are recommended by various guidelines. For the management of neuralgia either in acute or PHN stage, a stepped-care approach is recommended by guideline [7]. Even though adverse events are reported, this was the aspect of treatment patients were most satisfied. However, people with HZ were least satisfied with the perceived effectiveness of the antiviral and analgesic medication based on research using Treatment Satisfaction Questionnaire for Medication [15].

CM may offer an alternative and complementary treatment method to conventional medicine. In CM theory, HZ can be caused by Stagnant heat, retention of dampness, and attack of external toxin. Three CM textbooks [16-18] and one acupuncture practice guideline [12] are commonly used to guide the practice of CM therapies. Different CHM formulae were recommended according to syndrome differentiations of HZ, while acupuncture therapies were specified in different stages of lesion progression.
The efficacy and safety of CM therapies has been evaluated in various systematic reviews. Both CHM and acupuncture therapies showed benefit in shortening time to alleviate pain, improving cutaneous outcomes, and reducing PHN incidence rate compared with pharmacotherapies. Mild adverse events of CHM and acupuncture therapies were reported. The clinical evidence of CM therapies is limited by search strategy, study inclusion criteria, and statistical analysis methods. Rigorous systematic reviews are needed for evaluating the safety and efficacy of CM therapies more comprehensively.
Chapter 3. Methods of data mining and cluster analysis of classical literature

3.1 Introduction

Over thousands of years, information of aetiology and pathogenesis, symptoms and clinical management of Chinese medicine (CM) related to various diseases were described and explained in depth in the classical literature. Much of the information continues to guide the contemporary guidelines and textbooks for CM practice.

The primary guiding principle for classifying disease and formulating treatments in CM is syndrome differentiation (Bian zheng 辨证). To make sense of symptoms and their presentation in patients, CM practitioners group or cluster related symptoms together into categories to facilitate diagnosis. Although syndrome differentiations of herpes zoster (HZ) are described clearly in contemporary CM textbooks, differences in descriptions between classical and contemporary literature exist. Some of the classical literature citations such as cases reports and practitioners’ experiences often described symptoms only, without aligning them with a CM syndrome in texts.

For deeper understanding of the potential symptom/syndromes clusters, cluster analysis may be an advanced data mining approach to address this gap. Currently cluster analysis has been used to discover the potential relationships of symptoms, related syndromes and treatment approaches in the classical literature research. A better understanding of symptom/syndromes
clusters through this approach can enhance the current knowledge of diseases. This chapter details the general methods of data mining and cluster analysis of the classical literature of HZ.

3.2 Aims

This chapter aims to:

1. Provide the methods used for citation identification, data collection, coding and sorting of classical literature reporting on cases or treatment of HZ.

2. Describe the methods of descriptive and cluster analysis of data collected from classical CM literature.

3.3 Data collection and management

The data collection and mining work followed the Standard Operating Procedures (SOPs) produced by the China-Australia International Research Centre for CM. Similar projects on dementia and memory disorders have been published using these SOPs [102, 103].

3.3.1 Database

Zhong Hua Yi Dian (ZHYD) “Encyclopaedia of Traditional Chinese Medicine” (Version 5.0) [104] (Figure 3.1) is one of the biggest CM classical literature collections in the world. The ZHYD contains more than 1,000 CM books on CD-ROM from ancient times to the period of the Republic of China. The latest work included in the ZHYD is the Wai Ke Shi San Fang
Kao 外科十三方考 (published in 1947). Previous research comparing collections of the pre-modern traditional literature on CM has found the ZHYD to be suitable for systematic searches, for its size, electronic format and broad spread of genres [103, 105].

Figure 3.1 Example of the search screen and data obtainable using the Zhong Hua Yi Dian software

3.3.2 Identification of search terms

To identify the search terms in Chinese language, various sources were consulted including:

- CM dictionaries: Zhong Yi Fang Ji Da Ci Dian 中医方剂大辞典 (ZYFJDCD, Great Compendium of Chinese Medical Formulas). It is one of the largest compendiums contains 96,592 individual formula entries, extracted from 680 CM books. It is also a comprehensive classical CM dictionary that contains the ingredients, preparation, treatment principles, and the book source of each formula. By checking the information of each formula in the category of “herpes zoster”, terms related to HZ might be identified.

- Guidelines: Clinical Practice Guideline of Acupuncture for Herpes Zoster [12].

Consultation with a CM dermatologist was made to identify any additional search terms not located through the above searches. Search terms were approved after consultation with dermatologists and experts in Guangdong Provincial Hospital of CM.

Besides the common terms such as she chuan chuang 蛇串疮, chan yao 缠腰, and huo dan 火丹 which were all identified in ZYFJDCD, two “modern” terms pao zhen 疱疹 and she dan yu hou tong 蛇丹愈后痛 were also included in the search terms list. As the ZHYD contains the CM literature from the era of the Republic of China (1912 to 1949), these terms were considered to be relevant.

A total of 30 terms were used to search the ZHYD. The majority of the search terms described the lesion appearance, with the characters of “蛇” (snake), “带” (belt), “串” (string of beads), “缠” (encircling), and “龙” (dragon), and/or in combination with the location of the lesion with character of “腰” (waist). Some of the search terms used the pathogen of fire “火” or wind “风”, to describe the skin condition. The full list of the search terms is shown in
Appendix 1.

3.3.3 Data collection and extraction

Data collection work from ZHYD was done by two researchers (Kaiyi Wang, KW, and Haiying Liang, HL). Initially, each of the condition search terms was copied to the search field in the ZHYD. Each term was searched in the ZHYD software by both headings search function (Mu lu sou suo, 目录搜索, where the search term is found in the title/heading) and body text search function (Nei rong sou suo, 内容搜索, where the search term is found in the body text) to get the most comprehensive results. Relevant passages of text or headings which contained the search terms were displayed in the software. The number of hits (instances of the term) was also displayed. A Microsoft Excel® file was used to record the number of hits for each search term.

The second step was to extract data using the data extraction function in ZHYD. A separate Microsoft Excel® file for each search term was created by the software containing the preliminary information: keywords (关键词), book title and chapter (关键词所在章节), and body text (关键词所在章节对应的正文, that is, the passages of texts which included the search term). All Microsoft Excel® files were merged to a final file once the data extraction work had been done. Citations were reviewed to identify duplicates, which were excluded from further analysis. For each citation, the author and dynasty were obtained from a bibliography database of CM classical literature.
3.4 Data coding and scoring system

In order to facilitate analysis, coding was performed in Microsoft Excel®. This was undertaken independently by Kaiyi Wang and Haiying Liang. If disagreement occurred, resolution was sought by discussion. A third researcher (Tony Zhang) was available for consultation if needed, however this was not required.

Initially, a preliminary data sort of all the citations was undertaken to determine whether they were documenting a skin condition. A secondary sort was then undertaken to code any identified citations for citation type, description of condition and treatment of the condition (see Table 3.1). All citations were consequently coded as one of eight different types:

- code 0: not relevant to any skin condition citations;
- code 1: definition of skin condition citations;
- code 2: aetiology and pathogenesis citations;
- code 3: pharmacopeia citations;
- code 4: CHM treatment citations;
- code 5: acupuncture treatment citations;
- code 6: moxibustion treatment citations;
- code 7: other CM therapy treatment citations.

The original texts which contained both descriptions of the condition and treatment were separated into different columns in Microsoft Excel® for further analysis.
Table 3.1 Preliminary coding of the citations

<table>
<thead>
<tr>
<th>Items</th>
<th>Details or Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citation type</td>
<td>0=Not relevant to any skin condition, 1=Disease definition, 2=Aetiology and pathogenesis, 3=Pharmacopeia citation, 4=CHM treatments, 5=Acupuncture treatments, 6=Moxibustion treatments, 7=Other CM therapy treatments</td>
</tr>
<tr>
<td>Description of the condition in original citation</td>
<td>The original text</td>
</tr>
<tr>
<td>Treatment of the condition in original citation</td>
<td>The original text</td>
</tr>
</tbody>
</table>

After the preliminary coding work had been done, all of the relevant citations (excluding the citation type=0 not relevant) were further reviewed and coded according to description of symptoms (see Table 3.2). Each symptom was coded as “1” if present, or as “0” if absent. Symptoms were grouped according to category and allocated a code (eg S1, see Table 3.2)

Table 3.2 Symptom coding

<table>
<thead>
<tr>
<th>Symptoms Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion appearance (S1)</td>
<td>1. Belt 带</td>
</tr>
<tr>
<td></td>
<td>2. Snake 蛇</td>
</tr>
<tr>
<td></td>
<td>3. Encircling 缠/绕</td>
</tr>
<tr>
<td></td>
<td>4. String of beads 串珠</td>
</tr>
<tr>
<td></td>
<td>5. Patchy 斑片</td>
</tr>
<tr>
<td>Lesion type (S2)</td>
<td>1. Blister 疱/泡</td>
</tr>
<tr>
<td></td>
<td>2. Papules 疹</td>
</tr>
<tr>
<td></td>
<td>3. Erythema/red spot 红斑</td>
</tr>
<tr>
<td>Pain (S3)</td>
<td>1. Pain 痛</td>
</tr>
<tr>
<td></td>
<td>2. Burning pain 灼痛</td>
</tr>
<tr>
<td>Lesion color (S4)</td>
<td>1. Red 红</td>
</tr>
<tr>
<td></td>
<td>2. Yellow 黄</td>
</tr>
<tr>
<td></td>
<td>3. White 白</td>
</tr>
<tr>
<td>Itch (S5)</td>
<td>Itch 痒</td>
</tr>
<tr>
<td>Heat (S6)</td>
<td>Heat 热</td>
</tr>
</tbody>
</table>
Treatment details/ingredients including the Chinese herbal medicine formulae and herbs, acupuncture therapies and other CM treatments were also coded. The details included treatment methods (formula, single herb, acupuncture, and other therapy), formula name (for example, Long dan xie gan tang 龙胆泻肝汤), herbal ingredients (for example, cang zhu 苍术, chen pi 陈皮, etc.), acupuncture points, preparation type (decoction, granules, etc.), and administration (oral or topical).

Citations which included multiple descriptions of HZ (for example, different syndrome differentiations), were separated into multiple descriptions for statistical analysis and data mining. If the citations included multiple treatments, the citations were divided so that each description or treatment was counted separately for statistical analysis.

Some citations did not specify the herb ingredients. In these cases, I searched the book containing the citation to identify other instances of the same formula which did list the ingredients. If identified, these ingredients were used for analysis. If the ingredients were not identified from another entry from the same book, the citations were excluded from statistical analysis of ingredients.

### 3.5 Inclusion criteria

The typical presentation of HZ has not changed over time. Accordingly, the characteristic symptoms described in contemporary clinical HZ guideline were used as inclusion criteria for
classical literature. These included grouped blistering eruptions on a red base of skin, burning or stabbing pain with a unilateral dermatome distribution [7].

The HZ ocular disease might contain special diagnosis criteria (for example, symptoms were limited around the eyes, accompanied by headache) and CM treatment techniques may be different from those used for typical HZ. Citations which were judged to be HZ ocular disease were excluded from this research. After consultation and discussion with dermatologists and experts in Guangdong Provincial Hospital of CM, citations were categorised as follows:

1. Not relevant to HZ (code 0): based on the description of the citation, the disease is definitely not HZ.

2. No information or not enough information to permit judgment (code 1): if the citation described only one of symptoms S1, S2 and S3, and/or S4, and/or S5, and/or S6 (see Table 3.2).

3. “Possibly HZ” (code 2): if the citation described the symptoms containing any two of from S1, S2 and S3; and/or S4, and/or S5, and/or S6 (see Table 3.3 see note below).

4. “Most likely to be HZ” (code 3): if the citation described the symptoms containing all symptoms S1, S2 and S3; and/or S4, and/or S5, and/or S6.

The following table illustrates the disease judgment and codes for the citations:
Citations judged as “0” (not HZ) were reviewed to determine what other conditions they may be, and this was documented. Only “Possibly HZ” (code 2) and “Most likely to be HZ” (code 3) citations were eligible for further analysis.

### 3.6 Descriptive analysis

After the data extraction and coding work had been completed, data were transferred to Statistical Package for the Social Science (SPSS; version 21.0) software for further data analysis. Statistical analysis was conducted for the two categories of “possibly HZ” and “most likely to be HZ” separately:
1. Frequency analysis of search term: the total frequency of all search terms, and frequency of each search terms by dynasty (cross tabulation).

2. Symptom frequency: frequency analysis of all symptoms in included citations.

3. Treatment frequency: frequency analysis of CHM formulae and the standardised herbal ingredients. The herbal ingredients were standardised through a cross-referenced nomenclature list of commonly used CHMs published by the Chinese Medicine Board of Australia (CMBA, last updated September 2015) [106]. The reason for standardisation was due to the multiple names of the same herbs might be used in different citations. For example, *da huang* 大黃, *sheng jun* 生军, and *jiang jun* 将军 were the three common names of *Rheum rhabarbarum* L. used in the classical literature. The official name of this herb approved by CMBA is *da huang* 大黄, so herbal ingredients from the same plant with other names were standardised to *da huang* 大黄.

3.7 Cluster analysis

3.7.1 Data set

In order to discover the potential relationships of the HZ symptoms, cluster analysis was conduct for the data set of symptoms. The cluster analysis was conducted for citations judged to be “most likely to be HZ” citations only, as the symptoms described in these citations were the most relevant to HZ.
3.7.2 Similarity measurement

According to the basic theory of cluster analysis [107], the similarity (proximity), is used to identify how related the individuals are to each other in a data set. The data set included binary data (code 1= the symptom was present; code 0= the symptom was absent that is not described). Two individual symptoms \( i \) and \( j \), have a similarity coefficient \( S_{ij} \) of unity if both have identical values for variables [107]. For example, \( S_{\text{heat and belt}} \) means the similarity coefficient of unity of individual symptoms “heat” and “belt” in the included citations. The value differs in the scale of the interval between 0 and 1 generally, which show the likelihood of both individual symptoms being present. For example, \( S_{\text{heat and belt}} = 0.7 \) (70%), means that there is a 70% chance of both “heat” and “belt” both presented in all citations. Table 3.4 describes the relationship between individual symptoms \( i \) and \( j \).

<table>
<thead>
<tr>
<th>Individual Symptom ( i )</th>
<th>Outcome</th>
<th>1</th>
<th>0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual symptom ( j )</td>
<td>1</td>
<td>( a )</td>
<td>( b )</td>
<td>( a + b )</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>( c )</td>
<td>( d )</td>
<td>( c + d )</td>
</tr>
<tr>
<td>Total</td>
<td>( a + c )</td>
<td>( b + d )</td>
<td>( p = a + b + c + d )</td>
<td></td>
</tr>
</tbody>
</table>

\( a \): co-present of \( i \) and \( j \); \( b \): \( i \) presents without \( j \); \( c \): \( j \) presents without \( i \); \( d \): co-absence of \( i \) and \( j \); \( p \): all the relationships above.

A number of approaches for the \( S_{ij} \) are recommended [107]. An important consideration which determines the analytical approaches to use is to deal with the 0 - 0 matches, where neither symptom is present \( (d \) in Table 3.4).
In some data sets, the co-absence of two factors may be important for statistical analysis, for example, gender or blood type. For this data set, identification of the co-absence of both individual symptoms isn’t clinically useful, so the \( d \) count was not required. As a result, two similarity measures were selected; the Jaccard coefficient and Sneath and Sokal Measurement. The Jaccard coefficient (\( S_{ij} = \frac{a}{(a+b+c)} \)) excludes joint absences, with equal weight being given to matches and non-matches. The Sneath and Sokal Measurement (\( S_{ij} = \frac{a}{a+2(b+c)} \)) uses double weight given to non-matches. A third measurement, Gower and Legendre Measurement (\( S_{ij} = \frac{a}{a+0.5(b+c)} \)), was also considered; however, as this test is not possible in the available software [108] it was not able to be performed. In cluster analysis, the application of all available and applicable measurements is recommended [107].

### 3.7.3 Agglomerative hierarchical clustering methods

The process of grouping the individual items to the whole classification varies, according to different agglomerative hierarchical clustering methods [107]. The agglomerative method means the clustering process follows a “bottom up” approach, with each item (individual symptom of HZ in this case) starting in its own cluster, and grouping of clusters being merged as one moving up the hierarchy. In other words, cluster analysis began with \( n \) clusters each containing a single individual symptom, to a classification with all the individual symptoms. The specified agglomerative methods may provide a series of successive fusions of the individual symptoms into groups. The agglomerative hierarchical clustering methods of single linkage (or ‘nearest neighbour’ in SPSS), complete linkage (or ‘furthest neighbour’ in SPSS), average linkage (between group linkage and within groups linkage in SPSS) were
selected to conduct the analyses of these binary data sets. While weighted average linkage is also recommended, it is not available in SPSS software and was not conducted.

After the parameter of the similarity measurement and agglomerative method had been set, the results of the cluster analysis were displayed as dendrograms. A dendrogram is also known as tree diagram. The horizontal axis of the dendrogram represents the distance or dissimilarity between clusters, where a lower value indicates greater similarity, while the vertical axis represents the objects and clusters. Details of the selected agglomerative hierarchical clustering methods are shown in

<table>
<thead>
<tr>
<th>Method</th>
<th>Definition of Distance Between Clusters</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single linkage</td>
<td>Minimum distance between pair of individuals, one in one cluster, one in the other</td>
<td>Tends to produce unbalanced and straggly clusters, especially in large data sets. Does not take account of cluster structure</td>
</tr>
<tr>
<td>Complete linkage</td>
<td>Maximum distance between pair of individuals, one in one cluster, one in the other</td>
<td>Tends to compact clusters with equal diameters (maximum distance between objects). Does not take account of cluster structure</td>
</tr>
<tr>
<td>Average linkage (Between-group)</td>
<td>Joins the two clusters for which the average distance between members of those two clusters is the smallest</td>
<td>Tends to join cluster with small variances. Intermediate between single and complete linkage. Takes account of cluster structure. Relatively robust.</td>
</tr>
<tr>
<td>Average linkage (Within-groups)</td>
<td>Joins the two clusters for which the average distance between members of the resulting cluster will be smallest</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Brian S. 2010 [107]
between clusters, with single linkage applying the minimum distance, the complete linkage applying the maximum distance, while between-group and within-group applying the intermediate average distance. These are the main agglomerative methods used for hierarchical cluster analysis. A process recommended by Brian S. et al. [107] is to apply all the available agglomerative methods to hierarchical cluster analysis. Analysis of symptoms clusters were conducted based on each dendrogram generated, as per similarity measurement and hierarchical clustering methods. Sub-cluster analyses were conducted where dendrograms showed more small classifications of individual symptoms. A comparison of the dendrograms was conducted between the applied agglomerative methods, and clusters of symptoms were identified according to the characteristics of the dendrograms.

3.8 Chapter summary

This chapter generally describes the methods of data mining and cluster analysis of classical literature in this research. The comprehensive classical literature search was conducted in ZHYD. A total of 30 search terms were identified in CM textbooks, dictionaries, and guidelines, which were confirmed after consultation with dermatologists and experts. Data were exported and merged to a Microsoft Excel® file. After duplicates removal, citations were reviewed and coded. Relevant citations were further reviewed and coded according to description of symptoms. Based on the symptoms, the citations were categorised as four groups: most likely HZ citations, possibly HZ citations, citations contain no information or not enough information to permit a judgement, and not relevant to HZ citations. Treatment details of the most likely HZ and possibly HZ citations were also extracted and coded.
Data were transferred to SPSS software for further data mining after extraction and coding work had been completed. Descriptive analysis was conducted for the two categories of “possibly HZ” and “most likely to be HZ” separately. Frequency analysis of search terms, symptoms and treatments were conducted and analysed. The cluster analysis was conducted for “most likely to be HZ” citations only, to discover the potential relationships of the HZ symptoms. Two similarity measurements and four agglomerative methods were selected according to the data characteristics and functions available in SPSS software. Cluster results were displayed as dendrograms. Meaningful clusters of the HZ symptoms were identified after comparison among the dendrograms.
Chapter 4. Data mining and cluster analyses of classical literature

4.1 Introduction

Contemporary literature suggests the earliest citation of herpes zoster (HZ) is from the Zhu Bing Yuan Hou Lun 诸病源候论 dating back to 610 AD [100, 109, 110]. In this citation, the term zeng dai chuang 甑带疮 was used to describe HZ as a skin condition that encircles the waist (Original text: 甑带疮者，绕腰生). Another typical citation from Za Bing Yuan Liu Xi Zhu 杂病源流犀烛 (1773) named HZ as chan yao huo dan 缠腰火丹 and huo dai chuang 火带疮. This citation described HZ as “a skin disease distributes in the lumbar and thoracic region of the human body, with countless vesicles like a belt” (Original text: 缠腰火丹者，即火带疮，缠于带脉，故腰间生疮，累累如珠，如束带者然), which was similar to the symptoms described in conventional medicine and contemporary Chinese medicine (CM) [7, 9, 14, 16-18].

Over a long history, a complete CM system of terminology, symptoms, syndrome differentiations and therapies for HZ, has been developed from clinical practice and literature. The valuable information contained in the classical literature continues to influence and instruct contemporary CM practice. Currently, this information has not been systematically evaluated and analysed.

This chapter describes a systematic evaluation (data mining) of citations collected from Zhong Hua Yi Dian (ZHYD) 中华医典, one of the largest collections of CM classical
literature. Frequently used disease terms, symptoms and treatments in classical literature were statistically analysed and compared with modern evidence. Further, cluster analyses of the data were also conducted to discover the potential relationships between symptoms and implications for clinical practice. The methods used have been described in Chapter 3.

4.2 Aims

This chapter aims to:

1. Evaluate the CM interventions used for HZ in classical literature.
2. Examine the most frequently used herbs, formulae, and therapies through descriptive statistical analysis; and to compare management for HZ between modern and that recorded in the classical literature.
3. Discover the potential relationships of the HZ symptoms extracted from the classical literature through inferential statistics/cluster analysis.

4.3 Results

A total of 208 hits (instances of the term) were identified through title/heading search and 1,455 hits through body text search in ZHYD (Version 5.0) using the search terms separately. Many hits were identified by two or more search terms. Terms *huo dan 火丹* and *chan yao 缠腰* produced the greatest number of hits: 145 title/heading hits with 1,047 body text hits, and 16 title/heading hits with 106 body text hits, respectively (see Appendix 2). It is not surprising that term *huo dan 火丹* returned the greatest number of hits in the search of
The term *huo dan* was used to describe a wide range of diseases in ancient times including HZ, erysipelas, mumps, etc. Many terms such as *chan yao huo long*, *she dan yu hou tong*, *pao zhen*, and *she xing dan* which were included in the search failed to hit any title/heading or body text (see Appendix 2). These terms may have been used in texts which were not included in the ZHYD.

In total 1,107 citations (including the information of body texts related to the search terms, books, chapters) were collected from the database search (see Figure 4.1). Eight hundred and seventy-five citations were reviewed after duplicates were removed. During preliminary screening, citations were excluded for the following reasons: not classical citations (published after 1949, 56 citations), ocular disease (5 citations). Eight hundred and fourteen citations were then assessed to determine whether they referred to skin conditions. Preliminary information were coded.

Of these 814 citations, 136 citations were judged to be not relevant to any skin conditions and excluded. Two hundred and ninety-six citations were considered to be describing skin conditions not related to HZ (code 0), and 286 citations had no information or insufficient information to judge the likelihood of being HZ (code 1). Ninety-six citations which were considered to be possibly (code 2) or most likely (code 3) citations of HZ were included for further information extraction and data analysis. Results were presented in two categories: citations judged as “possible” HZ citations (62 citations, see full texts in Appendix 3) and those judged most likely to be HZ citations (34 citations, see full texts in Appendix 4) based
on symptoms descriptions. The following flow chart shows the data sorting and management process (Figure 4.1).

**Figure 4.1 Flow chart of the selection process of the classical literature citations**

4.3.1 Search terms and dynasty

Eighteen search terms identified citations that were possibly or most likely to be HZ. Forty-nine citations were identified by more than one search term. The search terms *chan yao* 纠腰 and *huo dan* 火丹 provided the greater number of possibly and most likely to be HZ citations: 54 and 44 citations respectively (Table 4.1). The most commonly used term in contemporary CM textbooks *she chuan chuang* 蛇串疮 was cited only 10 times (5.2% of total citations) in the included citations. The dataset suggests a change in terminology over time (Table 4.2).
Table 4.1 Number of citations identified by each search term

<table>
<thead>
<tr>
<th>Pinyin, Chinese Characters</th>
<th>Number of Citations Obtained By the Search Term</th>
<th>Percentage of Total Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan yao 缠腰</td>
<td>54</td>
<td>56.3%</td>
</tr>
<tr>
<td>Huo dan 火丹</td>
<td>44</td>
<td>45.8%</td>
</tr>
<tr>
<td>Chan yao huo dan 缠腰火丹</td>
<td>32</td>
<td>33.3%</td>
</tr>
<tr>
<td>She chan dan 蛇缠丹</td>
<td>13</td>
<td>13.5%</td>
</tr>
<tr>
<td>She chuan chuang 蛇串疮</td>
<td>10</td>
<td>10.4%</td>
</tr>
<tr>
<td>Huo dai chuang 火带疮</td>
<td>9</td>
<td>9.4%</td>
</tr>
<tr>
<td>Chan yao dan 缠腰丹</td>
<td>7</td>
<td>7.3%</td>
</tr>
<tr>
<td>She chan chuang 蛇缠疮</td>
<td>7</td>
<td>7.3%</td>
</tr>
<tr>
<td>She dan 蛇丹</td>
<td>5</td>
<td>5.2%</td>
</tr>
<tr>
<td>Bai she chan yao 白蛇缠腰</td>
<td>2</td>
<td>2.1%</td>
</tr>
<tr>
<td>Chan yao chuang 缠腰疮</td>
<td>2</td>
<td>2.1%</td>
</tr>
<tr>
<td>Huo dan chuang 火丹疮</td>
<td>2</td>
<td>2.1%</td>
</tr>
<tr>
<td>She ke chuang 蛇窠疮</td>
<td>2</td>
<td>2.1%</td>
</tr>
<tr>
<td>Chan yao long 缠腰龙</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Huo yao dai 火腰带</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Huo yao dai du 火腰带毒</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Zeng dai chuang 靓带疮</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Zhi zhu chuang 蜘蛛疮</td>
<td>1</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

Note: the total percentage exceeds 100 as many citations were identified by multiple search terms

4.3.1.1 “Possible” herpes zoster citations

A total of 17 search terms identified citations that were judged as “possibly” HZ. For search terms which yielded citations, the distribution of terms over time is shown in Table. 4.2.
Table 4.2 “Possible” herpes zoster citations per search term by dynasty

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan yao 缠腰</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>18</td>
<td>3</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>Huo dan 火丹</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>She chan dan 蛇缠丹</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Chan yao huo dan 缠腰火丹</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>She chan chuang 蛇缠疮</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Chan yao dan 缠腰丹</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Huo dai chuang 火带疮</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>She dan 蛇丹</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>She chuan chuang 蛇串疮</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>She ke chuang 蛇窠疮</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Bai she chan yao 白蛇缠腰</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chan yao long 缠腰龙</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Huo dan chuang 火丹疮</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Huo yao dai 火腰带</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Huo yao dai du 火腰带毒</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Zeng dai chuang 甑带疮</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Zhi zhu chuang 蜘蛛疮</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Note: many citations were identified by more than one search term, therefore the total number of citations by dynasty is greater than the total number of citations.*

The most frequently used terms were *chan yao 缠腰* (24 citations), *huo dan 火丹* (17 citations).
citations), *she chan dan* 蛇缠丹 (13 citations), *chan yao huo dan* 缠腰火丹 (seven citations), *she chan chuang* 蛇缠疮 (six citations), *chan yao dan* 缠腰丹 (five citations), *huo dai chuang* 火带疮 (five citations), and *she dan* 蛇丹 (five citations). The other terms were identified in only one or two citations. The majority of citations were from the Ming and Qing dynasties. The earliest citation was from *Zhu Bing Yuan Hou Lun* 诸病源候论 (610 AD) identified by the term *zeng dai chuang* 甑带疮 (Original text: 甑带疮者，绕腰生), which is also recognised by several contemporary CM literature [100, 109, 110]. In this citation, HZ was described as “a skin disease encircles the waist”. Although the location of the rash described in this citation was consistent with that in conventional medicine and contemporary CM textbooks [7, 17, 18], there was insufficient HZ characteristic symptoms to judge it to be the citation referred to HZ. The most recent citation was from the *Ben Cao Jian Yao Fang* 本草简要方 (1938) identified by term *she chan dan* 蛇缠丹 (Original text: 杂甘草擂醋搽蛇缠丹毒).

Another example of a “possible” HZ citation was from *Ben Cao Dan Fang* 本草单方 (1633), which described the skin condition as “*huo dai chuang* 火带疮, is encircling the waist” (Original text: 火带疮, 绕腰生者). Although the body text provided key characters “belt” (*dai* in pin yin or 带), and “encircling”, the lack of other characteristic HZ symptoms meant it was not able to be judged as most likely to be HZ.

### 4.3.1.2 “Most likely” to be herpes zoster citations

For the citations that were judged “most likely” to be HZ, the distribution of the search terms
is shown in Table 4.3. The most frequently used terms were *chan yao*缠腰 (30 citations), *huo dan* 火丹 (27 citations), *chan yao huo dan*缠腰火丹 (25 citations), *she chuan chuang* 蛇串疮 (eight citations), *huo dai chuang* 火带疮 (four citations), with other terms identifying only one or two citations. The “most likely” to be HZ citations were from Ming (five citations) and Qing dynasties (29 citations) only.

Fewer search terms identified citations that were judged “most likely” HZ. Terms *chan yao long* 缠腰龙, *huo yao dai du* 火腰带毒, *chan yao dan* 缠腰丹, *she dan* 蛇丹, *she ke chuang*蛇窠疮, *zeng dai chuang* 筛带疮, and *zhi zhu chuang* 蜘蛛疮 were not found in “most likely” HZ citations. The number of search terms identifying “most likely” HZ citations was lower than that for “possible” HZ citations. This may be due to the criteria for judgment of citations, where “possible” HZ citations may have included skin conditions other than HZ.

### Table 4.3 “Most likely” to be herpes zoster citations per search term by dynasty

<table>
<thead>
<tr>
<th>Search Term</th>
<th>Ming (1368-1644)</th>
<th>Qing (1636-1912)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Chan yao</em> 缠腰</td>
<td>5</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td><em>Huo dan</em> 火丹</td>
<td>5</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td><em>Chan yao huo dan</em>缠腰火丹</td>
<td>5</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td><em>She chuan chuang</em> 蛇串疮</td>
<td>0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td><em>Huo dai chuang</em>火带疮</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><em>Chan yao chuang</em>缠腰疮</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><em>Chan yao dan</em>缠腰丹</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><em>Bai she chan yao</em>白蛇缠腰</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><em>Huo dan chuang</em>火丹疮</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><em>She chuan chuang</em>蛇缠疮</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
The standard contemporary term for HZ *she chuan chuang* 蛇串疮 was identified since Qing dynasty in these citations. The earliest citation of *she chuan chuang* 蛇串疮 was in *Wai Ke Da Cheng* 外科大成 (1665), and the most recent citation in *Wai Ke Bei Yao* 外科备要 (1904).

The earliest citation judged “most likely” to be HZ from this search was from *Zheng Zhi Zhun Sheng - Yang Yi* 证治准绳·疡医 (1602), that was identified by four search terms *chan yao* 缠腰, *chan yao huo dan* 缠腰火丹, *huo dai chuang* 火带疮, and *huo dan* 火丹. This citation presents some information of symptoms and a severe condition causing death. A reasonable English translation for this earliest citation is:

Question: What is the skin condition that encircles the waist, with a string of beads?

Answer: This is called *huo dai chuang* 火带疮, with another name *chan yao huo dan* 缠腰火丹. If the people with this disease are not treated in time, the toxin invades into the body via umbilicus, causing distension and death. (Original Chinese text: 或问：绕腰生疮，累累如珠何如？曰：是名火带疮，亦名缠腰火丹。此证若不早治，缠腰已遍，則毒由脐入，膨胀不食而死。)

The symptoms described in this citation, such as “string of beads”, “waist”, are consistent with the contemporary definition of HZ which includes grouped vesicles rash and dermatomal distribution [7]. The citation also describes a severe condition causing death, for people not receiving prompt treatment and the “toxin invades into the body via umbilicus”.
HZ complications zoster encephalitis and meningitis are severe, potentially fatal results of HZ infection [80, 81]. As no further details were provided, whether this citation refers to HZ complications is unclear.

The most recent citation was from *Wai Ke Nei Yao* 外科备要 (1904), that was identified by four search terms: *chan yao* 缠腰, *huo dan* 火丹, *chan yao huo dan* 缠腰火丹, and *she chuan chuang* 蛇串疮. This citation described the symptoms and syndrome differentiation of HZ. A reasonable English translation for this most recent citation is:

“*Chan yao huo dan* 缠腰火丹 is also called *she chuan chuang* 蛇串疮. *Chan yao huo dan* 缠腰火丹 can be defined as two main types: dry and damp, and can be differentiated by the lesion colour: red and yellow. Both have string of beads. If this disease occurs in the lumbar and thoracic area, it is caused by Liver Fire.”

(Original Chinese text: 缠腰火丹 俗名蛇串疮，有干湿不同，红黄之异，皆如累累珠形。若单生腰肋，系肝火妄动。)

In this citation, the description of the lesions was found to be more similar to contemporary clinical medicine, with text fragments of “red”, “string of beads”, and “lumbar and thoracic area”. The term currently used for HZ *she chuan chuang* 蛇串疮, was also found in this citation.

Another typical description found in citations “most likely” to be HZ was from *Wai Ke Zheng Zhi Quan Shu* 外科证治全书 (1617). This citation contained a comprehensive explanation of...
the aetiology and pathogenesis, characteristics of the condition and extensive treatment options. The dry type chan yao huo dan 纠腰火丹 was characterized by red, patchy lesions, itchy and heat sensation, and was associated with the syndrome of heat and wind in the Liver and Gall Bladder. Dry type should be treated with the herbal formula Long dan xie gan tang 龙胆泻肝汤. Damp type was characterized by yellow lesions, or with white fluid filled vesicles unequal in size, and was due to damp-heat in the Liver and Spleen. Damp type could be treated with Wei ling tang 胃苓汤, in combination with herbs shan zhi zi 山栀子, fang feng 防风, and shi gao 石膏. Pricking the lesion to break the skin was also recommended for damp type HZ. The description of the skin condition in this citation was very similar to the contemporary clinical medicine. More recent citations included greater detail about the symptoms than earlier citations.

4.3.2 Symptoms

Twenty-five “most likely” HZ citations, and 26 “possible” HZ citations contained descriptions of symptoms. Citations which contained multiple descriptions of symptoms were separated for analysis. This resulted in 28 “most likely” to be HZ descriptions and 29 “possible” HZ descriptions being used for the data analysis (below) and data mining in section 4.5.

4.3.2.1 Symptoms in “possible” herpes zoster citations

Twenty-three “possible” HZ citations specified the location(s) of the rash (one description
specified two locations). Rash was most commonly located in the lumbar area (18 citations). Other locations were described as skin (generally, in two citations), and one each in Dai meridian (referring to the area around the waist from anterior to posterior in contemporary acupuncture theory [111]), neck, abdomen, limbs and all around the body. Five citations did not specify the location of the skin condition.

The most frequently described symptoms were “encircling”缠绕, and “red”红, found in 16 and 15 descriptions, respectively. Other frequently described symptoms included “snake”蛇 (10 descriptions), “pain”痛 (four descriptions), “belt”带 (three descriptions) and “blister”疱 (three descriptions). Symptoms “string of beads”串珠 “white”白, and “itchy”痒 was identified in only one “possible” HZ citation (Table 4.4).

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encircling缠绕</td>
<td>16</td>
</tr>
<tr>
<td>Red红</td>
<td>15</td>
</tr>
<tr>
<td>Snake蛇</td>
<td>10</td>
</tr>
<tr>
<td>Pain痛</td>
<td>4</td>
</tr>
<tr>
<td>Belt带</td>
<td>3</td>
</tr>
<tr>
<td>Blister疱/泡</td>
<td>3</td>
</tr>
<tr>
<td>String of beads串珠</td>
<td>1</td>
</tr>
<tr>
<td>White白</td>
<td>1</td>
</tr>
<tr>
<td>Itchy痒</td>
<td>1</td>
</tr>
</tbody>
</table>

4.3.2.2 Symptoms in “most likely” herpes zoster citations

Of the 28 “most likely” to be HZ descriptions, 26 descriptions specified the location(s) of the skin rash (one description specified two locations). Similar to the descriptions of “most
likely” to be HZ, the rash was most commonly located in the lumbar area (26 descriptions). One citation specified the location was *Shen shu* 肾俞, which referred to an acupuncture point on the lumbar area (BL23), 1.5 cm lateral to the lower border of the second lumbar spinous process. This finding is consistent with contemporary descriptions of HZ, where dermatomes innervated by the thoracic nerves are among the most common presentations [7].

**Table 4.5 Frequency of symptoms/descriptions in citations “most likely” to be herpes zoster**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encircling 绊/绕</td>
<td>21</td>
</tr>
<tr>
<td>Red 红</td>
<td>16</td>
</tr>
<tr>
<td>String of beads 串珠</td>
<td>13</td>
</tr>
<tr>
<td>Snake 蛇</td>
<td>11</td>
</tr>
<tr>
<td>Yellow 黄</td>
<td>9</td>
</tr>
<tr>
<td>Blister 疱/泡</td>
<td>8</td>
</tr>
<tr>
<td>Belt 带</td>
<td>7</td>
</tr>
<tr>
<td>Pain 痛</td>
<td>6</td>
</tr>
<tr>
<td>Heat 热</td>
<td>4</td>
</tr>
<tr>
<td>Patchy 斑片</td>
<td>2</td>
</tr>
<tr>
<td>Itchy 痒</td>
<td>2</td>
</tr>
<tr>
<td>Burning pain 灼痛</td>
<td>1</td>
</tr>
<tr>
<td>Papules 疹</td>
<td>1</td>
</tr>
<tr>
<td>Erythema/red spot 红斑</td>
<td>1</td>
</tr>
<tr>
<td>White 白</td>
<td>1</td>
</tr>
</tbody>
</table>

Twenty-one citations described the rash as “encircling” 绊/绕, and 16 descriptions described skin redness (红). Other frequently described symptoms included “string of beads” 串珠 (13 descriptions), “snake” 蛇 (11 descriptions), and “yellow” 黄 (nine descriptions). The symptoms/descriptions “patchy” 斑片, “papules” 疹, “erythema/red spot” 红斑, “burning pain” 灼痛, “yellow” 黄, and “heat” 热 were only identified in citations judged “most likely”
to be HZ. While some of these descriptions can be common to other skin conditions, several terms are unique to contemporary descriptions of HZ, including “burning pain” and “belt” (Table 4.5).

4.3.2.3 Summary of symptoms

Compared with the “possible” HZ citations, more characteristic symptoms of HZ were identified in the “most likely” to be HZ citations; likely due to their classification. For the “possible” HZ citations, fewer descriptions of rash locations were seen specified. For example, the symptom “string of beads” 串珠 was identified in 13 citations in the “most likely” to be HZ citations, but found in only one “possible” HZ citation. Other HZ characteristic symptoms “blister” 疱/泡 (eight in “most likely” versus three in “possible” HZ citations) and “belt” 带 (seven in “most likely” versus three in “possible” HZ citations) were seen more frequently in “most likely” to be HZ citations. Additionally, some symptoms were only described in the citations judged to be “most likely” to be HZ, there were: “yellow” 黄, “heat” 热, “patchy” 斑片, “burning pain” 灼痛, “papules” 疹, and “erythema/red spot” 红斑.

The combination of these terms of symptoms may be the better predictor to identify the HZ citations in classical CM literature.

4.3.3 Treatments

Citations that contained multiple treatments were separated for analysis, that is, 70 citations were separated into 103 treatments. Five acupuncture therapy and two praying therapy entries
were also identified the data pool. Details of the treatments were outlined and analysed.

4.3.3.1 Treatments in “possible” herpes zoster citations

In total, 44 of the 62 “possible” HZ citations described treatments. Details of the treatments are presented below.

4.3.3.1.1 Chinese herbal formulae

Forty-two of the 62 citations judged as possibly HZ described the Chinese herbal formulae. Fifty-three name and unnamed formulae were described. Two citations were pharmacopeia type entries, which described herbs **bai shan ni** 白鳝泥 and **jian chun luo** 剪春罗. Thirty-seven citations described 41 unnamed formulae, and 12 citations described eight named formulae. The most frequently cited formula was **Long dan xie gan tang** 龙胆泻肝汤, included in five “possible” HZ citations (Table 4.6). Other formulae were cited once in individual citation.

The majority of formulae were prescribed for topical use (37, 69.8%). Nine (9, 18.9%) formulae were for oral use, one was recommended for both oral and topical use, and five did not specify the route of administration. Named formulae were more commonly used orally (eight of 12 citations). For unnamed formulae, topical application was more common (36 of 41 citations)
### Table 4.6 Common formulae in “possible” herpes zoster citations

<table>
<thead>
<tr>
<th>Formula Name</th>
<th>Herb Ingredients</th>
<th>Number of Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long dan xie gan tang</td>
<td>Long dan cao 龙胆草, zhi zi 梔子, huang qin 黄芩, sheng di 生地, che qian zi 车前子, ze xie 泽泻, mu tong 木通, gan cao 甘草, dang gui 当归, lian qiao 连翘, huang lian 黄连, da huang 大黄 (All formulae were identified from the same book in different sections, and no variant was found)</td>
<td>5</td>
</tr>
<tr>
<td>Chai hu qing gan tang</td>
<td>Chai hu 柴胡, sheng di 生地, chi shao 赤芍, niu bang zi 牛蒡子, dang gui 当归, lian qiao 连翘, chuan xiong 川芎, huang qin 黄芩, zhi zi 梔子, hua fen 花粉, fang feng 防风, gan cao 甘草</td>
<td>1</td>
</tr>
<tr>
<td>Chu shi wei ling tang</td>
<td>Fang feng 防风, cang zhu 苍术, Fu ling 伏苓, chen pi 陈皮, hou pu 厚朴, shan zhi 山栀, mu tong 木通, ze xie 泽泻, hua shi 滑石, gan cao 甘草, bo he 柏叶, zhu ling 猪苓</td>
<td>1</td>
</tr>
<tr>
<td>Bai ye san 柏叶散 (topical)</td>
<td>Shi bai mo 石柏末, qing fen 轻粉, xiong huang 雄黄, qing dai 青黛, hua shi 滑石, han shui shi 寒水石, yin zhu 银朱, chen sha 辰砂, qian fen 铅粉, ce bai ye 侧柏叶, si gua ye 丝瓜叶</td>
<td>1</td>
</tr>
<tr>
<td>Jie she you 解蛇油 (NS)</td>
<td>Wu gong 蜈蚣</td>
<td>1</td>
</tr>
<tr>
<td>Jie zhu dan 解蛛丹 (NS)</td>
<td>Zhu ma gen 蜈蚣根, bing pian 冰片, qing fen 轻粉, ji dan ke 鸡蛋壳, deng cao hui 灯草灰, bai ming fan 白明矾</td>
<td>1</td>
</tr>
<tr>
<td>She dan yanfang 蛇丹验方(oral)</td>
<td>Zhi zhu 蜘蛛</td>
<td>1</td>
</tr>
<tr>
<td>Ru yi jin huang san 如意金黄散 (topical)</td>
<td>Ru yi jin huang san 如意金黄散 (ingredients NS), xin ji shui 新汲水, dian zhi 㨲汁</td>
<td>1</td>
</tr>
</tbody>
</table>

NS: not specified

### 4.3.3.1.2 Herbal ingredients

The ten most frequently used herbal ingredients in “possible” HZ citations are shown in Table 4.7. The most frequently used herb was *xiong huang* 雄黄. Most citations described topical application of this herb (14 out of the 16 citations), while only two of citations described this
herb for oral use. *Xiong huang* 雄黄 (realgar, arsenic disulphide), is a herb widely used in CM practice for resolving dampness and detoxifying. However, concerns have been raised of hepatic and renal toxicity with *xiong huang* 雄黄 [112]. This herb should be prescribed with caution, at a maximum dosage of 0.1 g per day [113].

Although there was a degree of uncertainty whether these citation refer to HZ, the majority of the most frequently used herbs were consistent with the herbs used in contemporary CM textbooks (Table 4.7) [16-18]. Their inclusion in the list of most frequently used herbs suggests that they may be used to treat skin conditions which have similar pathophysiology to HZ. Two herbs *lian qiao* 连翘 and *huang lian* 黄连 were on the most frequently reported list for “possible” HZ citations in classical literature, while not in the recommended list of contemporary CM textbooks. *Lian qiao* 连翘 and *huang lian* 黄连 are often used for clearing heat and detoxifying in CM practice, fitting with the treatment principle for the syndrome of heat in Liver meridian.

Table 4.7 Most frequently reported herbs in “possible” herpes zoster citations

<table>
<thead>
<tr>
<th>Herb Name</th>
<th>Scientific Name</th>
<th>No. of Citations (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xiong huang 雄黄</td>
<td>Arsenic disulphide</td>
<td>16</td>
</tr>
<tr>
<td>Gan cao 甘草</td>
<td><em>Glycyrrhiza</em> spp</td>
<td>8</td>
</tr>
<tr>
<td>Lian qiao 连翘</td>
<td><em>Forsythia suspensa</em> (Thunb.) Vahl</td>
<td>8</td>
</tr>
<tr>
<td>Long dan cao 龙胆草</td>
<td><em>Gentiana scabra</em> Bge.</td>
<td>7</td>
</tr>
<tr>
<td>Zhi zi 梔子</td>
<td><em>Gardenia jasminoides</em> Ellis</td>
<td>7</td>
</tr>
<tr>
<td>Che qian zi 车前子</td>
<td><em>Plantago asiatica</em> L.</td>
<td>5</td>
</tr>
<tr>
<td>Dang gui 当归</td>
<td><em>Angelica sinensis</em> (Oliv.) Diels</td>
<td>5</td>
</tr>
<tr>
<td>Huang lian 黄连</td>
<td><em>Coptis</em> spp</td>
<td>5</td>
</tr>
<tr>
<td>Mu tong 木通</td>
<td><em>Akebia quinata</em></td>
<td>5</td>
</tr>
<tr>
<td>Ze xie 泽泻</td>
<td><em>Alisma orientalis</em> (Sam.) Juzep.</td>
<td>5</td>
</tr>
</tbody>
</table>
4.3.3.1.3 Acupuncture and other therapies

Three citations described moxibustion therapy in the management of HZ. One citation described the location of application at the beginning and end of the lesion length (皮损两头), while the other two described the location to be “seven cun” (七寸处). In ancient times there was a saying that to kill a snake, the “seven cun” spot must be hit. The “seven cun” point is likely to be where the heart of a snake is located. This explains its application in HZ, which is described as being like a snake. Two citations described other techniques of prayer 祝由 as a form of therapy in the “possible” HZ citations.

4.3.3.2 Treatment in “most likely” herpes zoster citations

In all, 26 of the 34 “most likely” HZ citations described the treatments. Details of the treatments are presented as follows.

4.3.3.2.1 Chinese herbal formulae

Twenty-one citations described Chinese herbal formulae that included 39 formulae. Several citations described multiple formulae. Ten citations included unnamed formulae, and 20 citations included 16 named formulae. Four formulae were described in two or more citations (Table 4.8). The most frequently reported formula was Long dan xie gan tang 龙胆泻肝汤, described in five citations. As formulae from different books provided different sets of herbal ingredients, variants were seen among the formulae with the same names.
### Table 4.8 Common formulae in “most likely” herpes zoster citations

<table>
<thead>
<tr>
<th>Formula Name</th>
<th>Herb Ingredients</th>
<th>Number of Citations</th>
</tr>
</thead>
</table>
| Long dan xie gan tang (oral)  | **Variant 1**: Long dan cao 龙胆草, zhi zi 柿子, huang qin 黄芩, chai hu 柴胡, sheng di 生地, che qian zi 车前子, ze xie 泽泻, mu tong 木通, gan cao 甘草, dang gui 当归  
                                **Variant 2**: Long dan cao 龙胆草, zhi zi 柿子, huang qin 黄芩, sheng di 生地, che qian zi 车前子, ze xie 泽泻, mu tong 木通, gan cao 甘草, dang gui 当归, lian qiao 连翘, huang lian 黄连, da huang 大黄  
                                | 5                                                                               |
| Chai hu qing gan tang (oral)  | **Variant 1**: Chai hu 柴胡, sheng di 生地, chi shao 赤芍, niu bang zi 牛蒡子, dang gui 当归, lian qiao 连翘, chuan xiong 川芎, huang qin 黄芩, zhi zi 柿子, hua fen 花粉, fang feng 防风, gan cao 甘草  
                                **Variant 2**: Chai hu 柴胡, sheng di 生地, dang gui 当归, chi shao 赤芍, chuan xiong 川芎, lian qiao 连翘, niu bang zi 牛蒡子, huang qin 黄芩, zhi zi 柿子, tian hua fen 天花粉, gan cao 甘草, fang feng 防风  
                                | 4                                                                               |
| Bai ye san 柏叶散 (topical)  | **Variant 1**: Ce bai ye 侧柏叶, huang bo 黄柏, xiong Huang 雄黄, qing fen 轻粉, qiu yin fen 蚯蚓粪, da huang 大黄, chi xiao dou 赤小豆, bai ye zhi 柏叶汁  
                                **Variant 2**: Bai ye 柏叶, di long fen 地龙粪, da huang 大黄, huang bai 黄柏, chi xiao dou 赤小豆, xiong Huang 雄黄, qing fen 轻粉  
<pre><code>                            | 3                                                                               |
</code></pre>
<table>
<thead>
<tr>
<th>Formula Name</th>
<th>Herb Ingredients</th>
<th>Number of Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chu shi wei ling tang (oral)</td>
<td>Variant 3: Ce bai ye, di long fen, huang bo, da huang, xiong huang, chi xiao dou, qing fen</td>
<td></td>
</tr>
<tr>
<td>Chu shi wei ling tang</td>
<td>Variant 1: Fang feng, cang zhu, fu ling, chen pi, hou pu, shan zhi, mu tong, ze xie, hua shi, gan cao, bo he, bai zhu, zhu ling</td>
<td>2</td>
</tr>
</tbody>
</table>
The numbers of formulae used orally and topically were similar (19 and 17, respectively). The route of administration was not specified in three formulae. Unnamed formulae were more likely to be for topical use (nine citations, compared with one citation for oral use), and named formulae were more likely to be used orally (18 citations, compared with eight for topical use and three not specified).

As the contemporary CM textbook also recommends this formula for treating acute HZ [16-18], *Long dan xie gan tang* 龙胆泻肝汤 remains one of the most important formulae in the management of HZ from ancient times to the present day. However, the number of *Long dan xie gan tang* 龙胆泻肝汤 identified in this research is considerably small. Future research on other sources of classical literature (for example, *Zhong Hua Ben Cao Quan Shu* 中华本草全书) is needed to confirm or refute this finding.

*Chu shi wei ling tang* 除湿胃苓汤 was another formula common to both classical literature and contemporary texts, which is recommended in contemporary CM textbooks for treating HZ of the Spleen deficiency with damp retention syndrome.

In the classical citations, the commonly used formulae where the chief herb was *chai hu* 柴胡 were *Chai hu qing gan tang* 柴胡清肝汤 with variants. This formula is also recommended in contemporary CM textbooks [16-18]. Based on the actions of herbs listed in classical formulae and contemporary formula, formulae where the chief herb was *chai hu* 柴胡 used in
ancient times were mainly for clearing heat in the Liver and regulating $qi$, while the modern formulae are mainly functioning to regulate $qi$ only. This is not surprising, as contemporary CM textbooks tend to standardise syndrome differentiation and recommendation of formulae. For people with HZ of $qi$ stagnation and Blood stasis syndrome, *Chai hu shu gan san* 柴胡疏肝散 is the formula used to resolve this syndrome.

One topical formula cited in classical citations, *Bai ye san* 柏叶散, is not recommended in contemporary CM textbooks [16-18]. This may be due to one of the ingredients in this formula, *qing fen* 轻粉 (calomel), which may result in severe dermatitis, liver, and kidney failure [113]. Laboratory research suggests that the single daily dose of *qing fen* 轻粉 for topical application in adults should be less than 1.5 g. The hepatic and renal function of patients should be monitored when applying any product containing *qing fen* 轻粉 [38].

**4.3.3.2.2 Herbal ingredients**

In citations judged as “most likely” to be HZ, a total of 110 herbal ingredients were described. Some ingredients were excipients such as sesame oil 麻油/香油, vinegar 醋, and salt 盐, which were used in preparations to bind the herbs. As these ingredients have no intended therapeutic action, they were excluded from further analysis. A selection of the most frequently used herbs are described in Table 4.9. *Gan cao* 甘草 was the most frequently reported herb, found in 18 citations. *Gan cao* 甘草 is frequently used to harmonise ingredients in a formula according to CM formulation theory. While this may in part explain its inclusion in the list of most frequently used herbs, *gan cao* 甘草 has other therapeutic
effects relevant to dermatological conditions. *Gan cao* 甘草 is known to have steroid like effects [114], which may shorten the time to resolution of the rash and alleviate pain in acute HZ.

### Table 4.9 Most frequently reported herbs in “most likely” herpes zoster citations

<table>
<thead>
<tr>
<th>Herb Name</th>
<th>Scientific Name</th>
<th>No. of Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan cao 甘草</td>
<td>Glycyrrhiza spp</td>
<td>18</td>
</tr>
<tr>
<td>Zhi zi 梔子</td>
<td>Gardenia jasminoides Ellis</td>
<td>14</td>
</tr>
<tr>
<td>Huang qin 黄芩</td>
<td>Scutellaria baicalensis Georgi</td>
<td>12</td>
</tr>
<tr>
<td>Lian qiao 连翘</td>
<td>Forsythia suspensa (Thunb.) Vahl</td>
<td>10</td>
</tr>
<tr>
<td>Dang gui 当归</td>
<td>Angelica sinensis (Oliv.) Diels</td>
<td>9</td>
</tr>
<tr>
<td>Xiong huang 雄黄</td>
<td>Arsenic disulphide</td>
<td>9</td>
</tr>
<tr>
<td>Long dan cao 龙胆草</td>
<td>Gentiana scabra Bge.</td>
<td>8</td>
</tr>
<tr>
<td>Da huang 大黄</td>
<td>Rheum spp</td>
<td>8</td>
</tr>
<tr>
<td>Fang feng 防风</td>
<td>Saposhnikovia divaricata (Turcz.) Schischk.</td>
<td>7</td>
</tr>
<tr>
<td>Sheng di 生地</td>
<td>Rehmannia glutinosa Libosch.</td>
<td>7</td>
</tr>
<tr>
<td>Ze xie 泽泻</td>
<td>Alisma orientalis (Sam.) Juzep.</td>
<td>7</td>
</tr>
</tbody>
</table>

Another important note for the most frequently used herb list is *mu tong* 木通, which was described in six citations and included in the ingredient list of all citations that described *Long dang xie gan tang* 龙胆泻肝汤 (LDXGT). *Mu tong* 木通 has been sourced from a variety of species. *Akebia quinata* and *A. trifoliata* (Thunb.) Decne. are considered the official species for *mu tong* 木通, while *Clematis armandii* Franch. and *C. montana* Buch. Ham. are the official species for *chuan mu tong* 川木通. However, aristolochia species of *mu tong* 木通, which contain the toxin aristolochic acid, are considered to lead to the severe complication renal failure [115-117]. None of the classical citations specified which species of *mu tong* 木通 was used, nor did they described the adverse event in texts. In the Guidelines for Diagnosis and Treatment of Common Diseases of Dermatology in Traditional
Chinese Medicine 中医皮肤科常见病诊疗指南 [118], *mu tong* 木通 is not in the herbal ingredients recommendation list for HZ. This has been substituted with *tong cao* 通草, which has a similar function of resolving dampness without toxicity.

### 4.3.3.2.3 Acupuncture and other therapies

Five citations judged as “most likely” to be HZ described acupuncture therapies to manage symptoms. Four citations described the use of acupuncture techniques, three of which used a technique of pricking the lesion with a needle. One citation used a technique of pricking the lesions at the “head” or start of the lesion length (“snakeheads” 蛇头). No other citations describing acupuncture or other therapies were judged as “most likely” HZ.

### 4.4 Cluster analysis

In order to discover the potential relationships of the HZ symptoms described in the 34 “most likely” HZ citations (including 28 symptom descriptions), the symptoms described in section 4.2.2.2 were subjected to cluster analysis. The symptoms included lesion appearance (that is, belt, snake, encircling, string of beads, and patchy), lesion type (that is, blister, papules, and erythema/red spot), pain (that is, pain and burning pain), lesion colour (that is, yellow, red, and white), itch and heat. Results of the cluster analyses using different methods and similarity measurements are illustrated in dendrograms below.
4.4.1 Single linkage (nearest neighbour) method

The details of single linkage method have been described in Chapter 3. Single linkage method is one of the standard agglomerative hierarchical clustering methods for the binary data set. It defines the distance (similarity) between clusters as the minimum distance between the pair of individuals. Within this method, two approaches were used as parameters: Jaccard coefficient (JC) and Sneath and Sokal measurement (SM).

To interpret the data from the dendrogram, a basic rule is that items that are close together (have more similarity) will be linked near to the base of the X axis. The scale of X axis shows the distance between individuals/clusters, as calculated by SPSS software. The smaller the distance between individual symptoms/clusters, the closer relationship. All of dendrograms were reviewed and clusters split on the basis structure and appearance. A dotted line was manually added to each dendrogram to denote where clusters were split.

From the single linkage method dendrogram (Figure 4.2), with JC as the parameter of similarity, symptoms of \{patchy, itchy, papules, erythema/red spot, pain, heat, string of beads, yellow, snake, blister, encircling, red\} form a big cluster, while three individual symptoms \{belt\}, \{burning pain\}, and \{white\} were not belonging to or forming any cluster (sitting to the right of the dotted line).

Within the big cluster, several sub-clusters were also identified: \{patchy, itchy\}, \{papules, erythema/red spot\}, \{pain, heat\}, \{string of beads, yellow\}, and \{encircling, red\}.
From the dendrogram using single linkage method (Figure 4.3), with SM as the parameter of similarity, a big cluster of \{patchy, itchy, papules, erythema/red spot, heat, white, burning pain, pain, yellow, blister, belt, string of beads\} was identified, with three individuals \{snake\}, \{white\}, \{encircling\} which didn’t join any cluster. Two sub-clusters \{patchy, itchy\}, \{papules, erythema/red spot\} were seen with quite small distance from each other, suggesting they are closely related.
In contrast to single linkage, complete linkage defines the distance (similarity) between clusters as the maximum distance between the pair of individual, and tends to produce compact clusters with equal diameters. Two approaches of JC and SM were also used to conduct the analysis as below.

Four clusters of \{patchy, itchy, papules, erythema/red spot\}, \{pain, heat, burning pain\}, \{encircling, red, belt\}, \{string of beads, yellow, snake, blister\} were shown in the
dendrogram using the complete linkage of JC (Figure 4.4), with an individual symptom \{white\} did not belong to any cluster. Some sub-clusters were also identified as \{patchy, itchy\}, \{papules, erythema/red spot\}, \{pain, heat\}, \{encircling, red\}, and \{string of beads, yellow, snake\}.

Two main clusters were identified in the dendrogram where the similarity coefficient was SM: \{patchy, itchy, papules, erythema/red spot, pain, heat, burning pain, white, string of beads, yellow, snake, blister\}, and \{encircling, red, belt\} (Figure 4.5). Four sub-clusters:
{patchy, itchy, papules, erythema/red spot}, {pain, heat}, {string of beads, yellow, snake}, and {encircling, red} were also seen.

Figure 4.5 Complete linkage dendrogram: Sneath and Sokal Measurement

4.4.3 Average linkage (between groups) method

For average linkage methods, two agglomerative hierarchical clustering methods were used to conduct cluster analysis: between groups and within group methods, where the distance is defined as the average distance between individual symptoms. The between groups method considers the average distance between members of those two clusters is the smallest and
joins them together, while the within-group method considers the average distance between **members of the resulting cluster** will be smallest and joins them together. They both tend to join the cluster with small variances, and the definition of distance are intermediate between single and complete linkage. The cluster analysis were all conducted with the two parameters described previously. Dendrograms of average linkage (between groups) are shown as below. Moreover, dendrograms of average linkage (within group) are shown in the following section 4.4.4.

While applying average linkage (between group) method with the JC to the data set (Figure 4.6), two main clusters appeared as \{patchy, itchy, papules, erythema/red spot, pain, heat\}, and \{encircling, red, string of beads, yellow, snake, blister\}, with three symptoms \{belt\}, \{burning pain\}, \{white\} presented separately.

Some sub-clusters were also identified: \{patchy, itchy\}, \{papules, erythema/red spot\}, \{pain, heat\}, \{encircling, red\}, and \{string of beads, yellow, snake\}.
Figure 4.6 Average linkage (between groups) dendrogram: Jaccard coefficient

One big cluster containing \{patchy, itchy, papules, erythema/red spot, burning pain, pain, heat, white, string of beads, yellow, snake, blister, belt\} was shown in the dendrogram using SM, while a small cluster containing two symptoms of \{encircling, red\} was seen (Figure 4.7). Four sub-clusters of \{patchy, itchy, papules, erythema/red spot\}, \{burning pain, white\}, \{pain, heat\}, and \{string of beads, yellow, snake\} were identified from the big cluster.
Figure 4.7 Average linkage (between groups) dendrogram: Sneath and Sokal measurement

4.4.4 Average linkage (within groups) method

In the cluster analysis using the method of average linkage (within groups) with JC, two clusters were shown in the dendrogram (Figure 4.8). One was \{patchy, itchy, heat, pain, papule, erythema/red spot, blister, burning pain, white\}, and the other was \{string of beads, yellow, snake, encircling, red, belt\}. Several sub-clusters could be found in the dendrogram: \{patchy, itchy\}, \{papules, erythema/red spot\}, \{string of beads, yellow\}, and \{encircling, red\}. 

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When using average linking (within groups) with SM, no obvious cluster could be seen in the dendrogram. Two sub-clusters of \{patchy, itchy\}, and \{papules, erythema/red spot\} were apparent (Figure 4.9).

**Figure 4.8 Average linkage (within groups) dendrogram: Jaccard coefficient**
Figure 4.9 Average linkage (within groups) dendrogram: Sneath and Sokal measurement

4.4.5 Summary and discussions

The following table summarises the clusters and sub-clusters from the analysis above using different agglomerative hierarchical clustering methods with different similarity measurements.
Table 4.10 Summary of clusters in “most likely” herpes zoster citations

<table>
<thead>
<tr>
<th>Hierarchical Clustering Methods</th>
<th>Jaccard Coefficient Clusters</th>
<th>Jaccard Coefficient Sub-clusters</th>
<th>Sneath and Sokal Measurement Clusters</th>
<th>Sneath and Sokal Measurement Sub-clusters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single linkage (nearest neighbour) method</td>
<td>{Patchy, itchy, papules, erythema/red spot, pain, heat, string of beads, yellow, snake, blister, encircling, red}</td>
<td>{Patchy, itchy} {Papules, erythema/red spot} {Pain, heat} {String of beads, yellow} {Encircling, red}</td>
<td>{Patchy, itchy, papules, erythema/red spot, heat, white, burning pain, pain, yellow, blister, belt, string of beads} {Snake} {Red} {Encircling}</td>
<td>{Patchy, itchy} {Papules, erythema/red spot}</td>
</tr>
<tr>
<td>Complete linkage (Furthest neighbour) method</td>
<td>{Patchy, itchy, papules, erythema/red spot} {Pain, heat, burning pain} {Encircling, red, belt} {White} {String of beads, yellow, snake, blister}</td>
<td>{Patchy, itchy} {Papules, erythema/red spot} {Pain, heat} {Encircling, red} {String of beads, yellow, snake}</td>
<td>{Patchy, itchy, papules, erythema/red spot, pain, heat, burning pain, white, string of beads, yellow, snake, blister} {Encircling, red, belt}</td>
<td>{Patchy, itchy, papules, erythema/red spot} {Pain, heat} {Encircling, red} {String of beads, yellow, snake}</td>
</tr>
<tr>
<td>Hierarchical Clustering Methods</td>
<td>Jaccard Coefficient</td>
<td>Sneath and Sokal Measurement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------------</td>
<td>----------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clusters</td>
<td>Sub-clusters</td>
<td>Clusters</td>
<td>Sub-clusters</td>
</tr>
<tr>
<td>Average linkage (between groups) method</td>
<td>{Patchy, itchy, papules, erythema/red spot, pain, heat}</td>
<td>{Patchy, itchy}</td>
<td>{Patchy, itchy, papules, erythema/red spot, pain, heat, burning pain, white, string of beads, yellow, snake, blister}</td>
<td>{Patchy, itchy, papules}</td>
</tr>
<tr>
<td></td>
<td>{Encircling, red, string of beads, yellow, snake, blister}</td>
<td>{Papules, erythema/red spot}</td>
<td>{Papules, erythema/red spot}</td>
<td>{Burning pain, white}</td>
</tr>
<tr>
<td></td>
<td>{Belt}</td>
<td>{Encircling, red}</td>
<td>{Encircling, red}</td>
<td>{Pain, heat}</td>
</tr>
<tr>
<td></td>
<td>{Burning pain}</td>
<td>{String of beads, yellow, snake}</td>
<td>{String of beads, yellow, snake}</td>
<td>{String of beads, yellow, snake}</td>
</tr>
<tr>
<td></td>
<td>{White}</td>
<td></td>
<td>{Encircling, red}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average linkage (within groups) method</td>
<td>{Patchy, itchy, heat, pain, papules, erythema/red spot, blister, burning pain, white}</td>
<td>{Patchy, itchy}</td>
<td>No cluster identified</td>
<td>{Patchy, itchy}</td>
</tr>
<tr>
<td></td>
<td>{String of beads, yellow, snake, encircling, red, belt}</td>
<td>{Papules, erythema/red spot}</td>
<td></td>
<td>{Papules, erythema/red spot}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>{String of beads, yellow, snake}</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>{Encircling, red}</td>
<td></td>
<td>{Encircling, red}</td>
</tr>
</tbody>
</table>
4.4.5.1 General characteristics of the clustering results

This research has followed the process of selecting the applicable measurement by the characteristic of the variable (binary variables in this research) and consideration of co-absence (co-absence not relevant in this research). Several approaches for cluster analysis were employed. The next step is to compare the dendrograms and consider which has provided the most valuable and meaningful results [107].

Among the clustering results, many of the dendrograms did not show obvious classification of the symptoms. Big clusters plus several individual symptoms were seen in the dendrograms of single linkage method with JC and SM as similarity measurements, complete linkage method with SM, and average linkage (between group) method with SM. This is not surprising, for the reason that different similarity measurements and clustering methods may come up with various structures of clustering results [107].

The analysis of the average linkage (between group) method with JC and average linkage (within groups) method with JC contained two significant clusters in the classifying process. While differences of the symptoms contained in the clusters existed between these clustering methods, there were some symptoms in common as {patchy, itchy, papules, erythema/red spot, pain, heat} (Group 1 symptoms), and {encircling, red, string of beads, yellow, snake} (Group 2 symptoms). It is curious that almost all symptoms are related to the skin rash, while Group 2 symptoms appear to be unique characteristic of HZ. Further analysis of Group 1 and
2 symptoms will be discussed in the following section.

One cluster analysis using complete linkage method with JC, produced better classifications than all other dendrograms. Characteristic clusters were shown as:

- \{Patchy, itchy, papules, erythema/red spot\} (general symptoms of skin rash),
- \{Pain, heat, burning pain\} (characteristic symptoms of heat and fire disease in CM),
- \{Encircling, red, belt\} (characteristic symptoms of HZ), and
- \{String of beads, yellow, snake, blister\} (characteristic symptoms of HZ).

When comparing these clusters and Group 1 & 2 symptoms, Group 1 symptoms seemed to be representative of “general symptoms of skin rash” cluster plus “characteristic symptoms of heat and fire disease in CM” cluster (only “burning pain” was not included in Group 1), while Group 2 symptoms seemed to be the combination of the two clusters (“belt” and “blister” was not in Group 2).

Although a better classification was provided by complete linkage method with JC, one symptom \{white\} was separated from any cluster. When reviewing the other dendrograms, one interesting connection of \{white\} and \{burning pain\} was seen in the single linkage method with SM, complete linkage method with SM, and average linkage (between groups) method with JC. All of these dendrograms suggest the close relationship between these two symptoms in the descriptions of the “most likely” to be HZ citations. As a result, \{white\} was classified with \{burning pain\} in the following partition of all the symptoms.
A possible partition of all of the symptoms could be considered based on the Group 1 & 2 symptoms, and the clusters from the complete linkage method with JC as follows:

\{ \text{Patchy, itchy, papules, erythema/red spot} \}: This cluster contained symptoms related to skin rash generally. In conventional medicine, these symptoms may appear in the prodromal or vesicular and encrustation phase of HZ [9]. While these symptoms could also be observed in some other skin conditions such as erysipelas, epifolliculitis, and eczema, a proposed classification for this cluster is “symptoms related to skin rash”.

\{ \text{Pain, heat, burning pain, white} \}: These four symptoms were also the symptoms related to skin rash. “Pain (or burning pain)” and “heat” are the two typical symptoms in the heat and fire disease in CM, while “white” is related to damp-heat in the Liver and Spleen. In the original text from \textit{Wai Ke Zheng Zhi Quan shu} 外科证治全书, “white” referred to herpes with white colour (fluid in the vesicles) related to burning pain (see details of this citation in section 4.4.1.2); this citation shows the connection between these symptoms. In contemporary CM textbooks, these symptoms could be found in the heat-related syndromes of Stagnant heat in the Liver meridian, and damp and fire toxin (see details in Chapter 2, section 2.2.5.1).

An argument is that the syndrome of “qi stagnation and Blood stasis” may also have the symptom of “pain”. However, based on the classical citations identified from ZHYD, none of
the citation described this syndrome in their original texts. In contemporary CM textbook [16-18], this syndrome is more likely to occur after the resolution of acute rash in elderly people. None of the citations clearly described those conditions. Based on the grouped symptoms, a proposed classification for the cluster of symptoms is “characteristic symptoms of heat disease in CM”. When combining the above two clusters together, characteristic inflammation symptoms of erythema, pain, and heat were identified.

{Encircling, red, belt} and {String of beads, yellow, snake, blister}: These two clusters describe the main characteristic symptoms of HZ. When combining these symptoms together, a possible interpretation could be “herpes presents with yellow fluid on a red base, forming a belt on the skin, like a snake encircling”, which is consistent with the description from the conventional medicine and contemporary CM descriptions of HZ. As a result, these two clusters could be merged to form an overarching cluster named “characteristic symptoms of HZ”.

This research also identified sub-clusters in all of the eight dendrograms. The sub-clusters were all consistent with the clusters described above. The most frequently identified sub-clusters were:

- {patchy, itchy} (six sub-clusters),
- {pain, heat} (five sub-clusters),
- {string of beads, yellow, snake} (five sub-clusters),
- {encircling, red} (five sub-clusters), and
{papules, erythema/red spot} (four sub-clusters).

This finding strengthens the reliability of the classifications of all of the symptoms above.

The details of the partition of the symptoms from this cluster analysis is shown in Figure 4.10, with sub-clusters indicated with {}.

Based on the findings of the cluster analysis, the symptoms of HZ may be divided into three groups to induce a hypothetical overall symptom structure of HZ:

HZ = \{Symptoms related to heat disease\} and,

\{Symptoms related to skin rash\} and,

\{Characteristic symptoms related to HZ\}.

Figure 4.10 Classification of symptoms from cluster analysis: herpes zoster
4.4.5.2 Testing the theoretical symptom structure: the case of erysipelas

4.4.5.2.1 A discussion of erysipelas

_Huo dan_ 火丹, with its direct translation as “fire pellets” from the Chinese characters, refer to a series of “red rash” skin conditions. The Chinese character “fire” 火, suggests these diseases may be caused by the pathogens fire and heat. In this research, many citations were judged not likely to be HZ. Assessment of which conditions they might be were made, and diseases identified by the search term _huo dan_ 火丹 included erysipelas, acne, mumps, carbuncle, and epifolliculitis.

In the complete dataset of citations, 166 of the 334 (49.7%) “Not relevant to HZ” (code 0) citations were judged likely to be erysipelas based on the descriptions of the symptoms. It is interesting that all of these citations were identified by the search term _huo dan_ 火丹. In all citations identified by the term _huo dan_ 火丹 (221 in total) that were judged not relevant to HZ, the majority of citations (165, 74.7%) were considered likely to be erysipelas.

Erysipelas is caused by the infection of Group A streptococcus bacteria, involving dermis and upper subcutaneous tissue [119]. The clinical manifestation of erysipelas is similar to cellulitis, causing local signs of inflammation, such as heat, erythema, pain, and lymphangitis. The area most commonly affected by erysipelas is the face and lower limbs, but it can occur all around the human body, including ears, trunk, fingers, and toes [120]. Erysipelas is usually called _dan du_ 丹毒 or _huo dan_ 火丹 in CM. It is usually caused by pathogenic factors of heat toxin, combining with wind, Liver fire, or damp [16].
A typical citation of erysipelas was from You You Xin Shu 幼幼新书 (1150), in which the author described 19 different types of huo dan 火丹, based on the place of occurrence and symptoms. In this citation, some symptoms of “burning pain”, “erythema”, and “patchy” were described, which were also in the cluster of “Symptoms related to skin condition” summarised above. It appears that classical literature citations for HZ and erysipelas had some symptoms in common.

Twenty-seven citations identified by the search term huo dan 火丹 were judged “most likely” HZ citations in this research (section 4.3.1.2). Twenty-five (92.6%) of these citations were identified by the whole term chan yao huo dan 缠腰火丹. It could be inferred that huo dan 火丹 might be a whole classification of skin conditions in classical literature. “Most likely” HZ citations were mostly frequently identified by a specific term chan yao huo dan 缠腰火丹, within the huo dan 火丹 series skin conditions. The majority of huo dan 火丹 were used to describe erysipelas, based on the citations identified in this search.

4.4.5.2.2 Cluster analysis of huo dan 火丹 citations judged likely to be erysipelas

In order to verify whether the hypothetical symptom structure applies to other skin conditions, another cluster analysis was conducted. A total of 159 descriptions containing symptoms were selected from the huo dan 火丹 citations judged likely erysipelas. All of the symptoms were extracted and transferred to SPSS (21.0) for cluster analysis, following the
same cluster approach for “most likely” HZ citations.

The following table (Table 4.11) summarises the clusters and sub-clusters from the analysis of symptoms from huo dan 火丹 citations using different agglomerative hierarchical clustering methods with the different similarity measurements (JC and SM). All resultant dendrograms can be found in Appendix 5.

Based on the clustering results, all agglomerative hierarchical clustering methods with JC seemed more likely to group the symptoms of \{red, swelling, heat, pain, burning pain\}, \{yellow, white, itchy\}, and \{papules, erythema/red spot, patchy, encircling\} in clusters. The SM method did not provide meaningful cluster results, with little similarity between symptoms. In the dataset of descriptions judged likely erysipelas, a possible partition of all of the symptoms as follows:

\{Red, swelling, heat, pain, burning pain\}: Similar to one of the clusters from “most likely” HZ citations \{Pain, heat, burning pain, white\}, this cluster contained symptoms all related to heat disease in CM. “Characteristic symptoms of heat disease in CM” may be a proposed classification name for this cluster. The symptoms red, swelling, heat, and burning pain are the four typical manifestations of local signs of inflammation according to conventional medicine.
Table 4.11 Summary of clusters in likely erysipelas citations

<table>
<thead>
<tr>
<th>Hierarchical Clustering Methods</th>
<th>Jaccard Coefficient</th>
<th>Sneath and Sokal Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clusters</td>
<td>Sub-clusters</td>
</tr>
<tr>
<td><strong>Single linkage (nearest neighbour) method</strong></td>
<td>{Red, swelling, heat, pain, burning pain} {yellow, white, itchy} {papules, erythema/red spot, patchy, encircling}</td>
<td>{Red, swelling} {pain, heat, burning pain} {yellow, white}</td>
</tr>
<tr>
<td><strong>Complete linkage (Furthest neighbour) method</strong></td>
<td>{Red, swelling} {heat, pain, burning pain} {yellow, white, itchy, papules} {erythema/red spot} {patchy} {encircling}</td>
<td>{pain, burning pain} {yellow, white}</td>
</tr>
<tr>
<td><strong>Average linkage (between groups) method</strong></td>
<td>{Red, swelling, heat, pain, burning pain} {yellow, white, itchy, papules} {erythema/red spot} {patchy} {encircling}</td>
<td>{Red, swelling} {pain, heat, burning pain} {yellow, white, itchy}</td>
</tr>
<tr>
<td>Hierarchical Clustering Methods</td>
<td>Jaccard Coefficient</td>
<td>Sneath and Sokal Measurement</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>Clusters</td>
<td>Sub-clusters</td>
</tr>
<tr>
<td>Average linkage (within groups) method</td>
<td>{Red, swelling, heat, pain, burning pain, erythema/red spot, patchy}</td>
<td>{Red, swelling}</td>
</tr>
</tbody>
</table>
{Yellow, white, itchy}: This cluster contains the symptoms related to skin rash generally. Two signs are related to rash colour (“yellow” and “white”), with a symptom “itchy” describing a sensation of the patient. A proposed classification for this cluster would be “symptoms related to skin rash”.

{Papules, erythema/red spot, patchy, encircling}: Symptoms contained in this cluster refer to the appearance of skin rash more generally. The proposed classification for this cluster would also be “symptoms related to skin rash”.

When comparing all of the symptoms identified in the likely erysipelas citations with the “most likely” HZ citations, characteristic symptoms related to HZ “belt”, “snake”, “string of beads”, and “blister” were not identified in the erysipelas citations. In addition, one symptom “swelling” identified in erysipelas citations was not found in HZ citations. Characteristic HZ symptoms were found in descriptions of erysipelas in classical literature. This is likely due to the clinical manifestation of erysipelas as local signs of inflammation associated with heat disease in CM. “Swelling” is one of the prominent symptoms of inflammation, which is more likely to be described in erysipelas. That may explain why this symptom was not found in “most likely” HZ citations.

The details of the partition of the symptoms from this cluster analysis are shown in Figure 4.11.
4.4.5.2.3 A discussion of the key symptoms and the symptom structure in the *huo dan* 火丹 skin conditions

One cluster, “characteristic symptoms of heat disease in CM”, was identified in both HZ and erysipelas cluster analyses. Also referring to the term *huo dan* 火丹 (fire pellets), contains the Chinese character “huo”, which means “fire/heat” in Chinese. It can be inferred that the characteristic symptoms of heat disease may be the classification that all the *huo dan* 火丹 skin conditions have in common. When looking into the symptoms {red, swelling, heat, pain, burning pain}, these are the typical signs of inflammation. Findings suggest that there is overlap in the symptoms of heat disease in CM and symptoms cluster identified in *huo dan* 火丹 skin conditions. The characteristic symptoms of heat disease in CM may be the key
symptom classification in *huo dan* 火丹 skin conditions. In conventional medicine, clinical manifestation of local signs of inflammation are the key symptoms among these conditions.

Based on the cluster analysis of the “most likely” to be HZ citations, and the wryseipelas citations, a hypothetical modified formula that summarised the structure of the symptoms could be shown as follows:

$$HZ = \{\text{Symptoms of inflammation}\} \text{ and } \{\text{Symptoms related to skin rash}\} \text{ and } \{\text{Characteristic symptoms of HZ}\}$$

$$\text{Erysipelas} = \{\text{Symptoms of inflammation}\} \text{ and } \{\text{Symptoms related to skin rash}\}$$

Considering not all of the skin conditions have characteristic symptoms like HZ (for example, erysipelas), the characteristic symptoms of a certain skin condition may be or may not be contained in the symptoms structure for a given disease.

From these findings a formula was deduced for the other *huo dan* 火丹 skin conditions (Figure 4.12):

A certain *huo dan* 火丹 series skin condition =

$$\{\text{symptoms of inflammation}\} \text{ and } \{\text{Symptoms related to skin rash}\} \text{ or } \{\text{characteristic}$$
symptoms of the certain *huo dan* 火丹 skin condition;
better understanding of each disease categorised within the term could be achieved. A standardised hypothetical symptoms structure formula could be deduced in the following way:

Disease A = \{key symptoms coursed by pathogen X\} and
\{Symptoms related to the grouped diseases\} or \{characteristic symptoms of the disease A\}

4.5 Limitations

This research conducted comprehensive data mining using the ZHYD to identify the classical literature citations of HZ. The results were limited by the number of book collections contained in the database and the number of citations identified. Another collection of traditional texts on Chinese materia medica which contained more than 6,000 books has been developed but is not yet available electronically. This resource may provide future information on Chinese herbal medicine (CHM) treatment of HZ.

Results of cluster analysis were limited by the sample size of the included HZ symptoms, and available statistical tests for cluster analysis. Analysis using other methods may produce different results. In addition, the pre-defined citation inclusion criteria, is likely to have influenced the clustering results. For example, the judgment for “most likely” HZ citation was based on the symptoms combining lesion appearance, lesion type, and pain. Some citations that were judged to be “possible” HZ might in fact refer to “most likely” HZ, an aspect that could not be controlled.
This research proposes a modified hypothetical symptom structure formula to summarise *huo dan* 火丹 skin conditions and deduces a standard symptom structure formula for the diseases caused by a certain pathogen. Further research of its applicability in other diseases would provide further support for its accuracy and value.

### 4.6 Chapter summary

This chapter has systematically reviewed the classical evidence collected from ZHYD, one of the largest collections of CM classical literature in the world.

From this review, the earliest citation judged “most likely” to be HZ was from *Zheng Zhi Zhun Sheng - Yang Yi* 证治准绳·疡医 (1602). Citations were identified by one or multiple search terms. The most commonly used terms were *chan yao* 缠腰 and *huo dan* 火丹 in citations judged “most likely” or possibly to be HZ. From the “most likely” to be HZ citations, the symptoms described in classical literature are consistent with convention medicine.

CHM treatments for HZ in the classical literature were also consistent with contemporary CM textbooks. The most frequently reported formula was *Long dan xie gan tang* 龙胆泻肝汤. Some notable differences were herbs with associated toxicity being present in classical literature, which are not included in contemporary texts. Some herbs frequently used in ancient times are not recommended by current guidelines or textbooks, likely due to their
Hypothetical symptom structure of HZ has been proposed through cluster analysis of the symptoms from “most likely” HZ citations. Another cluster analysis of citations likely to be erysipelas was also conducted to verify the symptom structure, and discover the key symptoms in the huo dan 火丹 skin conditions. Findings show that the characteristic symptoms of heat disease in CM theory may be the key symptoms classification in huo dan 火丹 skin conditions. However, these results are limited by the sample size for cluster analysis.

Implication for clinical practice and research

This research highlights the long history of use of two formulae recommended in contemporary CM textbooks: Long dan xie gan tang 龙胆泻肝汤 and Chu shi wei ling tang 除湿胃苓汤. Other named formulae such as Chai hu qing gan tang 柴胡清肝汤 and Ru yi jin huang san 如意金黄散 (topical) were also reported to use in the management of HZ in ancient times. These formulae may be beneficial for management of HZ and further clinical evidence should be sought.

The hypothetical symptom structure of HZ provides a comprehensive understanding of HZ symptoms through inferential statistical techniques. Moreover, application of such a hypothetical model for symptoms structure formula may provide a new method for
discovering diseases caused by a certain pathogen based on CM theory. Future cluster analyses research will be of value in verifying and refining relevant symptom structure(s).
Chapter 5. General methods of systematic reviews

5.1 Introduction

Systematic reviews (SRs) and meta-analyses are recognised as the highest level of evidence according to the levels of evidence guidelines provided by the Australian National Health and Medical Research Council (NHMRC) [121]. The Cochrane Collaboration is recognised internationally as a leader in SR methodology, through gathering and summarizing the highest quality clinical evidence in Cochrane systematic reviews. The Cochrane Collaboration has been in transforming the way that healthcare decisions and policy are made since its establishment in 1993.

Systematic reviews summarise and evaluate empirical evidence critically to answer specific research questions. Systematic methods are applied to identify and evaluate eligible studies meeting pre-determined criteria. Through evaluating existing evidence and estimating the potential bias, more authentic conclusions and findings can be provided to healthcare policy makers and practitioners [122]. Systematic reviews also assess the methodological quality of the current clinical research evidence and highlight methodological shortcomings in the studies, suggesting directions for future research.

The clinical evidence from SRs published in Chinese language is insufficient to draw conclusions about the efficacy and safety of Chinese medicine (CM) for herpes zoster (HZ)
(see Chapter 2). To address this gap, SRs prepared with a more comprehensive search of both Chinese and English databases and more strict inclusion and exclusion criteria are needed.

This thesis provided a general overview of Chinese herbal medicine (CHM) and acupuncture treatment of HZ from randomised controlled trials, as well as more targeted systematic reviews of specific interventions. The methods for these reviews are described below.

5.2 Aims

This chapter aims to:

1. Present the general methods of overviews of modern literature reporting on CHM and acupuncture therapies for HZ in this research.

2. Present the general methods of SRs of modern literature reporting on Long Dan Xie Gan Tang (LDXGT) 龙胆泻肝汤, and acupuncture plus moxibustion in the management for HZ in this research.

5.3 Overview of randomised controlled trials of Chinese medicine treatments

The general methods of the overviews in this thesis followed the evidence based medicine research approach - Standard Operating Procedures (SOPs) provided by the China-Australia International Research Centre for Chinese Medicine (CAIRCCM).
5.3.1 Study inclusion criteria

5.3.1.1 Study design

Randomised controlled trials (RCTs) using Chinese herbal medicine (CHM) or acupuncture and related therapies to treat people with acute stage HZ were included in these SRs. Non-randomised controlled clinical trials (CCTs), and non-controlled studies identified from the comprehensive database searches were excluded.

5.3.1.2 Population

The definition of acute HZ is less than 28 days from onset of rash [9]. The SRs in this research included studies which included participants based on this criteria. All immunocompetent participants diagnosed with acute stage HZ were included in the SRs, with no limitation of gender or ethnicity. Diagnosis based on clinical presentation or laboratory confirmation (polymerase chain reaction/other laboratory confirmation) were accepted. Considering the medication or dosage might be different for people less than 18 years old, only adults (age ≥18 years) were included.

People with Ramsay Hunt syndrome, zoster encephalitis, zoster ocular diseases, zoster sine herpete, visceral HZ, disseminated HZ, and immunocompromised patients (eg Human Immunodeficiency Virus, cancer, diabetes, pregnant, breastfeeding) were excluded. Participants with post-herpetic neuralgia (PHN) stage were also excluded from this overview.
5.3.1.3 Interventions

Eligible interventions were CHMs (oral or topical CHMs), and acupuncture-related interventions (manual acupuncture/acupressure, electro-acupuncture, moxibustion, ear acupuncture/acupressure), used alone or in combination with the same category of CM therapies (for example, studies using acupressure plus electro-acupuncture as the intervention were included, while studies using CHM plus acupuncture therapies were excluded), or with conventional medicine.

Interventions involving complementary and alternative medicines not used in CM, or HZ vaccine were excluded. CM interventions other than CHM and acupuncture therapies were excluded, because some of the therapies are not commonly used outside of China and several interventions may not be permitted in some countries (for example, point injection and catgut embedding).

5.3.1.4 Comparators

Studies which used clinical practice guideline recommended management (antiviral therapy, pain management therapies) [7, 14], no treatment/waitlist, and placebo/sham treatment as control interventions were included. Studies which used CM therapies or treatments other than those recommended in clinical practice guidelines in the control group were excluded.
5.3.1.5 Outcome measures

The primary outcome was evaluation of pain measured on visual analogue scale (VAS) or other scales such as the MacGill pain questionnaire [123]). Secondary outcomes included PHN incidence, cutaneous outcomes, health-related quality of life (HRQoL), therapeutic effective rate (TER) and adverse events.

Pain severity

Zoster related pain is one of the characteristic symptoms of HZ. One of the most frequently used methods of assessing pain severity is the VAS pain scale, a 10 cm/100 mm line where 0 equates with no pain and 100 mm/10 cm is the maximum imaginable pain. Patients are instructed to mark along the line to indicate their level of pain. The MacGill pain questionnaire is another widely used method to assess the pain severity in clinical studies. It consists primarily of three categories of word descriptions for pain: sensory, affective and evaluative. The questionnaire also includes a 1-5 intensity scale to determine the experience of pain [123].

Incidence of postherpetic neuralgia

Various definitions of PHN have been used for clinical studies, varying from one to six months’ pain persisting after resolution of the HZ rash [124]. Studies which used a defined incidence of PHN were included from data analysis, others which used an undefined incidence of PHN were excluded.
Cutaneous outcomes

The cutaneous outcomes included time to resolution of herpes, time to formation of crusts, and time to resolution of crusts. Timing for measurement may have been made from the onset of the skin rash, randomization process, or beginning of treatment; all possibilities were included. Time was reported in either hours or days.

Health-related quality of life

HZ can remarkably reduce the quality of life of patients. Two disease specific questionnaires and two general wellbeing questionnaires were included. Disease specific questionnaires were the Zoster Brief Pain Inventory (ZBPI) [125] and the Zoster Impact Questionnaire (ZIQ) [125]. General wellbeing questionnaires included the Medical Outcomes Study 36-item Short Form Health Survey (SF36) [126], and the EuroQol-5 Dimensions (EQ-5D) [127].

1. The ZBPI is developed from the Brief Pain Inventory. In this questionnaire, an 11-point Likert scale (0-10) is used to rate the pain in four hierarchies (worst, least, average, and now) [125]. Seven functional categories are also assessed, including general activity, mood, walking ability, work, relations with others, sleep, and enjoyment of life.

2. The ZIQ measures the HZ patients' ability or desire to perform activities of daily living, which are not measured in the ZBPI (for example, eat, travel, shop, concentrate, do leisure activities, and be sexually active) [128]. The responses of ZIQ range from 0 (HZ does not interfere) to 10 (HZ completely interferes).
3. The SF36 and EQ-5D questionnaires measure the general health status. The SF36 evaluates quality of life in eight domains, including vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health [129]. The EQ-5D focuses on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression of patients [130].

*Therapeutic effective rate*

Chinese research guideline recommends TER as the main outcome measurement for treating HZ, where the minimum threshold for effectiveness is 30% resolution of lesion and significant decrease of pain [131]. Studies which used undefined TER were excluded.

*Adverse events*

Adverse event is the outcome measurement evaluating the safety profile of the interventions. Information included the nature and severity of the disease, the number of cases and action taken. Any reported unfavourable or unintended symptoms were included for analysis.

**5.3.2 Identification of studies**

The search terms for interventions and study designs are based on the search strategies developed by The China-Australia International Research Centre for Chinese Medicine [122], based at RMIT University.
5.3.2.1 Identification of search terms

As the comprehensive search was conducted in both English and Chinese language databases, search terms of both languages were identified using different methods. For English language database search, medical subject headings (MeSH) terms, clinical guidelines [7, 9], SRs [132-134], textbook [13], and general reviews [1] were consulted to identify relevant search terms. Search terms in Chinese language used for modern literature research were consistent with the classical literature research. The detail of identification process has been described in section 3.3.2 Identification of search terms. A number of CM textbooks [16-18], dictionary [135] and guideline [12] were consulted to identify the search terms. All of the Chinese terms were reviewed and approved by dermatologists and experts in Guangdong Provincial Hospital of CM.

Terms for interventions were grouped according to the broad categories of CHM and acupuncture. Search terms for different study designs were grouped into three categories: reviews, controlled clinical trials (RCT and CCT) and non-controlled studies (see Appendix 6). In this thesis, only RCTs were included for overviews and systematic reviews.

5.3.2.2 Databases

An initial comprehensive literature search was undertaken from database inceptions to February 2014, with an update search in February 2015. The search included four Chinese databases: CBM (China BioMedical Literature), CNKI (China National Knowledge Infrastructure), CQVIP (Chongqing VIP) and WanFang database; and five English databases:
PubMed, Embase, CINAHL (Cumulative Index of Nursing and Allied Health Literature), CENTRAL (Cochrane Central Register of Controlled Trials) and AMED (Allied and Complementary Medicine Database).

5.3.2.3 Search strategies and sample search strategy

The search strategy was based on combining three blocks of search terms: condition (HZ, zona, shingles, varicellovirus and variants), intervention (CHM, acupuncture and related therapies and variants) and study design (randomised controlled trial, controlled clinical trial and variants) (see Appendix 6). Considering the complexity of the Chinese language and the use of generic terms to describe the interventions, a more comprehensive list of search terms was used to ensure that all relevant citations were captured. References identified through database searches were downloaded from each database, and imported to EndNote reference management software for removal of duplicates.

5.3.3 Data collection and analysis

5.3.3.1 Selection of studies

Two researchers (Kaiyi Wang collected citations from Chinese databases, and Suzi Mansu from English databases) worked to screen and assess titles and abstracts identified from the searches according to the inclusion criteria. Studies were screened against the inclusion criteria outlined above. All full texts of potentially relevant studies were obtained for further assessment. When there were disagreements about the inclusion criteria, the two researchers
would resolve disagreement through discussion. A third researcher (Meaghan Coyle) was consulted when no agreement could be reached.

5.3.3.2 Data extraction

For eligible studies, data were extracted into a pre-defined Microsoft Excel® spread sheet provided by the research centre. The data extracted for each trial included:

- Characteristics: Author, publication year, setting, study design, blinding, number of arms, treatment and follow-up duration, syndrome differentiation, disease stage, severity, duration of condition, and participants (number, age and gender).
- Intervention and comparator: CM syndrome and principle of treatment, intervention and comparator details (type, frequency and duration, route of administration, treatment details).
- Outcomes: Results as reported by group for pain outcomes, cutaneous outcomes, HRQoL, TER, PHN incidence rate and adverse events.

Where there was missing or incomplete data, the trial author was contacted to obtain additional data or to seek clarification via email. If the missing or incomplete data was still not available, the data was excluded from analysis.

5.3.3.3 Data analysis

5.3.3.3.1 Overview of Chinese herbal medicine randomised controlled trials

A summary of the characteristics of included studies was prepared, including the number of
participants, age, gender, duration of HZ, CM syndrome differentiation, and comparators used. Details of CHM interventions, such as formula names, formula function, and herb ingredients, were also summarised and discussed.

5.3.3.2 Overview of acupuncture and related therapies randomised controlled trials

The same approach was applied for acupuncture and related therapies RCTs as was used for CHM RCTs. Acupuncture points and treatment approaches were summarised and discussed.

5.4 Systematic review of clinical evidence

In addition to the general overview, more targeted systematic reviews were conducted to evaluate the evidence for specific CM interventions. Two specific interventions were selected as the focus for the systematic reviews: the CHM formula LDXGT (Chapter 6), and acupuncture combined with moxibustion (Chapter 7). These interventions are both recommended by contemporary CM textbooks and guideline [12, 16-18]. No systematic reviews focussing on these intervention have been identified through English and Chinese database searches. The general methods for the systematic reviews in this thesis followed the methods of Cochrane Handbook for Systematic Reviews and Interventions [122].

5.4.1 Inclusion criteria

As the systematic reviews focussed on specific interventions, the inclusion criteria used in the overview of RCTs (section 5.3) were modified. This involved two key changes:
1. For the population, all age groups were included for the systematic reviews of Long dan xie gan tang 龙胆泻肝汤, compared with only adults being included in the general overview of CHM RCTs.

2. Only studies which used Long dan xie gan tang 龙胆泻肝汤 or acupuncture plus moxibustion alone were included. Studies using integrative medicine (CM plus pharmacotherapies as the intervention) were excluded from the systematic review.

The reason for the adjustment was that this research intended to provide more specific evidence of an individual treatment, rather than a general review of CM treatments for HZ. So, a broader age group and narrower intervention criteria were applied for systematic evaluation. All other inclusion criteria were consistent with those stated in section 5.3.

5.4.2 Identification of studies and data collection

As both the overview of CM therapies and systematic review of clinical evidence were produced from the same data set, the approach for identification of studies and data collection for the systematic review was the same as the overview of RCTs, which has been stated in section 5.3.2 and 5.3.3.

5.4.3 Data analysis for systematic reviews

5.4.3.1 Methodological quality assessment

Two researchers (Kaiyi Wang, Iris Zhou) assessed separately the risk of bias of each selected
study. Risk of bias was assessed as per the instructions of “The Cochrane Collaboration’s tool for assessing risk of bias” in Cochrane Handbook for Systematic Reviews of Interventions (V5.1.0) [122]. Forms of bias included selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias (baseline imbalances, risk from funding source, or claims of fraud). The trials were judged as “High risk of bias”, “Low risk of bias” or “Unclear” for each domain described above. If disagreement occurred, resolution was sought by discussion. A third researcher (Tony Zhang) was consulted if needed.

5.4.3.2 Statistical analysis

*Statistical analysis*

All statistical analyses were carried out in RevMan 5.3 [136]. Where the results of the trials present statistical and clinical homogeneity, meta-analysis was performed to estimate the efficacy of the intervention. For dichotomous data, risk ratios (RR) was used to describe the results. For continuous data, the calculated mean differences (MDs) were reported. All statistical methods were presented with 95% confidence intervals (CIs). A random effects model was used for all meta-analyses.

Results of the included studies were synthesized in a meta-analysis where the interventions were judged to be similar. Subgroup analysis was performed where applicable based on
detected clinical heterogeneity, and different interventions (eg. Modified LDXGT formula, and modified LDXGT formula plus other topical CHM).

**Investigation of heterogeneity**

The clinical heterogeneity was assessed by factors of participants (that is, age and gender), and trial design factors (that is, allocation concealment, blinding, treatment duration, and assessment methods of therapeutic effective rate). Statistical heterogeneity among the included studies for analysis was detected by examining the $I^2$ statistical result. The $I^2$ statistic is used to describe the proportion of total variation which is due to heterogeneity of the studies [137]. If the results of meta-analysis present chi-squared ($\text{Chi}^2$) test with $P<0.1$ and $I^2>50\%$, this was assessed as substantial heterogeneity (as per the Cochrane Handbook [122]). Where 10 or more studies were included in a meta-analysis, potential publication bias was planned to be explored by visual inspection of funnel plot for asymmetry. However, this was not possible due to the number of studies included for the meta-analyses in this research.

**5.5 Chapter summary**

This chapter introduces the general methods of overviews and systematic reviews of CHM treatments and acupuncture therapies in this research. A comprehensive literature search was undertaken in four Chinese and five English databases. In the overviews of CM treatments for HZ, RCTs using CHMs or acupuncture and related therapies to treat people with acute stage HZ were included. Studies which used clinical practice guideline recommended
management no treatment/waitlist, and placebo/sham treatment as comparators were included. The primary outcome was evaluation of pain. Secondary outcomes included PHN incidence, cutaneous outcomes, HRQoL, TER and adverse events. Data were extracted into a pre-defined form, including characteristics, intervention and comparator details, and outcome measurements of the studies. Summaries and discussions of the above information were prepared.

Two specific interventions: the CHM formula LDXGT and acupuncture combined with moxibustion were selected as the focus for the SRs. The general methods followed the methods of Cochrane Handbook for Systematic Reviews and Interventions in this thesis. Methodological quality of the included studies was assessed using the Cochrane Collaboration’s Risk of Bias tool. The statistical analyses were carried out in RevMan 5.3.
Chapter 6. Chinese herbal medicine for herpes zoster

6.1 Introduction

Currently, no overall review of Chinese herbal medicine (CHM) for herpes zoster (HZ) has been identified. Several systematic reviews (SRs) have focused on single herbs [138], CM formulae (dan shen 丹参 formulae) [21], and CM treatment principles (Huo xue hua yu 活血化瘀 formulae) [20]. Current clinical evidence from these SRs shows benefits for CHM in improving cutaneous outcomes and pain management compared to pharmaceutical therapies, with few side effects reported. However, the reviews were limited by diversity in intervention and comparator types. Long dan xie gan tang 龙胆泻肝汤 (LDXGT) is one of the formulae recommended in Chinese medicine (CM) textbooks to treat acute stage HZ. LDXGT has been widely used for many years, however, there remains a paucity of clinical evidence to support its use as a treatment of HZ.

6.2 Aims

In order to summarise the current evidence for CHM treatment of HZ, this chapter will provide an overview of randomised controlled trials (RCTs) of CHM treatments for HZ (the ‘general review’), and will evaluate the efficacy and safety of LDXGT formula systematically in people with HZ (SR).

To achieve these aims, I will summarise the characteristics of, and CHM treatments in RCTs for HZ. I will conduct a systematic evaluation of the efficacy and safety of one formula
(LDXGT) for HZ.

6.3 Methods

The methods for the general review of CHM treatments for HZ, and the SR of LDXGT were described in Chapter 5.

6.4 General review of Chinese herbal medicine for herpes zoster

A total of 31,943 citations were identified through the comprehensive databases search from inception to February 2014, with an update search run in February 2015. After titles and abstracts screening, 5,617 articles were retrieved for full-text eligibility assessment. Ninety-five RCTs were included for this general review (Figure 6.1). Details of formulae and herb ingredients used as the intervention in these studies were all extracted and analysed. Among the included studies, one study included two intervention arms evaluating two topical CHM formulae alone and the details of the two intervention arms were extracted separately. The remaining 94 studies used a two-arm parallel design. Seventy-nine RCTs integrated CHM formulae with pharmacotherapies as the intervention, while 15 RCTs used CHM formulae alone.
Figure 6.1 Flow chart of study selection process: Chinese herbal medicine

CHM, Chinese herbal medicine; CM, Chinese medicine; n: number; RCT: randomised controlled trial.
6.4.1 Characteristics of the included studies

A total of 7,864 adult participants were included in the RCTs [139-233], with median of mean age of 54.4 years in the data reported (see details in Table 6.1). For the studies that reported gender data, the number of male participants was greater than the number of female. The duration of HZ at the time of study inclusion, and the duration of treatment varied.

CM syndrome differentiations were used in the included studies in two ways: as an inclusion criterion for participants (11 studies) [144, 156, 161, 166, 175, 179, 185, 186, 190, 231, 233], and to guide the selection of CHM treatment (14 studies) [139, 144, 156, 161, 166, 175, 179, 185, 186, 190, 216, 218, 231, 233]. The syndromes used for inclusion criterion were also used for guiding CHM treatment in the same studies. The most frequently used syndromes were the pattern/syndrome of qi stagnation and Blood stasis (six studies), Stagnant heat in the Liver meridian (five studies), Liver-Gall Bladder dampness-heat (three studies), and pattern/syndrome of qi stagnation and Blood stasis (three studies). Other syndromes were reported in single studies individually (Table 6.1).

All of the studies adopted at least one type of guideline-recommended pharmacotherapy: antiviral therapies (91 studies, including acyclovir, famciclovir, valacyclovir, ganciclovir, and ribavirin), and/or analgesics (32 studies, including nonsteroidal anti-inflammatory drugs, gabapentin, steroids, and nerve block therapies). In the studies that reported the dosages of antiviral therapies, only eighteen (18) studies used doses which matched those recommended in clinical practice guidelines. Other studies used dosages lower than that recommended in guidelines.
Table 6.1 Chararistic of the included studies

<table>
<thead>
<tr>
<th>Items</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Characteristic</strong></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>7,864</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>18 to 90</td>
</tr>
<tr>
<td>Median of mean age (years)</td>
<td>54.4</td>
</tr>
<tr>
<td>Gender</td>
<td>4,129 males and 3,735 females</td>
</tr>
<tr>
<td>Duration of herpes zoster (mean)</td>
<td>1.2 days to 27 days</td>
</tr>
<tr>
<td>Duration of treatment (range)</td>
<td>5 days up to 6 weeks</td>
</tr>
<tr>
<td>Duration of treatment (median)</td>
<td>10 days</td>
</tr>
<tr>
<td><strong>Syndrome differentiation</strong></td>
<td></td>
</tr>
<tr>
<td>Syndromes used as an inclusion criterion for participants (n)</td>
<td>11</td>
</tr>
<tr>
<td>Syndromes used to guide the selection of CHM treatment (n)</td>
<td>14</td>
</tr>
<tr>
<td>Qi stagnation and Blood stasis (n)</td>
<td>6</td>
</tr>
<tr>
<td>Stagnant heat in the Liver meridian (n)</td>
<td>5</td>
</tr>
<tr>
<td>Liver-Gall Bladder dampness-heat (n)</td>
<td>3</td>
</tr>
<tr>
<td>Qi stagnation and Blood stasis (n)</td>
<td>3</td>
</tr>
<tr>
<td>Spleen dampness encumbrance (n)</td>
<td>1</td>
</tr>
<tr>
<td>Dampness encumbrance in Spleen meridian (n)</td>
<td>1</td>
</tr>
<tr>
<td>Spleen deficiency with dampness-heat (n)</td>
<td>1</td>
</tr>
<tr>
<td>Dampness-heat (n)</td>
<td>1</td>
</tr>
<tr>
<td>Dampness-heat-fire accumulation (n)</td>
<td>1</td>
</tr>
<tr>
<td>Pattern/syndrome of depressed Liver qi transforming into fire (n)</td>
<td>1</td>
</tr>
<tr>
<td>Blood stasis, Liver fire (n)</td>
<td>1</td>
</tr>
<tr>
<td>Liver-Gall Bladder fire (n)</td>
<td>1</td>
</tr>
<tr>
<td>Spleen dampness (n)</td>
<td>1</td>
</tr>
<tr>
<td>Dampness encumbrance (n)</td>
<td>1</td>
</tr>
<tr>
<td>Heat encumbrance (n)</td>
<td>1</td>
</tr>
</tbody>
</table>

n: number of studies

6.4.2 Characteristics of the Chinese herbal medicine treatments in the included studies

Eighty-three formulae, two single herbs and two chemical compounds were identified. Seventy formulae were named formulae (that is, were known classical formulae), and 13 were self-designed formula without names. Of the 70 named formulae, modified Long dan xie gan tang 龙胆泻肝汤 formula was the most frequently used, being evaluated in 25 RCTs. Chu shi wei ling tang (CSWLT) 除湿胃苓汤 was the second most frequently evaluated
formula (four studies in total). LDXGT and CSWLT are recommended by contemporary CM textbooks to treat syndromes of “Stagnant heat in the Liver meridian” and “qi stagnation and Blood stasis” respectively (see Chapter 2). Another two formulae described in Chapter 2, *Tao hong si wu tang* 桃红四物汤 and *Chai hu shu gan san* 柴胡疏肝散, were recommended to be used together. However none of the studies used them as a combination, and they were used separately. Besides the CM textbooks recommended formulae, a variety of formulae were evaluated in the studies, many of which were used only once or twice. It is not surprising that a large number of trials evaluated formulae other than those recommended in CM textbooks. It is common that different formulae are selected based on practitioners’ experience and preference to treat a specific patient’s syndrome. Regardless, the selection of different CHM approaches were guided by the core CM principle of “treatment according to syndrome differentiation”.

Guided by the CM textbook *Formulas 方剂学* [101], the function of the various formulae evaluated in these RCTs was determined. Formulae that have the function of clearing heat, and/or detoxifying were most commonly tested (50 formulae in total). Formulae with the function of activating Blood, and/or dispelling stasis were the second most frequently evaluated (24 in total). Other formulae included the functions of resolving dampness (six formulae), regulating qi (six formulae), tonifying qi (two formulae), cooling Blood and detoxifying (one formula), and moistening dryness and resolving itch (one formula). The main function of the formulae is consistent with the treatment principles for resolving the four main syndromes of HZ in CM. Table 6.2 summarises the details of CHM interventions in multiple included studies. The list of ingredients can be found in Appendix 7 at the end of this chapter.
Table 6.2 Summary of Chinese herbal medicines used in multiple included studies

<table>
<thead>
<tr>
<th>Formula Name (Pinyin or translation, Chinese)</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long dan xie gan tang 龙胆泻肝汤 ▲</td>
<td>25</td>
</tr>
<tr>
<td>Self-designed formulae (unnamed formulae) 自拟方</td>
<td>13</td>
</tr>
<tr>
<td>Chu shi wei ling tang 除湿胃苓汤 ▲</td>
<td>4</td>
</tr>
<tr>
<td>Modified xiao chai hu tang 加味小柴胡汤/小柴胡汤化裁</td>
<td>3</td>
</tr>
<tr>
<td>Xin huang pian (tablet) 新癀片</td>
<td>2</td>
</tr>
<tr>
<td>Wu wei xiao du yin 五味消毒饮</td>
<td>2</td>
</tr>
<tr>
<td>Tao hong si wu tang 桃红四物汤 ▲</td>
<td>2</td>
</tr>
<tr>
<td>Chai hu shu gan san 柴胡疏肝散 ▲</td>
<td>2</td>
</tr>
</tbody>
</table>

▲, CM textbooks recommended formulae

6.4.3 Characteristics of the herb ingredients

One hundred and fifty-eight different herbs were reported in the above formulae. Herbs were standardised through a cross-referenced nomenclature list of commonly used CHMs published by the Chinese Medicine Board of Australia (CMBA, last updated September 2015) [106]. This was due to multiple names of the herbs being used among these studies which refer to the same herbs (for example, zhi zi 栀子 and shan zhi zi 山栀子 are the two common used names of Gardenia jasminoides Ellis, while the standardised name of this herb is zhi zi 栀子). The details of the 11 most frequently used herbs are illustrated in Table 6.3.

Six of the herbs have the clinical function of clearing heat based on CM theory (gan cao 甘草, huang qin 黄芩, long dan cao 龙胆草, zhi zi 栀子, sheng di 生地, and ban lan gen 板蓝根) [234], while four herbs can be used to resolve dampness (huang qin 黄芩, long dan cao 龙胆草, ze xie 泽泻, and che qian zi 车前子). Other herbs have the functions of activating Blood (two herbs: dang gui 当归 and yan hu suo 延胡索), detoxifying (two herbs: gan cao 甘草 and ban lan gen 板蓝根), tonifying Blood (one herb: dang gui 当归), cooling Blood
(one herb: *sheng di* 生地), regulating *qi* (one herb: *chai hu* 柴胡), and tonifying *qi* (one herb: *gan cao* 甘草). Similar to the formulae evaluated in these studies, the main function of the herbal ingredients are consistent with the treatment principles for resolving the four main syndromes of HZ in CM theory.
Table 6.3 Most frequently used herbs in included randomised controlled trials

<table>
<thead>
<tr>
<th>Herb Name (Pinyin, Chinese)</th>
<th>Scientific Name</th>
<th>Pharmaceutical Name</th>
<th>Common English Name</th>
<th>Frequency</th>
<th>Function of the Herbs</th>
</tr>
</thead>
</table>
                           2. *Glycyrrhiza inflata* Bat.  
                           3. *Glycyrrhiza glabra* L. | Glycyrrhizae Radix et Rhizoma | Liquorice Root | 49 | Tonify qi, clear heat and detoxify |
| Huang qin 黄芩              | 1. *Scutellaria baicalensis* Georgi | Scutellariae Radix | Baical Skullcap Root | 43 | Clear heat and resolve dampness |
                           2. *Gentiana scabra* Bge.  
                           3. *Gentiana triflora* Pall.  
| Chai hu 柴胡                | 1. *Bupleurum chinense* DC.  
| Zhi zi 栀子                | 1. *Gardenia jasminoides* Ellis | Gardeniae Fructus | Cape Jasmine Fruit | 38 | Clear heat |
| Dang gui 当归               | 1. *Angelica sinensis* (Oliv.) Diels | Angelicae Sinensis Radix | Chinese Angelica | 36 | Tonify and activate Blood |
| Ban lan gen 板蓝根           | 1. *Isatis indigotica* Fort. | Isatidis Radix | Isatis Root | 31 | Clear heat and detoxify |
| Ze xie 泽泻                 | 1. *Alisma orientalis* (Sam.) Juzep. | Alismatis Rhizoma | Oriental Waterplantain Rhizome | 31 | Resolve dampness |
| Che qian zi 车前子           | 1. *Plantago asiatica* L.  
6.4.4 Discussion

Findings from this general review showed that many study participants were older people, and more male participants were included in the studies. Global epidemiology reports showed that HZ is more common in older people and in women [30, 31, 34]. The reason for the gender-related difference is unclear.

CM syndrome differentiation was widely used in these trials, either as an inclusion criterion for participants or as guidance for CHM treatment. Current CM textbooks included four main syndromes: Stagnant heat in the Liver meridian, Spleen deficiency with damp retention, damp and fire toxin, and qi stagnation and Blood stasis. In the included studies, heat in the Liver meridian, and qi stagnation and Blood stasis were the two most frequently described syndromes. This might provide an explanation of why the formulae which have the function of “clearing heat, and/or detoxifying”, and “activating Blood, and/or dispelling stasis” were most commonly evaluated in these studies. Although there were various syndromes described in these studies, the key CM concepts being described in RCTs included heat, damp, fire, Liver, Spleen, qi stagnation and Blood stasis, which echoes the syndromes seen in CM textbooks and clinical guidelines.

All of the studies used guideline recommended pharmacotherapies as comparators. However, less than one-fifth of the studies used the guideline recommended dosage. None of the studies provided a rationale for dosing. The use of a sub-threshold dose of anti-virals as comparators may exaggerate the efficacy of CHM treatments in the clinical research. The evidence of CHM in the management of HZ from the modern literature is limited by the dosage that these studies used, among other factors.
Based on the current evidence of CHM formulae from this general review, formulae LDXGT and CSWJT recommended in contemporary CM textbooks were both used in two or more studies. While *Tao hong si wu tang* 桃红四物汤 and *Chai hu shu gan san* 柴胡疏肝散 are recommended by textbooks to be used together, none of the included RCTs evaluated this combination. *Tao hong si wu tang* 桃红四物汤 was one of three formulae used in two studies [161, 218], where formula selection was based on syndrome differentiation. The individual use of *Tao hong si wu tang* 桃红四物汤 may be due to two reasons. The first reason relates to the use of syndrome differentiation, where included studies appear to use one formula for one syndrome. The second reason relates to clinical practice. Based on clinician’s experience and knowledge of the patient’s symptoms and syndrome, one formula is selected and modified to add herbs which address the syndrome and symptoms. In the case of *Tao hong si wu tang* 桃红四物汤, the modifications may include key herbs from *Chai hu shu gan san* 柴胡疏肝散. In this situation, the formula is called modified *Tao hong si wu tang* 桃红四物汤, and is not referred to as *Tao hong si wu tang* 桃红四物汤 plus *Chai hu shu gan san* 柴胡疏肝散. From this angle, clinical practice differs from the CM textbooks.

LDXGT was the most commonly used formula among the CHM treatment, and nine of the most frequently used herbal ingredients are listed ingredients of LDXGT, which highlights the importance of this formula in the management of HZ. When considering the function of formulae and herbal ingredients in these studies, most were used to treat the four main syndromes mentioned in the CM textbooks.

The modern literature evidence showed consistency with the classical literature evidence in this research. LDXGT was the most frequently reported formula in both classical and modern
literature. The majority of the most frequently used herbs in modern literature were also the most commonly reported herbal ingredients in “most likely” HZ citations (see Chapter 4, section 4.4.3.2.2 Herbal ingredients). Evidence showed that the information about treatments in classical literature continues to guide the contemporary CM research.

6.5 Systematic review of LDXGT for herpes zoster

6.5.1 Rationale for selecting LDXGT for systematic review

According to the three current standard CM textbooks used in China: *External Chinese medicine 9th edition* [16], *Chinese medicine integrated with Western medicine of Dermatology and Venereology 2nd edition* [17], and *External Chinese medicine 1st edition* [18], HZ is categorized as four main syndrome differentiations. One of these syndromes, Stagnant heat in the Liver meridian, is more commonly seen during the acute stage [16]. LDXGT formula is recommended in CM textbooks to treat this syndrome [16-18], with practitioners advised to modify the formula based on the patient’s individual symptoms. The core herbal ingredients of modified LDXGT generally used in practice include *long dan cao* 龙胆草 (Gentiana species), *zhi zi* 栀子 (Gardenia jasminoides Ellis.), *huang qin* 黄芩 (Scutellaria baicalensis Georgi), *mu tong* 木通 (Akebia quinata Thunb. Decne), *ze xie* 泽泻 (Alisma orientalis Sam. Juzep.), *che qian zi* 车前子 (Plantago species), *chai hu* 柴胡 (Bupleurum species), *gan cao* 甘草 (Glycyrrhiza species), *dang gui* 当归 (Angelica sinensis Oliv. Diels), and *sheng di* 生地 (Rehmannia glutinosa Libosch)[118].

According to the findings from the general review of CHM in the management of HZ, LDXGT was the most frequently used formula in the included studies, accounting for around 20% of all the CHM interventions. This highlights the importance of LDXGT in the CHM...
management of HZ. Although LDXGT formula has been recommended by CM textbooks and widely used for HZ for many years, the clinical evidence has not been synthesized yet to provide a quantification of the likely treatment effect of this formula. Search of the literature did not identify any English or Chinese SRs evaluating LDXGT formula in the management for HZ. To address this gap, this research conducted a SR to evaluate the efficacy and safety of randomised controlled trials of LDXGT formula compared with pharmacotherapy. This SR has been published online in *Phytotherapy Research* [235].

**6.5.2 Results**

**6.5.2.1 Descriptions of studies**

A total of 31,906 citations were identified (see Figure 6.2). After screening titles and abstracts, 117 full-text articles were retrieved for eligibility assessment. Twenty-six RCTs of LDXGT enrolling 2,955 participants were included in the review.

All studies were conducted in both inpatient and outpatient departments of hospitals in China. The age of participants ranged from 11 to 81 years, and the median of the mean age in studies that reported age was 36.1 years. For studies that reported participant gender, 1,623 were male and 1,244 were female (see Table 6.4). One study reported two drop outs in both the intervention and control groups due to loss of contact [147]. All of the studies referred to clinical symptoms for diagnosis, and none of them reported used laboratory detection to confirm the diagnosis.
The outcome measures reported in the included RCTs varied. Outcomes included time to resolution of pain [147, 236-239], PHN incidence [147, 238, 240], time to resolution of lesions [147, 236-238], time to formation of crust [147, 236-239], and cure and therapeutic
effective rates [140, 147, 155, 236-258]. No studies reported VAS pain score or health-related quality of life (HRQoL). The studies reporting on the therapeutic effective rate (TER) used different methods to evaluate effectiveness. Measurement of effectiveness was based on lesion count (\( \geq 30\% \) reduction in lesion count and significant reduction of pain considered as effective) [140, 155, 237, 239, 241-244, 246-248, 250, 253-255, 257, 258], symptom severity (resolution in pain and lesion count considered as effective) [240, 245, 249, 252, 256], or change in pain severity (30% or greater change from baseline considered as effective) [147, 236, 251].

6.5.2.2 Details of intervention

All studies administered modified LDXGT formula decoction orally to participants, with treatment duration varying from seven days to one month (Table 6.4). Twelve studies used modified LDXGT formula alone [147, 155, 241-245, 249, 250, 252, 254, 255], one study combined LDXGT with other CHM formula for oral use [140], and the remaining 13 studies combined LDXGT with topical CHM formula [236-240, 246-248, 251, 253, 256-258]. All studies used antiviral therapies as their comparators, with acyclovir and valacyclovir the most common pharmaceuticals used. Other pharmaceuticals included analgesic therapies [155, 238, 240, 248, 249, 253, 256] and vitamins B1 and B12 [140, 155, 237, 239, 240, 248, 249, 252, 257, 258].
### Table 6.4 Characteristics and intervention details of the included trials of LDXGT

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Treatment Duration, Follow-up Duration</th>
<th>Duration of Condition</th>
<th>No. of Participants Randomised/Assessed, Dropouts</th>
<th>Age (mean (±SD) or range)</th>
<th>Dose</th>
<th>Comparators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ding, 2011 [241]</td>
<td>7 days, NS</td>
<td>Total: 2-7 days</td>
<td>I: 26/26, 0 C: 24/24, 0 I: 16-63 C: NS</td>
<td>One package, one dosage per day.</td>
<td>Acyclovir 0.2 g, 5 times per day, po; acyclovir cream bid ext.</td>
<td></td>
</tr>
<tr>
<td>Gu, 2008 [242]</td>
<td>10 days, 2 courses, NS</td>
<td>I: 2-19 days C: 2-29 days</td>
<td>I: 66/66, 0 C: 62/62, 0 I: 17-70 C: 18-62</td>
<td>One package, one dosage per day.</td>
<td>Acyclovir 0.4 g, qid, po.</td>
<td></td>
</tr>
<tr>
<td>Li, 2012 [243]</td>
<td>7 days, NS</td>
<td>Total: 1-4 days</td>
<td>I: 109/109, 0 C: 105/105, 0 Total: 28-73</td>
<td>One package, three dosages per day.</td>
<td>Acyclovir (5 mg/kg). iv; methylrosanilinium chloride solution or calamine lotion, ext.</td>
<td></td>
</tr>
<tr>
<td>Li, 2010 [244]</td>
<td>10 days, 2 courses, NS</td>
<td>I: 2-19 days C: 2-29 days</td>
<td>I: 60/60, 0 C: 60/60, 0 I: 17-70 C: 18-68</td>
<td>One package, one dosage per day.</td>
<td>Acyclovir 0.4 g, qid, po.</td>
<td></td>
</tr>
<tr>
<td>Lin, 2014 [245]</td>
<td>7 days, NS</td>
<td>NS</td>
<td>I: 50/50, 0 C: 50/50, 0 I: 20-70 C: 22-68</td>
<td>One to three packages, three to six dosages per day.</td>
<td>Acyclovir 0.2-0.8 g, 5 times per day, po.</td>
<td></td>
</tr>
<tr>
<td>Liu, 2001 [249]</td>
<td>7-10 days, NS</td>
<td>Total: &lt;1 week</td>
<td>I: 81/81, 0 C: 40/40, 0 I: m=41 C: m=45</td>
<td>One package, two dosages per day.</td>
<td>Moroxydine hydrochloride 0.2g; vit B1 20 mg; cimetidine 0.2 g; indomethacin 25 mg, tid, po.</td>
<td></td>
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<td>First Author, Publication Year</td>
<td>Treatment Duration, Follow-up Duration</td>
<td>Duration of Condition</td>
<td>No. of Participants Randomised/Assessed, Dropouts</td>
<td>Age (mean (±SD) or range)</td>
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<tr>
<td>Shi, 2013 [250]</td>
<td>10 days, NS</td>
<td>I: m=13.4 (2-21) days C: m=15.3 (2-27) days</td>
<td>I: 29/29, 0 C: 29/29, 0</td>
<td>I: 18-69 C: 21-70</td>
<td>One package, one dosage per day.</td>
<td>Acyclovir 0.4 g, qid, po.</td>
</tr>
<tr>
<td>Shi, 2001 [155]</td>
<td>7 days, NS</td>
<td>I: 2-10 days C: 2-9 days</td>
<td>I: 60/60, 0 C: 40/40, 0</td>
<td>I: m= 34.7 C: m= 36.1</td>
<td>One package, two dosages per day.</td>
<td>Acyclovir 0.2 g, five times per day; vit B1 20 mg; indomethacin 25 mg tid, po; polyinosinic-polycytidylic acid injection 2 mg qd, im.</td>
</tr>
<tr>
<td>Wang, 2008 [252]</td>
<td>NS, NS</td>
<td>I: m=8.3 (3-15) days C: m=9.6 (2-22) days</td>
<td>I: 51/51, 0 C: 51/51, 0</td>
<td>I: 20-52 C: 18-50</td>
<td>One package, two dosages per day.</td>
<td>Vit B1 20 mg; vit C 0.3 g; indomethacin 25 mg, tid, po; ribavirin 0.5 g; penicillin 4.8 million IU qd, iv.</td>
</tr>
<tr>
<td>Xu, 2014 [254]</td>
<td>7 days, NS</td>
<td>NS</td>
<td>I: 109/109, 0 C: 109/109, 0</td>
<td>Total: 30.2±3.1</td>
<td>One package, three dosages per day.</td>
<td>Acyclovir iv; methylrosanilinium chloride solution or Calamine lotion ext.</td>
</tr>
<tr>
<td>Yang, 2014 [255]</td>
<td>NS, NS</td>
<td>I: m=15.2 (3-24) days C: m=15.5 (4-25) days</td>
<td>I: 20/20, 0 C: 20/20, 0</td>
<td>I: 18-69 C: 19-67</td>
<td>One package, one dosage per day.</td>
<td>Acyclovir 0.5 g, tid, po (antibiotics when infection).</td>
</tr>
<tr>
<td>Zhou, 2004 [147]</td>
<td>10 days, 3/7/11/15/28 days</td>
<td>I: 2.3±0.7 days C: 2.4±0.6 days</td>
<td>I: 76/74, 2 C: 76/74, 2</td>
<td>I: 41.2±16.5 C: 38.5±17.2</td>
<td>One package, two or three dosages per day.</td>
<td>Acyclovir 0.2 g, 5 times per day, po.</td>
</tr>
<tr>
<td>First Author, Publication Year</td>
<td>Treatment Duration, Follow-up Duration</td>
<td>Duration of Condition</td>
<td>No. of Participants Randomised/Assessed, Dropouts</td>
<td>Age (mean ±SD) or range</td>
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<tr>
<td><strong>Modified LDXGT formula &amp; other CHM formula (oral)</strong></td>
<td></td>
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<tr>
<td>Jiang, 2010 [140]</td>
<td>7 days, NS</td>
<td>1-7 days</td>
<td>I: 110/110, 0 C: 110/110, 0</td>
<td></td>
<td></td>
<td>Valacyclovir 0.25 g, tid, po; thymosin 30 mg, qd, iv; vit B12 0.25 mg im, qd.</td>
</tr>
<tr>
<td><strong>Modified LDXGT formula &amp; other CHM formula (topical)</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Fu, 2014 [236]</td>
<td>10 days, 1 month</td>
<td>Total: 1-7 days</td>
<td>I: 30, 0 C: 30, 0</td>
<td>Total: 18-70</td>
<td></td>
<td>Valacyclovir 0.3 g, bid, po.</td>
</tr>
<tr>
<td>Li, 2011 [240]</td>
<td>1-2 weeks, NS</td>
<td>NS</td>
<td>I: 70, 0 C: 50, 0</td>
<td>Total: 18-65</td>
<td></td>
<td>Polyinosinic-polycytidylic acid injection 2 mg; vit B12 100 mg, im, every 2 days; vit B1 10 mg; aspirin 0.3 g tid, po.</td>
</tr>
<tr>
<td>First Author, Publication Year</td>
<td>Treatment Duration, Follow-up Duration</td>
<td>Duration of Condition</td>
<td>No. of Participants Randomised/Assessed, Dropouts</td>
<td>Age (mean ±SD) or range</td>
<td>Dose</td>
<td>Comparators</td>
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<tr>
<td>Li, 2013 [237]</td>
<td>14 days, NS</td>
<td>NS</td>
<td>I: 114, 0 C: 106, 0</td>
<td>I: 54.3±10.46 C: 55.31±10.43</td>
<td>Decoction: One package, two dosages per day; <em>Kang fu xin ye</em> (ingredients, NS), bid, ext.</td>
<td>Acyclovir 0.2 g qid; vit B12 50 μg tid, po; mupirocin cream qid, ext.</td>
</tr>
<tr>
<td>Liu, 2012 (a) [246]</td>
<td>1 month, 1 year follow for Intervention group</td>
<td>Total: 1-7 days</td>
<td>I: 64, 0 C: 64, 0</td>
<td>I: m=57 (51-63) C: m=58 (43-64)</td>
<td>One package, one dosage per day; <em>Er wei ba du san</em> (<em>xiong huang and bai fan</em>), bid, ext.</td>
<td>Acyclovir 0.75 g qd, iv; acyclovir cream bid, ext.</td>
</tr>
<tr>
<td>Liu, 2014 [245]</td>
<td>14 days, NS</td>
<td>NS</td>
<td>I: 60, 0 C: 60, 0</td>
<td>I: 52.81±4.25 C: 51.38±4.89</td>
<td>Decoction: One package, three dosages per day; <em>Bing chan</em> cream (ingredients NS), tid, ext.</td>
<td>Acyclovir 0.5 g; cefoxitin 4.0g, qd, iv.</td>
</tr>
<tr>
<td>Liu, 2012 (b) [248]</td>
<td>7 days, NS</td>
<td>NS</td>
<td>I: 15, 0 C: 15, 0</td>
<td>I: m=48 (16-60) C: m=50 (16-60)</td>
<td>Decoction: One package, two dosages per day; <em>Qing liang gao</em> (ingredients NS), bid, ext.</td>
<td>Acyclovir 0.4 g tid; vit. B1 10 mg tid; vit B12 500 μg tid, po (fenbid po, when necessary).</td>
</tr>
<tr>
<td>First Author, Publication Year</td>
<td>Treatment Duration, Follow-up Duration</td>
<td>Duration of Condition</td>
<td>No. of Participants Randomised /Assessed, Dropouts</td>
<td>Age (mean (±SD) or range)</td>
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<td>Comparators</td>
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<tr>
<td>Shi, 2002 [238]</td>
<td>7 days, NS</td>
<td>I: m=5.4(2-10) days C: m=6.3 (3-11) days</td>
<td>I: 61, 0 C: 61, 0</td>
<td>I: m=56.2 (11-81) C: m=55.3 (12-79)</td>
<td>Decoction: One package, three dosages per day; <em>Liu shen wan</em> (ingredients NS), 1-2 times per day, ext.</td>
<td>Acyclovir 10 mg/kg qd, iv; indomethacin 25 mg, tid, po (methylrosanilinium chloride solution or calamine lotion when necessary).</td>
</tr>
<tr>
<td>Wang, 1999 [251]</td>
<td>NS, NS</td>
<td>NS</td>
<td>I: 96, 0 C: 60, 0</td>
<td>I: m=46 (25-66) C: m=43 (23-62)</td>
<td>Decoction: One package, three dosages per day; <em>Qing dai san</em> (<em>qing dai, hua shi, and sheng shi gao</em>), tid, ext.</td>
<td>Moroxydine hydrochloride tablets 0.2 g, tid, po; penicillin 8 million IU qd, iv.</td>
</tr>
<tr>
<td>Wang, 2007 [253]</td>
<td>14 days, NS</td>
<td>I: 1-13 days C: 1-15 days</td>
<td>I: 64, 0 C: 42, 0</td>
<td>I: 14-65 C: 17-72</td>
<td>Decoction: One package, two dosages per day; <em>San huang cream</em> (<em>da huang, huang bai, huang qin, and bing pian</em>), qd, ext.</td>
<td>Acyclovir 0.2 g, tid, po; polyinosinic-polycytidylic acid injection 4 ml, every 2 days, im; ribavirin 400 mg, qd, iv (indomethacin, VOLTAREN® when necessary).</td>
</tr>
<tr>
<td>Ye, 2000 [256]</td>
<td>21 days, NS</td>
<td>I: 2-6 days C: 1-7 days</td>
<td>I: 33, 0 C: 33, 0</td>
<td>I: m=52.3 (30-65) C: m=50.1 (32-60)</td>
<td>Decoction: One package, three dosages per day; <em>Jin huang san</em> (ingredients NS), bid, ext.</td>
<td>Acyclovir 250 mg, tid, iv; cimetidine 0.4 g qd, iv; indomethacin 25 mg, tid; prednisone 10 mg tid, po; acyclovir cream bid, ext (antibiotics when necessary).</td>
</tr>
<tr>
<td>First Author, Publication Year</td>
<td>Treatment Duration, Follow-up Duration</td>
<td>Duration of Condition</td>
<td>No. of Participants Randomised /Assessed, Dropouts</td>
<td>Age (mean (±SD) or range)</td>
<td>Dose</td>
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<tr>
<td>Zheng, 2009 [257]</td>
<td>NS, NS</td>
<td>I: 1-30 days C: 3-30 days</td>
<td>I: 32, 0 C: 32, 0</td>
<td>I: 15-75 C: 15-65</td>
<td>Decoction: One package, two dosages per day; CM herbs (xiong huang, bing pian, yun nan bai yao, and lv cha): 3-5 times per day, ext.</td>
<td>Acyclovir 0.1-0.2 g tid, po; vit B12 250-500 μg; vit B1 100mg qd, im; acyclovir cream 3-5 times per day, ext.</td>
</tr>
<tr>
<td>Zhou, 2011 [239]</td>
<td>14 days, NS</td>
<td>I: 5 days - 2 months C: 7 days - 2 months</td>
<td>I: 40, 0 C: 40, 0</td>
<td>I: 45.2±18.5 C: 47.7±16.3</td>
<td>Decoction: One package, three dosages per day; Qing huang san (qing dai, huang bai, chuan xiong, huang lian, and yan hu suo) bid, ext.</td>
<td>Acyclovir 0.4 g tid; vit B1 10 mg tid, po; acyclovir cream tid, ext.</td>
</tr>
<tr>
<td>Zhu, 2004 [258]</td>
<td>10 days, NS</td>
<td>Total: m=4.1 (2-8) days</td>
<td>I: 30, 0 C: 30, 0</td>
<td>Total: 18-72</td>
<td>Decoction: One package, two dosages per day; Calamine lotion: ext.</td>
<td>Acyclovir 0.2 g 5 times a day, vit B12 qd, po.</td>
</tr>
</tbody>
</table>

bid, twice a day; C, control group; ext, external use; I, intervention group; im, intramuscular injection; iv, intravenous injection; m, mean; NS, not specified; po, oral use; qd, once a day; qid, four times a day; SD, standard deviation; tid, three times a day; vit, vitamin.
6.5.2.3 Methodological quality

Methodological quality of included studies was low to moderate (see Figure 6.3) Two studies were assessed as low risk of bias for sequence generation as a random number generator was used [236, 255]. Three studies were assessed as high risk as they randomized participants according to visit order [239, 242, 252]. None of the studies mentioned the method of allocation concealment, and all were assessed as unclear risk. For blinding of participants, personnel and outcome assessors, no details were provided and the potential risk for all studies was assessed as unclear. One study reported loss of contact with two participants in both the intervention and control groups. As the number of withdrawals and reasons were equal across groups, the study was assessed as low risk for incomplete outcome data [147]. In all other studies, data were available for all participants, and were assessed as low risk of bias. None of the studies provided the details of the trial protocol or trial registration, and were all assessed as unclear risk for selective outcome reporting. One study was assessed as unclear risk for other bias as the intervention group size was double that of the control group with no reason provided [249]. All other studies were assessed as low risk of bias for other bias as no baseline imbalances, risk from funding source, or claims of fraud were identified.
Figure 6.3: Summary of risk of bias assessment of included studies
6.5.3 Effects of the intervention

6.5.3.1 Modified LDXGT alone

Twelve studies compared the clinical effect of modified LDXGT formula alone with pharmacotherapy [155, 239, 241-245, 249, 250, 252, 254, 255].

6.5.3.1.1 Time to resolution of pain

One study reported that resolution of pain was achieved 2.6 days earlier in those who received modified LDXGT formula compared to pharmacotherapy, with significant statistical difference shown (MD -2.60 days; 95% CI -3.61 to -1.59) (see Figure 6.4) [147].

![Figure 6.4 Modified LDXGT vs pharmacotherapy: time to resolution of pain](image)

6.5.3.1.2 Cutaneous outcomes

One study reported that time to resolution of lesions was achieved 0.5 days earlier in the participants who received modified LDXGT, compared to pharmacotherapy (MD -0.50 days; 95% CI -0.94 to -0.06) (see Figure 6.5) [147].

![Figure 6.5 Modified LDXGT vs pharmacotherapy: cutaneous outcomes](image)
The study also showed benefits of modified LDXGT alone in shortening the time to formation of crusts by 1.2 days compared to pharmacotherapy (MD -1.20 days; 95% CI -2.31 to -0.09) (see Figure 6.6) [147].

6.5.3.1.3 Postherpetic neuralgia incidence rate

One study reported the PHN incidence rate [147]. In this study, PHN was defined as pain continuing after resolution of crusts. No significant difference between modified LDXGT and pharmacotherapy groups was seen regarding incidence of PHN (RR 0.29; 95% CI 0.06 to 1.33) (see Figure 6.7).
6.5.3.1.4 Therapeutic effective rate

Eight studies reported on TER referring to the Chinese research guideline, which defines measurement of effectiveness based on lesion count (≥30% reduction in lesion count and significant reduction of pain considered as effective) [131]. Statistical heterogeneity was detected for the outcome TER (I²=67%), so data were not pooled for analysis (see Figure 6.8) [155, 241-244, 250, 254, 255]. The majority of studies showed no benefit of LDXGT alone in improving symptoms.

![Figure 6.8 Modified LDXGT vs pharmacotherapy: therapeutic effective rate (based on guideline)](image)

One study reported on TER referring to the Therapeutic Index (TI). Therapeutic Index was calculated as follows:

\[
\frac{\text{Symptoms Scores before treatment} - \text{Symptoms Scores post treatment}}{\text{Symptoms Scores before treatment}} \times 100\%
\]

where TI >30% was considered as effective [147]. No significant difference was seen in TI between intervention and pharmacotherapy (RR 1.03; 95% CI 0.98 to 1.08) (see Figure 6.9).
Three studies reported on TER using investigator-developed criteria, where all defined effectiveness as “resolution of part of redness, pain and lesions, with crusts remained and PHN occurred”. Since the assessment of resolution of above symptoms was not clear, the decision was made not to pool the result together to conduct meta-analysis and results are presented individually (see Figure 6.10). Results from all individual studies showed benefits of using modified LDXGT alone, with improved TER based on investigator-developed criteria compared with pharmacotherapy [245, 249, 252].

6.5.3.1.5 Cure rate

Twelve studies reported on the cure rate using the same definition: resolution of all clinical symptoms [155, 239, 241-245, 249, 250, 252, 254, 255]. Results of meta-analyses showed
that modified LDXGT alone could significantly improve the chance of resolving both cutaneous and pain symptoms compared with pharmacotherapy (RR 1.62, 95% CI 1.47 to 1.79; I²=0%) (see Figure 6.11).

![Figure 6.11 Modified LDXGT vs pharmacotherapy: cure rate](image)

**6.5.3.2 Modified LDXGT plus other oral Chinese herbal medicine formula**

One study combined modified LDXGT with other oral CHM formula [140]. TER and cure rate were the two outcome measures reported. Results showed that modified LDXGT plus *Chuan xiong cha tiao san* 川芎茶调散 formula improved the effective rate more than pharmacotherapy based on reduction in lesion count (RR 1.29; 95% CI 1.13 to 1.48) (see Figure 6.12).
Figure 6.12 Modified LDXGT plus oral Chinese herbal medicine vs pharmacotherapy: therapeutic effective rate

Benefits were also seen in improving the cure rate defined as resolution of all clinical symptoms (RR 1.53; 95% CI 1.07 to 2.19), although variation in results was indicated by wide confidence intervals (see Figure 6.13).

Figure 6.13 Modified LDXGT plus oral Chinese herbal medicine vs pharmacotherapy: cure rate

6.5.3.3 Modified LDXGT plus other topical CHM formula

Thirteen studies combined LDXGT with topical CHM formula as intervention, which was compared with pharmacotherapy [236-240, 246-248, 251, 253, 256-258].

6.5.3.3.1 Time to resolution of pain

Four studies reported on time to resolution of pain [236-239]. Meta-analysis was not possible due to considerable heterogeneity which couldn’t be explained through planned sensitivity
analysis ($I^2=94\%$). Results from all individual studies showed resolution of pain occurred earlier in those who received modified LDXGT plus other topical CHM formula (see Figure 6.14).

**Figure 6.14** Modified LDXGT plus topical Chinese herbal medicine vs pharmacotherapy: time to resolution of pain

### 6.5.3.3.2 Cutaneous outcomes

Three studies reported on time to resolution of lesions [236-238]. Studies could not be pooled for meta-analysis due to considerable heterogeneity which couldn’t be explained through planned sensitivity analysis ($I^2=52\%$). Resolution of lesions occurred earlier in two studies which combined LDXGT with other topical CHM formula (see Figure 6.15).
Figure 6.15 Modified LDXGT plus topical Chinese herbal medicine vs pharmacotherapy: time to resolution of lesions

Four studies reported on time to formation of crusts [236-239]. Crusts formation was achieved 1.13 days earlier with LDXGT plus other topical CHM formula than with pharmacotherapy (95% CI -1.44 to -0.83; I²=13%) (see Figure 6.16).

Figure 6.16 Modified LDXGT plus topical Chinese herbal medicine vs pharmacotherapy: time to formation of crusts

6.5.3.3.3 Postherpetic neuralgia incidence rate

Two studies reported on PHN incidence, but did not describe the criteria for assessment [238, 240]. The results demonstrated a significant reduction in the incidence of PHN in those who received modified LDXGT formula plus other topical CHM formula compared to those who received pharmacotherapy (RR 0.14; 95% CI 0.03 to 0.74; I²=32%) (see Figure 6.17)
6.5.3.3.4 Therapeutic effective rate

Eight studies which reported on the TER based on reduction in lesion count were pooled for meta-analysis [237, 239, 246-248, 253, 257, 258]. The chance of achieving a 30% or greater reduction in lesion count with LDXGT plus other topical CHM formula was 1.12 that of pharmacotherapy (95% CI 1.06 to 1.17; $I^2=13\%$) (see Figure 6.18).

One study reported on TER using the TI calculation method, and defined TI >30% as effective) [236]. No significant difference was seen between intervention and pharmacotherapy in effective rate based on reduction of symptoms scores (see Figure 6.19).
Three other studies reported on TER using investigator-developed criteria [240, 251, 256]. The decision was made not to pool the results together to perform meta-analysis, since no clear assessment criteria was provided. Results from all of the individual studies show TER was better in those who received LDXGT plus topical CM formula than pharmacotherapy (see Figure 6.20).

6.5.3.3.5 Cure rate

Twelve studies reported on the cure rate [147, 236, 237, 240, 246-248, 251, 253, 256-258]. Cure rate was defined as resolution of all clinical symptoms among these studies. At the end of treatment, the chance of resolving both cutaneous and pain symptoms with LDXGT plus...
other topical CHM formula was 1.33 times that of pharmacotherapy (95% CI 1.22 to 1.45; $I^2=25\%$) (see Figure 6.21).

### Figure 6.21 Modified LDXGT plus topical Chinese herbal medicine vs pharmacotherapy: cure rate

#### 6.5.4 Adverse events

Three cases of gastrointestinal (GI) adverse events were reported in the intervention group in one study [147]. In the pharmacotherapy groups, two cases of vertigo and fatigue and 10 cases of GI adverse events were reported in four studies [140, 147, 250, 255].

#### 6.5.5 Discussion

##### 6.5.5.1 Discussion of systematic review of LDXGT in the management of herpes zoster

Findings from this review showed that when used alone, modified LDXGT shortened the time to relieve pain effectively. The combination of modified LDXGT with topical formulae may reduce time to resolution of pain, although statistical heterogeneity was detected. LDXGT alone or in combination with other topical CHM formula reduced the incidence of PHN and improved cutaneous outcomes. None of the studies reported on HRQoL, therefore
the impact of LDXGT for this outcome remains unclear. LDXGT was found to improve the
cure rate and TER when used alone, or in combination with either oral or topical CHMs.
These results should be interpreted with caution, as considerable statistical heterogeneity was
detected and the outcome has not been validated.

Modified LDXGT was well tolerated by patients, with fewer side effects reported than
pharmacotherapy, although few studies reported on this outcome. GI complaints are common
adverse events with CHM [259, 260]. Adverse events were reported in studies using
acyclovir or valacyclovir as the comparator. Vertigo, fatigue and GI discomfort are all known
side effects of these antiviral therapies. Modified LDXGT may be considered a safe therapy
for HZ based on the trials in this review.

No SRs of LDXGT were identified through the database search. The benefits seen with
modified LDXGT plus other topical formulae in this review were similar to those seen with
dan shen 丹参 and huo xue hua yu 活血化瘀 formulae in terms of incidence of PHN and
TER [20, 21]. In CM theory, formulae such as those based on dan shen 丹参 and huo xue hua
yu 活血化瘀 formulae are clinically recommended for pain after resolution of the lesions [16,
261]. Therefore, this review of LDXGT is clinically important in evaluating CHM for
addressing the acute symptoms of HZ.

The pathogenesis of acute pain and cutaneous symptoms in HZ is the inflammatory response
and necrosis of the varicella zoster virus infected sensory nerve [14]. The key herb in
LDXGT, *long dan cao* 龙胆草 (*Gentiana scabra* Bunge.), has been evaluated in experimental studies, with evidence supporting anti-inflammatory actions. Secoiridoid glycosides from *long dan cao* 龙胆草 (*Gentiana scabra* Bunge.) have been shown to inhibit activity of interleukin-6 (IL-6), nitric oxide (NO), and tumour necrosis factor alpha (TNFα) in lipopolysaccharide (LPS) induced RAW264 cells [262], and interleukin-2 (IL-2) in bone-marrow derived dentritic cells (BMDCs) [263], suggesting inflammatory mediation. The anti-inflammatory actions of the constituents may contribute to relieving the acute inflammatory response in patients with HZ, which may contribute to the clinical effect of hastening alleviation of pain and improving cutaneous outcomes of LDXGT formula.

This review also found that the incidence of PHN in people who received LDXGT combined with topical CHM was less than those who received pharmacotherapy. The constant chronic pain in PHN arises from inflammatory damage to peripheral nerves and the central nervous system caused by the virus or immune response, and secondary changes in the nociceptive pathway [9, 264]. The anti-inflammatory actions of the herbs in LDXGT may contribute to the lower PHN incidence rate seen in this review.

Antiviral therapy is recommended as first-line therapy for HZ in clinical practice guidelines [7, 9, 14]. The dose recommended for valacyclovir is one gram three times daily for seven days, and for acyclovir is 0.8 gram five times daily for seven days (5 to 7.5 mg/kg, three times daily for intravenous therapy) [7]. None of the included studies used the dosage as recommended, nor did they provide a rationale for dosing. No Chinese guidelines for
conventional medical management of HZ could be identified to explain the doses used in included studies. Therefore, it is unclear whether the benefit with LDXGT seen in this review would be different when compared with accepted dosing regimens.

Several studies used comparators other than those recommended in guidelines [140, 155, 239, 240, 249, 251, 252, 257, 258]. This included other antivirals and vitamins. In China, the prescribing practice for HZ often combines antiviral and analgesic therapy with vitamins B1 and B12 to repair infected nerves and regulate the function of synaptic transmission [265, 266]. It is unclear whether the addition of vitamin B1 or B12 alters the efficacy of antiviral and analgesic therapies, and results should be interpreted in light of this.

### 6.5.5.2 A further discussion of therapeutic effective rate used in LDXGT studies

Therapeutic effective rate (TER) is an important outcome measurement in CM research, and was utilised in the studies included in the SR of LDXGT. Twenty-five out of the 26 included studies reported this outcome. However, the assessment criteria for TER differed among these studies. The TER reported in included studies fell into one of three categories (described below).

#### 6.5.5.2.1 Resolution of lesion count

Nine studies [140, 155, 237, 239, 243, 246, 248, 253, 254] referred to the criteria described in *The Standard of Diagnosis and Assessment of Treatment Effects of Dermatological Conditions in Chinese Medicine* 中医病症诊断疗效标准 [131]. This guideline is widely
used in clinical practice and research. The HZ section of this guideline recommends TER as the main outcome measurement for treating HZ, where the minimum threshold for effectiveness is 30% resolution of lesion.

One study [247] used the criteria from Clinical Dermatology 临床皮肤病学 [267]. In this textbook, the resolution of lesion count is also the criterion for assessment. However, the minimum threshold for effectiveness in this textbook (70%) is much higher than the guideline recommends. For the purpose of meta-analysis, it was considered appropriate to pool this data with those using the guideline above, since $\geq 70\%$ resolution of lesion is certainly within the range of $\geq 30\%$.

### 6.5.5.2.2 Resolution of herpes zoster-related symptoms

Six studies [240, 245, 249, 251, 252, 256] used investigator-developed criteria to assess the participant’s symptoms as cured, improved or not improved. The methods for assessment were not clear. The description provided in included studies referred to “resolution of part of redness, pain and lesions, with crusts remained and PHN occurred” as the criteria for improvement. No explicit value of the resolution of any symptoms was provided. The description that “PHN occurred” is unusual, as this would not be considered as an improvement. This may be an error in the reporting of assessment criteria in these studies. The results of these studies were considered not appropriate to pool for meta-analysis. As such, data were presented individually.
6.5.5.2.3 Therapeutic Index

Three studies used the TI to assess symptoms. In studies which reported this outcome, researchers stated that this method was adapted from the guideline, where the minimum threshold for effectiveness is 30% of TI. The difference between TI and the guideline is that TI includes a scoring system for calculation, which covers lesion count, pain and PHN incidence rate. Compared with the guideline, the scoring system used to calculate the treatment effect is an improvement on the subjective TER, eg. patient pain sensation evaluated in the studies of HZ. However, the detail of the scoring system was not provided by these studies, which further limits interpretation. Table 6.5 summarizes the different assessing criteria of TER.
### Table 6.5 Different criteria of calculating therapeutic effective rate

<table>
<thead>
<tr>
<th>Items</th>
<th>Assessing Criteria</th>
<th>Cure</th>
<th>Significant Improvement</th>
<th>Improvement</th>
<th>No Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Standard of Diagnosis and Assessment of Treatment Effects of Dermatological Conditions in Chinese Medicine (《中医病症诊断疗效标准》)</td>
<td>Resolution of lesion count and pain</td>
<td>Resolution of lesion and pain</td>
<td>NA</td>
<td>Resolution of lesion count (\geq 30%), and significant decrease of pain</td>
<td>Resolution of lesion count &lt;30%, and pain still exists</td>
</tr>
<tr>
<td>Clinical Dermatology (《临床皮肤病学》)</td>
<td>Resolution of lesion count</td>
<td>Resolution of lesion (\geq 95%)</td>
<td>NA</td>
<td>Resolution of lesion count (\geq 70%)</td>
<td>No change or worse</td>
</tr>
<tr>
<td>Resolution of herpes zoster-related symptoms (self-made criteria)</td>
<td>Resolution of herpes zoster-related symptoms</td>
<td>Resolution of part of redness, pain and lesions, with crusts remained and PHN occurred</td>
<td>NA</td>
<td>Part of the redness, pain, and lesion disappear, with crusts, and PHN</td>
<td>No improvement</td>
</tr>
<tr>
<td>TI</td>
<td>TI: ([(\text{symptoms scores before treatment})-(\text{symptoms scores post treatment})]/(\text{symptoms scores before treatment}) *100%]</td>
<td>(\text{TI}=100%)</td>
<td>(\text{TI}&gt;60%)</td>
<td>(60%&gt;\text{TI}&gt;30%)</td>
<td>(\text{TI}&lt;30%)</td>
</tr>
</tbody>
</table>

NA, not applicable; PHN, post-herpetic neuralgia; TI, therapeutic index
6.5.6 Limitations of the LDXGT systematic review

The findings of this review are limited by the methodological quality of the included studies. Few studies reported details relating to the risk of bias domains sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, and this is likely to contribute to bias and heterogeneity. The validity of the evidence for LDXGT was limited by the variability in both intervention and comparator groups. The outcomes reported in the included studies have not been validated, and none of the studies reported on HRQoL. The findings should be interpreted in light of these limitations.

6.5.7 Chapter summary

6.5.7.1 Implication for future research

The overview of the CHM treatments for HZ showed that a variety of formulae, single herbs and chemical compounds isolated from the herbs had been evaluated by various RCTs. However, the evidence of CHM treatments for HZ is limited by the sub-threshold dosage of antiviral therapies as guidelines recommended. Exaggeration of the efficacy of CHM treatments may occur when conducting the clinical trials.

Meta-analysis in this research showed modified LDXGT formula shortened the time to resolution of pain, reduced the incidence of PHN, and improved cutaneous outcomes compared with pharmacotherapies. However, the small number and poor quality of the included studies is insufficient to draw a valid evaluation of the efficacy of LDXGT formula.
Rigorous RCTs on LDXGT formula are needed to provide stronger evidence regarding the efficacy and safety of the formula.

For future clinical research, several key points in the design of RCTs can be taken into consideration based on the findings from this SR:

- Proper randomisation, allocation concealment, and blinding methods.
- Interventions: use guideline recommended pharmacotherapies and appropriate dosage.
- Participants: Refer to CM diagnostic criteria for syndrome differentiation as inclusion criteria for the participants. The age range of the participants should be another consideration (eg. Antiviral therapies are recommended to the people with HZ older than 50 years).
- Outcome measurements: As HZ has a significant impact on patients’ quality of life, HRQoL questionnaires should be included for outcome measurements.

6.5.7.2 Implication for clinical practice

According to the general review of CHM and the classical literature research (see Chapter 4), LDXGT was the most frequently reported or cited formulae in both classical and modern literature included in this research. The contemporary CM textbook also recommends LDXGT to treat HZ patients with Stagnant heat in the Liver meridian syndrome. The symptoms contained in this syndrome are similar to the description of HZ in conventional medicine, which may be an explanation that LDXGT is one of the most common CHM treatments in managing HZ in clinical practice. Although the valid conclusion of the efficacy
of LDXGT formula had not been established, the formula was well tolerated by the participants with few mild adverse events reported. As satisfaction with efficacy of conventional medication is still unmet for people with HZ [15], LDXGT may be a potential formula as an alternative therapy in the management of HZ.
Chapter 7. Acupuncture therapies for herpes zoster

7.1 Introduction

Acupuncture has been shown to be an effective treatment for some types of pain, and various skin conditions [268], and may provide benefit during the acute stage of herpes zoster (HZ) [269]. Published systematic reviews (SRs) [22-28] focusing on a diverse range of acupuncture techniques (for example, manual acupuncture, moxibustion) and other CM therapies (for example, cupping) for HZ have been identified through database searches. The evidence from SRs showed that acupuncture therapies shortened the time to resolution of pain, reduced the incidence of post-herpetic neuralgia (PHN), and improved cutaneous outcomes compared with pharmacotherapies (refer to Chapter 2). However, the reviews were limited by the databases searched, diversity in intervention and comparator types. The evidence from these SRs is insufficient to draw conclusions about the efficacy and safety of acupuncture therapies for HZ.

Acupuncture and moxibustion are recommended in CM clinical practice guidelines for treating the acute symptoms of HZ [12], and are frequently used in combination in clinical practice. However the efficacy and safety of the combination of acupuncture with moxibustion for HZ remains unknown.

To address these gap, this chapter will provide an overview of randomised controlled trials (RCTs) of acupuncture treatments for HZ (the ‘general review’), and will evaluate
systematically the efficacy and safety of acupuncture plus moxibustion compared with pharmacotherapy in the management of HZ (the ‘systematic review’).

7.2 Aims

This chapter aimed to:

1. To summarise the characteristics and acupuncture treatments in RCTs for HZ.
2. To conduct a systematic evaluation of the efficacy and safety of acupuncture plus moxibustion for HZ.

7.3 Methods

The methods for the general review of acupuncture therapies for HZ, and the SRs of acupuncture plus moxibustion has been described in Chapter 5.

7.4 Overview of acupuncture therapies for herpes zoster

A total of 37,717 citations were identified through the comprehensive database searches from inception to February 2014, with an update search run in February 2015. After titles and abstracts screening, 5,913 articles were retrieved for full text eligibility assessment. Twenty-seven (27) RCTs were included for this general review (Figure 7.1) [270-296]. All studies were conducted in China.
Details of acupuncture therapies evaluated in these studies were extracted and analysed. Among the included studies, two studies included more than one treatment arm [275, 283]. Details of the intervention arms were extracted separately. One arm in each study included the intervention fire needling, which is not common practice outside of China. This arm of each study was excluded from analysis. The other treatment arms evaluated manual acupuncture and moxibustion, and were included in this review. The remaining 25 studies used a two-arm parallel design, using acupuncture therapies alone or in combination with pharmaceutical therapies as intervention, compared with pharmaceutical therapies.
7.4.1 Characteristics of the included studies

A total of 2,286 participants were included in the RCTs, whose age ranged from 18 to 85 years. The median of mean age was 51 years in the studies that reported mean age. For the studies which reported gender data, the number of male participants was slightly more than
the number of female (1,006 males and 957 females respectively). The duration of HZ at the
time of study inclusion varied, ranging from one day to 20 days. The duration of treatment
also varied, from a minimum of five up to 28 days. The median treatment duration was 10
days. Eleven studies reported follow-up assessment, ranging from 14 days to three months
(see Table 7.1) [270, 274, 275, 279, 280, 283, 286, 287, 290, 292, 295].

One study used syndrome differentiation to guide diagnosis and treatment [282]. The CM
syndromes described in the study were consistent with the guideline: Spleen deficiency with
dampness encumbrance, and pattern/syndrome of qi stagnation and Blood stasis. Differences
existed in the treatment approaches used in acupuncture therapy RCTs in this Chapter
compared to Chinese herbal medicine (CHM) RCTs in Chapter 6. The Chinese acupuncture
guideline [12] describes the selection of points and treatment approach according to HZ
stage. For example, in the prodromal phase, ashi 阿是穴 points are selected. While no
guideline is available for CHM, the treatment approaches are selected based on syndrome
differentiations. Therefore, it was not surprising that only one study reported syndrome
differentiation.

All studies used at least one type of guideline recommended pharmacotherapy as the
comparator: antiviral therapies (26 studies, including acyclovir, famciclovir, valacyclovir, and
moroxydine), and/or analgesics (eight studies, including NSAIDS, carbamazepine,
gabapentin, steroids, and nerve block therapies). Eight studies used vitamin B as an adjunct to
pharmacotherapy, which is commonly used in China to aid nerve repair [297, 298]. However,
vitamin B is not a guideline recommended treatment for HZ. The evidence for vitamin B
remains unclear as to whether it could improve the efficacy of antiviral or analgesic therapies.
Two studies used other therapies in addition to pharmacotherapies: patient education [284], and semiconductor laser (on irradiation nerve root and pain points) [273]. In the studies which reported the dosages of antiviral therapies, only five studies used doses which matched those recommended in clinical practice guidelines. Other studies used dosages lower than that recommended in guidelines.

7.4.2 Characteristics of the acupuncture interventions

The interventions in the included RCTs contained various acupuncture therapies: manual acupuncture, surrounding acupuncture, electro-acupuncture, plum blossom needling, and moxibustion. Different acupuncture approaches were adopted individually or in combination with other acupuncture techniques. Eight studies integrated acupuncture therapies with pharmacotherapies. Details of the different acupuncture therapies are illustrated below.

Manual acupuncture

Manual acupuncture is one of the most commonly used techniques of stimulating acupuncture points, where the skin is penetrated by thin metal needles manually [299]. Thirteen studies involved manual acupuncture as the intervention [277-282, 287, 288, 291-294, 296], five of which were integrated with pharmacotherapies as the intervention [272, 278-281]. Only one study used manual acupuncture alone [281] while others were all combined with other acupuncture techniques.
Table 7.1 Characteristics and intervention details of the included randomised controlled trials

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Treatment Duration, Follow-up Duration</th>
<th>Duration of Condition (mean ±SD or range) (days)</th>
<th>No. of Participants Randomised /Assessed, Dropouts</th>
<th>Age (mean or range)</th>
<th>Gender (male/ female)</th>
<th>Acupuncture Points</th>
<th>Comparators (antiviral and pain management only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acupuncture (including manual, electro, surrounding) alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li, 2011 [283]</td>
<td>10 days, 60 days</td>
<td>I: 6.03, C: 5.26</td>
<td>I: 100/94, 6 C: 100/95, 5</td>
<td>I: 43.83 C: 46.42</td>
<td>I: 45/49 C: 34/61</td>
<td>SA: <em>Ashi</em> points 阿是穴; EA: <em>Huatuojiaji</em> points 华佗夹脊穴, TE6 Zhigou 支沟, SI3 Houxi 后溪</td>
<td>Valacyclovir 0.3 g, bid, po; vitamin B1, po, tid</td>
</tr>
<tr>
<td>Zhou, 2013 [289]</td>
<td>10 days, NS</td>
<td>I: 3.09, C: 3.49</td>
<td>I: 30/30, 0 C: 30/30, 0</td>
<td>I: 51.29 C: 54.59</td>
<td>I: 14/16 C: 13/17</td>
<td>MA: <em>Huatuojiaji</em> points 华佗夹脊穴, TE6 Zhigou 支沟, SI3 Houxi 后溪; SA: rash area</td>
<td>Valacyclovir 0.3 g, bid, po</td>
</tr>
<tr>
<td>Zhang, 2014 [292]</td>
<td>10 days, NS</td>
<td>I: 5.17, C: 5.03</td>
<td>I: 30/30, 0 C: 30/30, 0</td>
<td>I: 51.64 C: 47.79</td>
<td>I: 15/10 C: 15/10</td>
<td>EA: <em>Huatuojiaji</em> points 华佗夹脊穴, <em>Ashi</em> points 阿是穴</td>
<td>Acyclovir 0.3 g, tid, po; carbamazepine 0.1 g, qd, po</td>
</tr>
<tr>
<td>Acupuncture (including manual, electro, surrounding) in combination with pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luo, 2008 [272]</td>
<td>7 days, NS</td>
<td>I: 1-5, C: 1-4</td>
<td>I: 40/40, 0 C: 36/36, 0</td>
<td>I: 58 C: 60</td>
<td>I: NS C: NS</td>
<td>MA: PC6 Neiguan 内关, ST36 Zusanli 足三里, TE6 Zhigou 支沟, GB34 Yanglingquan 阳陵泉,<em>Huatuojiaji</em> points 华佗夹脊穴, <em>Ashi</em> points 阿是穴; SA: rash area;</td>
<td>Acyclovir 0.2 g, five times per day, po; vitamin B12, im, qd</td>
</tr>
<tr>
<td>Chen, 2010 [281]</td>
<td>10 days, NS</td>
<td>Total: 7.4</td>
<td>I: 46/46, 0 C: 46/46, 0</td>
<td>NS</td>
<td>I: NS C: NS</td>
<td>MA: <em>Huatuojiaji</em> points 华佗夹脊穴, <em>Ashi</em> points 阿是穴; LR3 Taichong 太冲, LR2 Xingjian 行间, GB34</td>
<td>Famciclovir 0.25 g, tid, po; vitamin B1, po, tid</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>NS, NS</td>
<td>I: 4.6, C: 4.3</td>
<td>I: 54.8, C: 56.2</td>
<td>I: 20/20, C: 20/18</td>
<td>MA: TE6 Zhigou 支沟, LR3 Taichong 太冲, ST36 Zusanli 足三里, GB34 Yanglingquan 阳陵泉, GB41 Zulingqi 足临泣, LI4 Hegu 合谷, TE5 Waiguan 外关, EX-HN5 Taiyang 太阳, BL40 Weizhong 委中; SA: rash area</td>
<td>Acyclovir 0.2 g, five times per day, po</td>
</tr>
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<td>----------------------------------------</td>
</tr>
<tr>
<td>Lin, 2012 [287]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nerve block, qd</td>
<td></td>
</tr>
<tr>
<td>Zheng, 2010 [280]</td>
<td>10 days, 3 months</td>
<td>Total: 1-20</td>
<td>I: 40/40, 0</td>
<td>C: 38/38, 0</td>
<td>NS</td>
<td>I: NS C: NS</td>
<td></td>
</tr>
<tr>
<td>Zhang, 2012 [285]</td>
<td>NS, NS</td>
<td>Total: &lt;7</td>
<td>I: 50/50, 0</td>
<td>C: 50/50, 0</td>
<td>I: 52.3, C: 52.6</td>
<td>I: NS C: NS</td>
<td>Famciclovir 0.25 g, tid, po; Acyclovir ointment, five times per day, ext; vitamin B1, po, tid</td>
</tr>
</tbody>
</table>

**Yanglingquan 阳陵泉, SP6 Sanyinjiao 三阴交, SP10 Xuehai 血海, SP9 Yinlingquan 阴陵泉, EX-HN3 Yintang 印堂, GB14 Yangbai 阳白, EX-HN5 Taiyang 太阳, GB7 Qubin 曲鬓, GB8 Shuaigu 率谷, TE17 Yifeng 膈风, GB20 Fengchi 风池, LI15 Jianyu 肩髃, TE14 Jianliao 肩髎, SI9 Jianzhen 肩贞, SI10 Naoshu 腭俞, SP21 Dabao 大包, LR14 Qimen 期门, LR13 Zhangmen 章门, EX-HN15 Jingbaolao 颈百劳, GB27 Wushu 五枢**
### Plum blossom needling in combination with pharmacotherapy

<table>
<thead>
<tr>
<th>Authors</th>
<th>Duration</th>
<th>NS</th>
<th>Rash Area</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deng, 2008</td>
<td>7 days</td>
<td>NS</td>
<td>I: 25/25, 0</td>
<td>Famciclovir 0.25 g, bid, po</td>
</tr>
<tr>
<td>Jiang, 2010</td>
<td>20 days</td>
<td>NS</td>
<td>I: 50</td>
<td>Huatuojiaji points 华佗夹脊穴</td>
</tr>
<tr>
<td>Wang, 2010</td>
<td>5 days</td>
<td>&lt;7</td>
<td>I: 30-75</td>
<td>Acyclovir 0.25 g, tid, po; acyclovir ointment, bid, ext.</td>
</tr>
<tr>
<td>Wen, 2014</td>
<td>10 days</td>
<td>30</td>
<td>I: 23-82</td>
<td>Acyclovir 0.2 g, tid, po; diclofenac sodium enteric coated sustained release capsules 0.1 g, qd, po; vitamin B1, po, tid</td>
</tr>
<tr>
<td>Yue, 2009</td>
<td>NS, 14 days</td>
<td>NS</td>
<td>I: 39/39, 0</td>
<td>Famiciclovir 0.25 g, tid, po</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Duration</td>
<td>Initial</td>
<td>Control</td>
<td>Initial</td>
</tr>
<tr>
<td>-------------</td>
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<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Lei, 2013 [290]</td>
<td>7 days, 14 days</td>
<td>I: 1-3, C: NS</td>
<td>I: 40/40, 0 C: 40/40, 0</td>
<td>I: 53.25 C: 52.69</td>
</tr>
<tr>
<td>Zhao, 2010 [279]</td>
<td>10 days, 4 weeks</td>
<td>Total: &lt;7 days</td>
<td>I: 53/53, 0 C: 52/52, 0</td>
<td>I: 50.5 C: 49.6</td>
</tr>
<tr>
<td>Lu, 2004 [270]</td>
<td>10 days, 3 months</td>
<td>I: 3-10, C: 4-9</td>
<td>I: 28/28, 0 C: 28/28, 0</td>
<td>I: 55<del>73 C: 56</del>68</td>
</tr>
<tr>
<td>Liu, 2010 [275]</td>
<td>10 days, 90 days</td>
<td>I: 4.96, C: 5.03</td>
<td>I: 30/30, 0 C: 30/30, 0</td>
<td>I: 47.91 C: 47.79</td>
</tr>
<tr>
<td>Bao, 2011 [282]</td>
<td>10 days, NS</td>
<td>I: 2<del>10, C: 2</del>8</td>
<td>I: 32/32, 0 C: 32/32, 0</td>
<td>I: 51 C: 53</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Treatment Duration</td>
<td>I: C Therapy</td>
<td>I: C Symptoms</td>
<td>C: C Symptoms</td>
</tr>
<tr>
<td>--------------</td>
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<td>--------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Li, 2011 [283]</td>
<td>10 days, 60 days</td>
<td>I: 5.56, C: 5.26</td>
<td>I: 100/94, 6 C: 100/95, 5</td>
<td>I: 47.54 C: 46.42</td>
</tr>
<tr>
<td>Wang, 2011 [284]</td>
<td>10 days, NS</td>
<td>Total: &lt;7</td>
<td>I: 64/58, 6 C: 56/56, 0</td>
<td>I: 63.5 C: 62.3</td>
</tr>
<tr>
<td>Chen, 2012 [288]</td>
<td>10 days, NS</td>
<td>I: 3–6, C: 2–5</td>
<td>I: 31/31, 0 C: 31/31, 0</td>
<td>I: 38–72 NS</td>
</tr>
<tr>
<td>Lin 2012 [287]</td>
<td>10 days, 30 days</td>
<td>I: 4.37, C: 4.54</td>
<td>I: 32/32, 0 C: 30/30, 0</td>
<td>I: 53.26 C: 52.42</td>
</tr>
<tr>
<td>Li, 2014 [293]</td>
<td>10 days, NS</td>
<td>Total: 1–7</td>
<td>I: 32/32, 0 C: 30/30, 0</td>
<td>I: 34.1 C: 35.2</td>
</tr>
<tr>
<td>Yang, 2014 [294]</td>
<td>14 days, NS</td>
<td>I: 5.13, C: 4.77</td>
<td>I: 29/29, 0 C: 30/30, 0</td>
<td>I: 38.79 C: 41.97</td>
</tr>
</tbody>
</table>

**Acupuncture plus plum blossom needling plus moxibustion alone**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Treatment Duration</th>
<th>I: C Therapy</th>
<th>I: C Symptoms</th>
<th>C: C Symptoms</th>
<th>Acupuncture Points</th>
<th>Moxibustion</th>
<th>Adjunct Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang, 2014 [292]</td>
<td>10 days, 3 months</td>
<td>I: 6.36, C: 5.64</td>
<td>I: 25/25, 0 C: 25/25, 0</td>
<td>I: 63.72 C: 60.2</td>
<td>MA: LI11 Quchi 曲池, LI4 Hego 合谷, ST36 Zusanli 足三里</td>
<td></td>
<td>Valacyclovir 0.3 g, bid, po; vitamin B1, po, tid</td>
</tr>
<tr>
<td>Sun, 2015 [296]</td>
<td>10 days, NS</td>
<td>I: 1-15, C: 1-13</td>
<td>I: 50/50, 0</td>
<td>C: 50/50, 0</td>
<td>I: 38</td>
<td>C: 38</td>
<td>MA: rash area, LI11 Quchi 曲池, LI4 Hegu 合谷, ST36 Zusanli 足三里, SP6 Sanyinjiao 三阴交, LR3 Taichong 太冲</td>
</tr>
</tbody>
</table>

**Plum blossom needling plus moxibustion alone**

| Yang, 2012 [286] | 7 days, 30 days | I: 5.1, C: 5.2 | I: 63/60, 3 | C: 60/60, 0 | I: 47.1 | C: 46.3 | Rash area, Huatuojiaji points 华佗夹脊穴, LI11 Quchi 曲池, TE5 Waiguan 外关, ST36 Zusanli 足三里, LR3 Taichong 太冲 | Valacyclovir 0.3 g, bid, po; acyclovir cream, 5-6 times per day, ext; vitamin B1, po, tid |

bid., twice a day; C, control group; ext., external used; EA, electro-acupuncture; I, intervention group; m, mean; MA, manual acupuncture; Moxi, moxibustion; NS, not specified; PB, plum blossom needling; po, oral used; qd., once a day; SA, surrounding acupuncture; SD, standard deviation; tid., three times a day
A total of 43 acupuncture points were selected across these studies and the point selection varied. The most frequently used acupuncture points were LR3 *Taichong* 太冲 (in seven studies), *ashi* points 阿是穴 (or rash area, in six studies), GB34 *Yanglingquan* 阳陵泉 (six studies), ST36 *Zusanli* 足三里 (six studies), *Huatuojiaji* points 华佗夹脊穴 (points parallel 0.5 cun to the spine) (five studies), LI4 *Hegu* 合谷 (five studies), SP6 *Sanyinjiao* 三阴交 (five studies), LI11 *Quchi* 曲池 (four studies), TE6 *Zhigou* 支沟 (four studies), and EX-HN5 *Taiyang* 太阳 (four studies). Details of these top ten frequently used points are shown in Table 7.2.

**Table 7.2 Ten most frequently used acupuncture points in the included studies**

<table>
<thead>
<tr>
<th>Acupuncture Points</th>
<th>Pinyin/Chinese Character</th>
<th>Frequency</th>
<th>Point Function [111]</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR3</td>
<td><em>Taichong</em> 太冲</td>
<td>7</td>
<td>Subdues Liver yang, expels interior wind, promotes the smooth flow of Liver qi, calms the mind.</td>
</tr>
<tr>
<td><em>Ashi</em> (or rash area)</td>
<td><em>Ashi points</em> 阿是穴</td>
<td>6</td>
<td>“Where is the pain, where is the point for treatment”</td>
</tr>
<tr>
<td>GB34</td>
<td><em>Yanglingquan</em> 阳陵泉</td>
<td>6</td>
<td>Promotes the smooth flow of Liver qi, resolves damp-heat, removes obstructions from the channel, and rebellious qi.</td>
</tr>
<tr>
<td>ST36</td>
<td><em>Zusanli</em> 足三里</td>
<td>6</td>
<td>Benefits Stomach and Spleen, tonifies qi and Blood, dispels cold, strengthens body, regulates nutritive and defensive qi, raises yang, expels wind and damp, and resolves oedema.</td>
</tr>
<tr>
<td><em>Huatuojiaji</em> points</td>
<td><em>Huatuojiaji points</em> 华佗夹脊穴</td>
<td>5</td>
<td>Regulate the qi between zang and fu.</td>
</tr>
<tr>
<td>LI4</td>
<td><em>Hegu</em> 合谷</td>
<td>5</td>
<td>Dispels exterior wind, releases the exterior, stimulates the dispersing function of the Lungs, stops pain, removes obstructions from the channel, tonifies qi and consolidates the exterior, clears heat.</td>
</tr>
<tr>
<td>SP6</td>
<td><em>Sanyinjiao</em> 三阴交</td>
<td>5</td>
<td>Strengthens Spleen, resolves damp, promotes function of Liver and smooth flow of Liver qi, nourishes</td>
</tr>
</tbody>
</table>
Blood and yin, moves and cools Blood and eliminates stasis, stops pain, calms mind.

<table>
<thead>
<tr>
<th>Acupuncture Point</th>
<th>Name</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LI11</td>
<td>Quchi曲池</td>
<td>4</td>
</tr>
<tr>
<td>TE6</td>
<td>Zhigou支沟</td>
<td>4</td>
</tr>
<tr>
<td>EX-HN5</td>
<td>Taiyang太阳</td>
<td>4</td>
</tr>
</tbody>
</table>

Expels exterior wind, clears heat, cools Blood, resolves dampness, regulates nutritive qi and Blood, and benefits the sinews and joints.

Regulates qi, removes obstructions from the channel, removes obstructions from the Large Intestine, clears heat, and expels wind.

Dispels wind, clears heat, and alleviates pain.

Three main point functions were evident: regulating qi (LR3 Taichong 太冲, GB34 Yanglingquan 阳陵泉, Huatuojiaji points 华佗夹脊穴, SP6 Sanyinjiao 三阴交, and TE6 Zhigou 支沟), clearing heat (LI4 Hegu 合谷, LI11 Quchi 曲池, TE6 Zhigou 支沟, and EX-HN5 Taiyang 太阳), and resolving damp (GB34 Yanglingquan 阳陵泉, ST36 Zusanli 足三里, SP6 Sanyinjiao 三阴交, and LI11 Quchi 曲池). Currently there is no acupuncture point recommendation for manual acupuncture in the Chinese guideline [12]. Findings indicated that point selection for manual acupuncture was consistent with the guidance of the three main syndromes (Stagnant heat in the Liver meridian, Spleen deficiency with damp retention, and qi stagnation and Blood stasis) described in Chinese guideline [12]. All of the most frequently used points have an analgesic effect in clinical practice, and this finding highlights that principles of treatment with acupuncture are similar to pharmacotherapy.

**Surrounding acupuncture**

Surrounding acupuncture (SA) is a kind of acupuncture therapy which intends to strengthen the efficacy of manual acupuncture [300]. When practicing SA, needles are inserted obliquely at a 15° angle to surround the lesion site [12]. Nine studies used SA in combination with other acupuncture therapies as intervention [270, 272, 278-280, 282, 283, 287, 291]. All
studies applied SA around the rash area as the guideline recommends [12]. The rash area is recognised as a kind of *ashi* point in the guideline, involving the painful spots and vesicular areas [12].

*Electro-acupuncture*

Electro-acupuncture (EA) is a developed acupuncture therapy. Electric stimulation is applied to acupuncture points to promote the efficacy of manual acupuncture [111]. Seven studies used EA in their intervention [275, 279, 283-285, 289, 293]. Two studies used EA alone [285, 289], while others combined it with other acupuncture approaches. *Huatuojiaji* points 华佗夹脊穴, that are recommended for treating HZ in contemporary guideline [12], were selected in all of the studies; three studies combined with this approach with *ashi* points [275, 284, 289, 292], and one study selected multiple points [285]. The finding also showed that the point selection in the included studies was consistent with recommendations in contemporary acupuncture guidelines [12].

*Plum blossom needling*

Six studies used plum blossom needling as the intervention [271, 273, 279, 286, 292, 296]. All of the studies tapped the pyonex needle on the rash area as the guideline recommended, and one study tapped on multiple acupuncture points (*Huatuojiaji* points 华佗夹脊穴, LI11 *Quchi* 曲池, TE6 *Zhigou* 支沟, ST36 *Zusanli* 足三里, and LR3 *Taichong* 太冲) [286]. Contemporary acupuncture guideline recommends plum blossom needling should be practiced on *ashi* points with *Huatuojiaji* points 华佗夹脊穴 (when the rash occurs on the trunk) or GV14 *Dazhui* 大椎 (rash on facial and head region) [12]. However, only one study [271] followed the acupuncture guideline [12]. In this study, the multiple points selected for
tapping also followed the three main syndrome differentiations (see manual acupuncture above). The main purpose for plum blossom needling is to clear Stagnant Blood and relieve the pain [111], which may be a mechanism of this therapy to treat the syndrome of qi stagnation and Blood stasis of HZ.

**Moxibustion**

To improve the immunity of patients and prolong the analgesic effect [111], seventeen studies adopted moxibustion therapies as the intervention [270, 274-277, 282-284, 286-288, 290, 292-296]. Most of the studies followed the guideline and applied the moxibustion on the *ashi* points 阿是穴 (or rash area), while two studies selected *Huatuojiaji* points 华佗夹脊穴 [276] and *zhizhu* point 蜘蛛穴 [295] respectively. *Zhizhu* point 蜘蛛穴 is a special acupuncture point selection method for moxa cone moxibustion [301]. By measuring the patient’s head circumference using a thread, the centre of the thread is placed at the front of the patient’s neck and ends placed on the patient’s back, with both ends level. Moxa cones are placed at the level of the thread ends. One study described the rash area as ‘snake head 蛇头’ (where the first rash appears), ‘snake eye 蛇眼’ (the rashes surrounding the snake head), and ‘snake tail 蛇尾’ (the farthest rash from snake head). Similar description can also be found in the classical literature, in which pricking lesion were applied (see Chapter 4, 4.4.3.2.3 Acupuncture and other therapies).

### 7.4.3 Discussion

Participants in included RCTs were older people, which is similar to the general review of CHM therapies in Chapter 6. More male participants were included in these studies than
females. Global epidemiology reports showed higher incidence rate of HZ in women [30, 31, 34]; the reason for the gender difference is not clear.

A variety of different acupuncture approaches have been evaluated by RCTs included for this review. The acupuncture approaches and the selection of acupuncture points in the majority of the studies were consistent with the contemporary guideline [12]. The acupuncture points selection varied among studies which used manual acupuncture as intervention. Although there are no acupuncture points recommended for manual acupuncture in contemporary guideline, the function of the most commonly used acupuncture points echoes the three main syndromes described in the acupuncture guideline [12]. From this review, many studies combined different acupuncture approaches as intervention, as it may strengthen the clinical efficacy. More research has to be conducted to confirm the efficacy of combination of different acupuncture approaches compared with the individual approach.

Among the studies included for this general review, only five studies used the guideline recommended dosage of pharmacotherapies as comparators, a finding also seen in the general review of CHM therapies in Chapter 6. The evidence of acupuncture therapies in the management of HZ from the modern literature is limited by the dosage that these studies used, among other factors. The use of a sub-threshold dose of pharmacotherapies as comparators may exaggerate the efficacy of acupuncture treatments in the clinical research. More rigorously designed clinical research is needed to address this gap.

7.5 Systematic review of acupuncture plus moxibustion for HZ

As the combination of acupuncture plus moxibustion was commonly evaluated in the general
review described previously, this combination of interventions was selected for further evaluation of efficacy and safety. This SR has been accepted for publication in *Dermatologic Therapy* [302].

7.5.1 Descriptions of the studies

Database searches identified more than 37,000 citations (Figure 7.1). More than 11,000 were excluded based on screening of titles and abstracts, and the full text of almost 6,000 studies were reviewed. Nine RCTs (945 participants) met the inclusion criteria (Table 7.3) [270, 275, 282-284, 288, 293, 294, 303]. All studies were conducted in China, and compared the combination of acupuncture plus moxibustion with pharmacotherapy. Two studies included more than one treatment arm, and those additional treatment arms were excluded from this review [275, 283].

The sample size of included studies ranged from 56 [270] to 400 participants [283], and the median sample size was 62. Participants were recruited from hospital outpatient departments [275, 284, 293, 294, 303], inpatient departments [288], or both inpatient and outpatient departments [275, 283, 294]. The duration of HZ ranged from one [275, 283, 293, 294] to 10 days [270, 282]. Treatment was provided for two weeks in one study [294], and for 10 days in remaining studies. Four studies reported follow-up assessment, which was made at 30 days [303], 60 days [283], or 90 days/three months [270, 275]. Two studies lost participants to follow up (n=32) [283, 284] (Table 7.3).
### Table 7.3 Characteristics and intervention details of the included trials of acupuncture and moxibustion

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Treatment Duration, Follow-up Duration</th>
<th>Duration of Condition (mean ±SD or range) (days)</th>
<th>No. of Participants Randomised /Assessed, Dropouts</th>
<th>Age (mean or range)</th>
<th>Gender (male/ female)</th>
<th>Acupuncture Points</th>
<th>Comparators (antiviral and pain management only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu, 2004 [270]</td>
<td>10 days, 3 months</td>
<td>I: 3-10, C: 4-9</td>
<td>I: 28/28, 0 C: 28/28, 0</td>
<td>I: 55–73 C: 56–68</td>
<td>I: 17/11 C: 16/12</td>
<td>SA: rash area; Moxi: rash area</td>
<td>Carbamazepine 0.1 g, qd, po; Moroxydine 0.6 g, qd, po</td>
</tr>
<tr>
<td>Liu, 2010 [275]</td>
<td>10 days, 90 days</td>
<td>I: 4.96, C: 5.03</td>
<td>I: 30/30, 0 C: 30/30, 0</td>
<td>I: 47.91 C: 47.79</td>
<td>I: 16/14 C: 13/17</td>
<td>EA: Ashi points 阿是穴 points, Huatuojiaji points 华佗夹脊穴; Moxi: Ashi points 阿是穴 points</td>
<td>Valacyclovir 0.3 g, bid, po; carbamazepine 0.1 g, tid, po; vitamin B1, po, tid</td>
</tr>
<tr>
<td>Bao, 2011 [282]</td>
<td>10 days, NS</td>
<td>I: 2–10, C: 2–8</td>
<td>I: 32/32, 0 C: 32/32, 0</td>
<td>I: 51 C: 53</td>
<td>I: 19/13 C: 17/15</td>
<td>MA: LI11 Quchi 曲池 , TE5 Waiguan 外关, SP6 Sanyinjiao 三阴交, SP10 Xuehai 血海, ST36 Zusanli 足三里, LR14 Qimen 期门, LR3 Taichong 太冲, GB34 Yanglingquan 阳陵泉; SA: rash area; Moxi: rash area</td>
<td>Acyclovir 0.8 g, tid, po</td>
</tr>
<tr>
<td>Li, 2011 [283]</td>
<td>10 days, 60 days</td>
<td>I: 5.56, C: 5.26</td>
<td>I: 100/94, 6 C: 100/95, 5</td>
<td>I: 47.54 C: 46.42</td>
<td>I: 50/50 C: 50/50</td>
<td>SA: Ashi points 阿是穴; EA: Huatuojiaji points 华佗夹脊穴, TE6 Zhigou 支沟, SI3 Houxi 后溪; Moxi: Ashi points 阿是穴</td>
<td>Valacyclovir 0.3 g, bid, po; vitamin B1, po, tid</td>
</tr>
<tr>
<td>First Author, Publication Year</td>
<td>Treatment Duration, Follow-up Duration</td>
<td>Duration of Condition (mean ±SD or range) (days)</td>
<td>No. of Participants Randomised /Assessed, Dropouts</td>
<td>Age (mean or range)</td>
<td>Gender (male/ female)</td>
<td>Acupuncture Points</td>
<td>Comparators (antiviral and pain management only)</td>
</tr>
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<tr>
<td>Wang, 2011 [284]</td>
<td>10 days, NS</td>
<td>Total: &lt;7</td>
<td>I: 64/58, 6</td>
<td>I: 63.5</td>
<td>I: 26/32</td>
<td>EA: <em>Huatuoji</em> points 华佗夹脊穴, <em>Ashi</em> points 阿是穴; Moxi: rash area;</td>
<td>Valacyclovir 0.3 g, bid, po; prednisone 10 mg, tid, po; acyclovir cream, 6 times per day, ext.</td>
</tr>
<tr>
<td>Chen, 2012 [288]</td>
<td>10 days, NS</td>
<td>I: 3<del>6, C: 2</del>5</td>
<td>I: 31/31, 0</td>
<td>I: 38~72 NS</td>
<td>I: NS</td>
<td>rash area</td>
<td>Acyclovir 0.25 g, bid, iv; acyclovir ointment, ext.</td>
</tr>
<tr>
<td>Lin 2012 [287]</td>
<td>10 days, 30 days</td>
<td>I: 4.37, C: 4.54</td>
<td>I: 32/32, 0</td>
<td>I: 53.26</td>
<td>I: 17/15</td>
<td>MA: LI4 Hegu 合谷, LR3 Taichong 太冲, EX-HN5 Taiyang 太阳, TE6 Zhigou 支沟, GB34 Yanglingquan 阳陵泉; SA: rash area; Moxi: rash area;</td>
<td>Acyclovir 0.8 g, 5 times per day po; acyclovir cream, 5 times per day, ext.</td>
</tr>
<tr>
<td>Li, 2014 [293]</td>
<td>10 days, NS</td>
<td>Total: 1-7</td>
<td>I: 32/32, 0</td>
<td>I: 34.1</td>
<td>I: 19/13</td>
<td>MA: <em>Huatuoji</em> points 华佗夹脊穴, <em>Ashi</em> points 阿是穴; EA: <em>Huatuoji</em> points 华佗夹脊穴 (the ones above and below); Moxi: <em>Ashi</em> points 阿是穴;</td>
<td>Valacyclovir 0.3 g, bid, po; vitamin B1, po, tid; vitamin B12, po, tid</td>
</tr>
<tr>
<td>Yang, 2014 [294]</td>
<td>14 days, NS</td>
<td>I: 5.13, C: 4.77</td>
<td>I: 29/29, 0</td>
<td>I: 38.79</td>
<td>I: 11/18</td>
<td>rash area</td>
<td>Acyclovir 0.4 g, tid, po; gabapentin 0.3 g, tid, po; acyclovir ointment, ext.</td>
</tr>
</tbody>
</table>

bid., twice a day; C, control group; ext., external used; EA, electro-acupuncture; I, intervention group; MA, manual acupuncture; Moxi, moxibustion; NS, not specified; po, oral used; qd., once a day; SA, surrounding acupuncture; SD, standard deviation; tid., three times a day
### 7.5.2 Details of the intervention

All studies evaluated the combination of acupuncture plus moxibustion against pharmacotherapy. Studies used various acupuncture approaches, including manual acupuncture [282, 288, 293, 294, 303], inserting needles surrounding the lesion sites (SA) [270, 282, 283, 303], and electro-acupuncture [270, 282, 283, 303] (see Table 7.3). As all approaches are typical of acupuncture clinical practice, it was considered suitable to pool results for analysis. The most commonly used acupuncture approach was to treat the rash area (five studies) [270, 284, 288, 294, 303] or to use *ashi* points *阿是穴* (local tender points, or points surrounding the rash area; four studies) [275, 283, 284, 293] or *Huatuojiaji* points 华佗夹脊穴 (points parallel to the spine; four studies) [275, 283, 284, 293]. Other commonly reported acupuncture points were GB34 *Yanglingquan* 阳陵泉 [282, 303] and LR3 *Taichong* 太冲 (two studies each) [282, 303].

Treatments used in the comparator groups included guideline recommended treatments, alone or in combination with other treatments (see Table 7.3). Two studies compared acupuncture plus moxibustion to antiviral therapy alone (acyclovir) [288, 303], three studies used antiviral therapy such as acyclovir [282] and valacyclovir [283, 293] in combination with vitamins (B1, B12 or derivatives) [282, 293] or vitamins and saline compresses [283]. One study used the antiviral drug moroxydine in combination with the anticonvulsant carbamazepine [270], and three studies used antiviral drugs acyclovir [294] or valacyclovir [275, 284] with pain medications gabapentin [294], prednisone [284], or carbamazepine [275] and other treatments [275, 284, 294]. Vitamins B1 and B12 are commonly used in China to aid nerve repair. Of the nine studies, only one [303] used antiviral therapy at doses recommended in clinical practice guidelines [14].
7.5.3 Outcome measurements

All studies reported on at least one of the pre-specified outcome measures. Of the two primary outcomes, one study reported on pain intensity using visual analogue scale (VAS) score [283], and two studies reported on time to resolution of pain [284, 303]. Therapeutic effective rate (TER) was the most frequently reported secondary outcome (six studies) [275, 282, 284, 288, 294, 303]. The TER is a global assessment of symptoms, where a 30% or greater improvement in skin lesions and significant pain reduction constitutes a clinical effect. Five studies reported time to crust formation [275, 283, 284, 293, 303], four studies reported time to cessation of new lesion formation [275, 283, 293, 303] and incidence of PHN at either one [283, 303] or three months [270, 275] after resolution of the rash, three reported time to resolution of the rash [283, 284, 293], and two studies reported adverse events [275, 283].

7.5.4 Methodological quality

Three studies used a random number generator [275, 284, 303] and one used computer based central randomisation [283]; all were assessed as low risk of bias for sequence generation. The remaining studies did not provide sufficient information about randomisation processes, and were judged to be at unclear risk of bias. One study which used central allocation was judged as low risk of bias for allocation concealment [283], while all others were judged as unclear risk due to insufficient detail. Due to the nature of the intervention and comparator, it was not possible to blind participants and personnel to group allocation, and all studies were judged to be at high risk of bias. One study reported blinding outcome assessors to group allocation [283], and was considered to be at low risk of bias for this domain. One study reported participant loss but did not describe the reasons [283]. As the number of dropouts was similar in both groups, this study was judged as low risk of bias. Another study reported
loss to follow up [284] (n=6), but the number in each group was not specified. This study was judged as unclear risk of bias. Other studies reported data for all participants randomised and were judged as low risk. One trial was registered [283], but the details provided were insufficient, and the study was considered as unclear risk of bias for selective outcome reporting. No trial protocol or registration was available for all other studies, which were at unclear risk of bias (see Figure 7.2).

Figure 7.2 Summary of risk of bias assessment of included studies
7.5.5 Effects of the intervention

7.5.5.1 Pain related outcomes

Pain intensity

One study reported on VAS pain scores at the end of treatment and at 60 days [283]. Pain score at end of treatment was 8.25 mm lower in those who received acupuncture plus moxibustion compared to valacyclovir plus vitamin B1 and saline compress, with significant statistical difference shown (MD -8.25 mm; 95% CI -12.36 to -4.14) (Figure 7.2). Whilst statistically significant, this result is less than a 1 cm difference between groups. This is unlikely to be clinically meaningful, particularly when considering the wide variation in results and the trial being unblinded. This effect was not sustained at follow up (MD -1.62 mm; 95% CI -3.39 to 0.15).

Figure 7.3 Visual analogue scale pain scores

Time to resolution of pain

Two studies reported time to resolution of pain [284, 303]. One study did not specify the time from which measurement was made [284], and data were excluded from this outcome. The other study reported the time from start of treatment to resolution of pain [303]. Pain resolution was achieved 6.59 days earlier in the participants who received acupuncture plus moxibustion compared to oral and topical acyclovir (MD -6.59 days; 95% CI -8.07 to -5.11). It should be noted that topical acyclovir is not effective for HZ and is not recommended in
clinical practice guidelines [14].

7.5.5.2 Cutaneous outcomes

Time to resolution of rash

Three studies reported on time to resolution of rash [283, 284, 293]. Two studies didn’t specify the time point from which measurement was made, and were not analysed [284, 293]. One study reported the time from rash onset to resolution [283]. Resolution of the rash occurred 3.4 days earlier in the acupuncture plus moxibustion group than in the comparator group (valacyclovir plus vitamin B1 and saline compress; MD -3.4 days; 95% CI -3.71 to -3.09).

Time to crust formation

Five studies reported on time to crust formation [275, 283, 284, 293, 303]. Three studies didn’t specify the time point from which measurements were made, and were excluded from the analysis [275, 284, 293]. Crust formation measured from rash onset occurred 1.42 days earlier in those who received acupuncture plus moxibustion compared with those who received valacyclovir plus vitamin B1 and saline compress (MD -1.42 days; 95% CI -1.52 to -1.32) [283]. When measured from the start of treatment, benefit was also seen with acupuncture plus moxibustion compared with oral and topical acyclovir [303], with crust formation occurring 1.64 days earlier (MD -1.64 days; 95% CI -2.87 to -0.41).

Time to cessation of new lesion formation

Four studies reported the time to cessation of new lesion formation [275, 283, 293, 303], with two excluded from analysis due to lack of detail about the time from which measurements were made [275, 293]. Acupuncture plus moxibustion resulted in a lesser time to cessation of
new lesion formation compared with valacyclovir, vitamin B1 and saline compress when measured from rash onset (MD -0.29 days; 95% CI -0.35 to -0.23) [283]. When measured from start of treatment, acupuncture plus moxibustion reduced the time to cessation of new lesions compared with oral and topical acyclovir (MD -1.26 days; 95% CI -2.16 to -0.36) [303].

7.5.5.3 Incidence of postherpetic neuralgia

Four studies reported on the incidence of PHN [270, 275, 283, 303]. Sub-group analysis was performed according to PHN definition (one/three months after resolution of the rash). Meta-analysis showed a significant reduction in the incidence of PHN (one month after rash resolution) in those who received acupuncture plus moxibustion compared to pharmacotherapy (two studies; RR 0.29; 95% CI 0.16 to 0.53; $I^2=0\%$) [283, 303]. In studies which measured PHN three months after rash resolution, no statistical difference was seen (two studies; RR 0.16; 95% CI 0.02 to 1.35; $I^2=0\%$) [270, 275].

7.5.5.4 Therapeutic effective rate

Of the six studies which reported TER, one study reported data in a different way to that described in the guideline [294]. This study was excluded from analysis. The chance of achieving a 30% or greater improvement in lesions and significant pain reduction with acupuncture plus moxibustion was 2.67 that of pharmacotherapy (RR 2.67; 95% CI 2.03 to 3.52; $I^2=43\%$).

7.5.6 Adverse events

Two cases of haematoma and five cases of bleeding were reported in the intervention group.
of one study [283]. The adverse events were mild and the symptoms were relieved by local pressing or massage. One study reported that there was no adverse event observed in either intervention or control group [275], while the other studies did not mention adverse events [270, 275, 282, 284, 288, 293, 294, 303].

7.5.7 Discussion

The findings from this systematic review suggest potential benefit from acupuncture and moxibustion in reducing pain intensity, improving rash healing, and reducing the incidence of PHN, although few studies reported these outcomes. Meta-analysis of five studies showed improvement in lesions and significant reduction in pain based on the therapeutic effective rate. TER has not been validated, and should be interpreted with caution.

Acupuncture and moxibustion were well tolerated by patients, with few mild side effects reported. Bleeding and haematoma are the most common adverse events with acupuncture [304-306], resulting from needles puncturing the capillary vessels [111]. Due care minimises the risk of this occurring. Although no adverse events were reported related to moxibustion in the included studies, appropriate distance between burning moxibustion cigar and acupuncture points should be maintained to avoid empyrosis [111].

The findings in relation to incidence of PHN require further investigation. There is no consensus on the definition of PHN, but pain persisting three months after the resolution of the rash is generally accepted as the clinical definition and is used for research purposes [124]. When assessed at one month, acupuncture plus moxibustion reduced the incidence of PHN more than pharmacotherapy. No such benefit was seen when assessed at three months. This result may be due to the definition used. Pain from acute stage HZ has been reported to take
up to 61 days to resolve [307]. In this review, fifty cases of pain were reported one month after rash resolution, while six cases (all in the comparator group) were reported three months after resolution of the rash. This follows the trend for zoster related pain to resolve over time, and is not likely to be an indicator of the efficacy of acupuncture plus moxibustion.

The pathogenesis of acute pain in HZ is the inflammatory response and necrosis of the varicella zoster virus infected sensory nerve [14]. Acupuncture and moxibustion are both important analgesic therapies in the acute stage of HZ [12]. The analgesic effect of acupuncture has been well-researched. Acupuncture promoted cortical endocrine involvement through evoking endogenous opiates, such as β-endorphin, encephalin, dynorphin, and endomorphin [308]. Other research suggests acupuncture could produce anti-inflammatory effects via the autonomic nerve system in animal models [309]. The mechanism of the anti-nociception effect of electro-acupuncture is still unclear. Recent animal studies showed that electro-acupuncture may alleviate inflammation by suppressing certain pain-related molecular, protein and mRNA pathways [310-312].

Antiviral therapy (with or without analgesic therapy) is recommended as first line therapy for immunocompetent patients over 50 years of age [7, 9, 14]. The recommended dose of antiviral drug valacyclovir is one gram three times daily for seven days, and for oral acyclovir is 0.8 g five times a day for seven days [7]. Only one study included in this review used the guideline recommended dosage [303], while the dosage of the other studies included in this review was considerably less than those recommended in guidelines. One study used the anticonvulsant carbamazepine as analgesic therapy for managing acute zoster pain (0.1 g per day) [270], which was also lower than the guideline recommended dosage (0.4 to 1.2 g per day) [7]. None of the included studies described referring to clinical practice guidelines, and
no Chinese guidelines for conventional medical management of HZ could be identified to verify the dosage of antiviral and anticonvulsant therapies. Finally, several studies [284, 288, 294, 303] used topical application of antiviral therapy, which is contrary to clinical practice guidelines. Therefore, the clinical relevance of the findings of this review are uncertain.

Several studies included in this review used vitamin B medications or derivatives, which are not recommended in clinical practice guidelines. In China, the prescribing practice for acute stage of HZ often combines vitamin B1 and B12 for repairing infected nerves and regulating the function of synaptic transmission [297, 298]. It is unclear whether the addition of vitamin B1 or B12 alters the efficacy of valacyclovir, and results should be interpreted in light of this.

7.5.8 Limitation
Many of the studies included in this review had methodological flaws which limits interpretation of the results. There was a lack of detail about the randomisation process, blinding and outcome assessment. These factors are likely to influence the reliability of the results. With the exception of the VAS, few outcomes in HZ research have been standardised or validated. With a complex intervention like acupuncture, the selection of objective outcomes becomes even more important to minimise bias in the results.

7.6 Chapter summary

7.6.1 Implication for future research
From the overview of acupuncture therapies, a variety of different acupuncture techniques were evaluated by the included studies. Only a small number of studies used clinical guideline recommended dosages. The use of a sub-threshold dosage was also seen in the
overview of CHM in Chapter 6, which may exaggerate the efficacy of acupuncture therapies in clinical research. Among other factors, the modern literature evidence of acupuncture therapies for HZ is limited by the dosage the studies used.

Systematic review of acupuncture plus moxibustion showed the intervention reduced pain intensity, improved rash healing, and reduced the incidence of PHN compared to pharmacotherapies. Overall there is insufficient evidence from high quality studies reporting on objective outcomes. The lack of detail relating to some outcomes such as time to resolution of pain or rash limited evaluation of the evidence. Further research comparing acupuncture plus moxibustion to guideline recommended doses of pharmacotherapy, which report definitions used for outcomes and which use the accepted definition for PHN are needed.

For future clinical research using acupuncture therapies as interventions, the feasibility may be another concern in Australia. Current acupuncture guideline recommends the acupuncture therapies should be practiced on patients once daily, with an average treatment duration for ten days (see Table 2.9) [12]. When the target participants are older people, it may be inconvenient or difficult for them to have a daily visit to the clinic. Alternative solutions may include conducting the trial in in-patient department or home visiting practice, but these may cause difficulty in recruiting patients or significant cost.

7.6.2 Implication for clinical practice

According to the general review of acupuncture therapies in the management for HZ, most of the therapies and acupuncture points selection were consistent with the contemporary acupuncture guideline. Although differences were seen in point selection of manual
acupuncture, the main function of points followed the treatment principle for the main syndromes of HZ. Many of the studies combined multiple acupuncture therapies as the intervention to strengthen the efficacy. For clinical practice, the combination of different acupuncture therapies or integrate with pharmaceutical treatments may be considered in the management of HZ.

Although the clinical interpretation of the results from meta-analysis was limited by the methodological flaws, the combination of acupuncture and moxibustion were well tolerated by patients, with few mild side effects reported. As the treatment efficacy of the pharmacotherapies is not meeting the expectations of people with HZ [15], acupuncture and moxibustion may offer an alternative treatment option in the management of HZ. The acupuncture treatments may be appropriate for people with HZ for which antivirals are not indicated.

As per discussion in 7.6.1, it is sometimes difficult for senior people to have daily visit to the clinic seeking for guideline recommended acupuncture treatments. For clinical practice, acupuncture treatments could be integrated with other CM therapies such as Chinese herbal medicine to promise the clinical effects.
Chapter 8. Experimental evidence of the most frequently used herbs for herpes zoster

8.1 Introduction

As stated in Chapter 6, a range of Chinese herbal medicine (CHM) formulae and individual herbs were used for the management of herpes zoster (HZ). A CHM formula Long dan xie gan tang (LDXGT) 龙胆泻肝汤, which contained the majority of the most frequently used herbs, showed clinical benefits in hastening alleviation of pain, in improving cutaneous outcomes, and in reducing the incidence rate of postherpetic neuralgia (PHN). The clinical efficacy of the formulae and herbs is mediated by their constituents. Experimental studies on LDXGT formula showed a promotion of macrophage phagocytosis and lymphocyte transformation in mice [313]. The physiological effects of the herbal ingredients have been evaluated in various laboratory studies, and their key biological actions are summarised below.

8.2 Aims

This chapter will examine and provide a general review on the experimental evidence of the most frequently reported herbs in clinical studies in further detail to identify possible mechanisms of action related to HZ.

8.3 Methods

As this chapter was aiming to conduct a general review of the experimental evidence,
literature search process was different from the systematic reviews which adopted more comprehensive methods in the previous chapters. A literature search was conducted in PubMed from inception to July 2016, with language being limited to English. Key words included pinyin of the herbs (for example, longdancao, longdan, and long dan cao), scientific names (for example, Gentiana scabra Bunge., Gentiana manshurica Kitag., and Gentiana triflora Pall.), and key chemical compounds isolated from the herbs described in the pharmacopeia of Chinese herbs (for example, secoiridoids, entiopicroside, sweroside and svertiamarin) [314]. A whole list of the key words of the herbs are shown in Appendix 8. In vivo or in vitro studies which described mechanisms relevant to HZ were included. Experimental evidence of each herb was summarised and synthesised into a general review.

8.4 Experimental evidence

8.4.1 Experimental evidence for Gentiana species (long dan cao 龙胆草)

In addition to being used for HZ, Gentiana scabra Bunge. has been widely used in Chinese medicine (CM) practice to treat inflammation, chronic hepatitis, rheumatism, cholecystitis and fungal infection. The anti-inflammatory actions of Gentiana scabra Bunge. compounds have been well researched. Much of the research has come from studies of Gentiana scabra Bunge. and Gentiana triflora Pall. The key findings of the main chemical compounds are as described below.

8.4.1.1 Iridoids and secoiridoids

Secoiridoid glycosides are the major constituents of Gentiana scabra Bunge. species and Gentiana triflora Pall. species [262, 315, 316]. More than 20 kinds of secoiridoids had been isolated and purified in laboratory research, including gentiopicroside, sweroside and
swertiamarin. The inhibitory actions of these compounds against several inflammatory cytokines and pro-inflammatory enzymes have been shown in vitro (see below). While long dan cao 龙胆草 is traditionally sourced from Gentiana scabra Bunge. and Gentiana triflora Pall., compounds found in these two herbs have also been isolated from Gentiana lutea ssp. Symphyandra species. In chicken embryonic fibroblast gentiopicroside, secoiridoids, sweroside and swertiamarin have demonstrated wound healing activity [317].

**Tumour necrosis factor α**

Tumour necrosis factor alpha (TNFα) has been identified as a key mediator in many immune-mediated inflammatory diseases [318]. Previous studies have shown secoiridoids isolated from Gentiana scabra Bunge. and Gentiana triflora Pall. species demonstrated weak inhibition of TNFα in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells [262, 316]. Stronger inhibition of TNFα was seen with deglicosylscabraside in LPS-stimulated bone marrow-derived dendritic cells (BMDCs) [319].

**Interleukins**

Interleukins (ILs) are a group of cytokines that are expressed by various leucocytes such as T helper cells and natural killer cells. Interleukins promote inflammatory responses and are implicated in a wide range of inflammatory diseases [320]. Secoiridoid glycosides isolated from Gentiana scabra Bunge. species inhibited IL-6 production by LPS-stimulated RAW 264.7 cells [262]. IL-6 inhibition was also seen in LPS-stimulated BMDCs, in addition to inhibition of IL-12 [319]. The suppression of interleukins may be one mechanism through which Gentiana scabra Bunge. produces anti-inflammatory effects.

**Nitric oxide**
Nitric oxide (NO) plays a key role in the response to inflammatory stimuli in macrophages, which involves the pro-inflammatory enzyme inducible nitric oxide synthase (iNOS) [321]. Secoiridoid glycosides from *Gentiana scabra* Bunge. showed suppression effects on production of NO, induced by LPS in RAW 264 cells [262]. Gentiolactone, a secoiridoid dilactone from *Gentiana triflora* Pall., was found to inhibit the expression of iNOS in LPS-induced RAW 264 cells [316].

**Cyclooxygenase-2**

Cyclooxygenase-2 (Cox-2), a pro-inflammatory enzyme, converts free fatty acids to prostanoids leading to inflammation. Gentiolactone isolated from *Gentiana triflora* Pall. has demonstrated an inhibitory effect on LPS-stimulated RAW 264 cells at the messenger ribonucleic acid (mRNA) level, indicating another mechanism pathway of the anti-inflammatory action of the secoiridoid [316].

**8.4.1.2 Triterpenes**

Few studies were identified which examined the biological actions of triterpenes in inflammation or immunomodulation. Triterpenes isolated from the rhizomes and roots of *Gentiana scabra* Bunge. demonstrated inhibitory activity against indoleamine 2, 3-dioxygenase (IDO) [322]. Inhibition of IDO increases the rate at which tryptophan is converted to kynurenine [323], which in turn suppresses T-cell activation and induces T-cell death. Preliminary evidence from this study suggest a potential role for triterpenes in modulating the immune response.
8.4.2 Experimental evidence for *Gardenia jasminoides* Ellis. (*zhi zi* 栀子)

*Gardenia jasminoides* Ellis. (*zhi zi* 栀子) has been widely used in treating inflammatory diseases in CM. Two main constituents, genipin and geniposide isolated from *Gardenia jasminoides* Ellis. have been researched for their anti-inflammatory effects and mechanism of action on the nociceptive pathway.

8.4.2.1 Genipin

Genipin has been shown to have anti-inflammatory effects through its inhibitory action on inflammatory cytokines and pro-inflammatory enzymes [324, 325]. Genipin was found to suppress iNOS expression and consequently reduce NO release in LPS-stimulated RAW 264.7 cells [325]. In the same study, genipin was found to relieve the croton oil-induced ear oedema in mice when applied topically. Suppression of COX-2 may be one pathway for reducing inflammation. Genipin exhibited significant anti-inflammatory effect on carrageenan-induced rat paw oedema in a latter study by Koo *et al.* [324]. In the carrageenan-induced air pouch model, genipin demonstrated a similar reduction in volume of exudate and nitrite levels as dexamethasone. The inhibitory effect on NO production and COX-2 expression may have contributed to its anti-inflammatory effect.

8.4.2.2 Geniposide and other constituents

Geniposide is another iridoid isolated from *Gardenia jasminoides* Ellis. and its anti-inflammatory actions have been explored in some experimental studies [326, 327]. Geniposide has been shown to inhibit expression of NO, prostaglandin E2 (PGE$_2$), TNF$\alpha$ and IL-6 in LPS-stimulated RAW 264.7 murine macrophage cells and peritoneal macrophages [327]. Geniposide also suppressed iNOS and COX-2 expression by downregulating mRNA
transcription levels. The inhibition of NO and PGE\(_2\) may explain the biological actions of geniposide in reducing inflammation.

In addition to genipin and geniposide, 6α-hydroxy-geniposide, 6β-hydroxygeniposide, ixoroside and shanzhiside showed significant inhibition of IL-2 secretion by human peripheral blood T-cells, which were co-stimulated by phorbol myristate acetate and anti-CD28 monoclonal antibodies [326].

### 8.4.3 Experimental evidence for *Scutellaria baicalensis* Georgi. (*huang qin* 黄芩)

*Scutellaria baicalensis* Georgi. (*huang qin* 黄芩) contains various compounds including flavonoids, flavone glycosides and chalcones, which have potential anti-inflammatory and immunomodulatory actions [328, 329]. Baicalin, a flavonoid, has been found to inhibit inflammatory cytokines IL-6 production and IL-6 receptor mRNA expression in HEK 293 T-cells [329]. Baicalein, another constituent of *Scutellaria baicalensis* Georgi. demonstrated inhibition of NO and nuclear factor-κB (NF-κB) production in LPS-activated mouse microglial cells [328]. Two flavonoids, baicalein and wogonin, exhibited suppression of NO production and iNOS expression in LPS-stimulated RAW 264.7 macrophage cells. *Scutellaria baicalensis* Georgi. may improve symptoms of HZ through suppressing inflammatory cytokines and pro-inflammatory enzymes.

### 8.4.4 Experimental evidence for *Bupleurum* species (*chai hu* 柴胡)

The herb *chai hu* 柴胡 used in CHM is mainly sourced from two species *Bupleurum chinense* DC., and *Bupleurum scorzonerifolium* Willd [314]. Two key groups of chemical compounds have been isolated from *Bupleurum* species: triterpene saponines and volatile oils [314]. D-
limonene, a volatile oil, and its main circulating metabolites limonene-1,2-diol and perillic acid have been examined for their immunomodulatory effects in many studies. These constituents demonstrated inhibitory action against the production of interferon-gamma (IFN-γ), interleukins, and TNFα by CD3+CD4+ T-cells, and the production of IFN-γ, IL-2 and TNFα by CD3+CD8+ T-cells [330].

D-limonene also demonstrated similar dose-dependent inhibition of the expression of pro-inflammatory cytokines and enzymes in the research by Yoon et al, which may contribute to reducing the inflammation of sensory nerve caused by HZ [331]. In this study, d-limonene showed inhibition of the expression of interleukins and TNFα, decreased the production of NO and PGE2, and decreased expression of iNOS and COX-2 in LPS stimulated RAW 264.7 murine macrophage cells.

The metabolite perillic acid showed suppressing action of IL-2 and IL-10 production in human mitogen-activated T-cells and peripheral blood mononuclear cells (PBMC) [332]. In the same study, perillic acid also decreased levels of phosphorylated mitogen activated protein kinases (MAPK), which are believed to be involved in the responses to pro-inflammatory cytokines [333]. Limonene and perillic acid also showed an immunomodulatory effect in BALB/c mice by increasing white blood cell count, bone marrow cell count, plaque forming cells in the spleen and circulating antibody count [334].

8.4.5 Experimental evidence for Rehmannia glutinosa Libosch (di huang 地黄)

Rehmannia glutinosa Libosch (di huang 地黄) is one of the most commonly used herbs in CM practice to treat haematological conditions, insomnia and diabetes, in addition to HZ. Iridoids and iridoid glycosides, sugars, organic acids and amino acids are the four main
groups of constituents isolated from this herb [314]. One study demonstrated the immunomodulatory action of *Rehmannia glutinosa* Libosch that may contribute to improving the inflammation symptoms of HZ [335]. *Rehmannia glutinosa* polysaccharides (RGP), a sugar contained in the herb, showed a significant promoting effect of B and T lymphocyte proliferation in mice spleens. Being stimulated with RGP, the production of IL-2 and IFN-γ by T lymphocyte was upregulated significantly [335]. The water extract of *Rehmannia glutinosa* Libosch in the research by Baek et al. [336], demonstrated the suppression of the expression of pro-inflammatory genes including TNFα, MCP-1, IP-10, COX-2, and iNOS.

8.4.6 Experimental evidence for *Angelica sinensis* (Oliv.) Diels (*dang gui* 当归)

*Angelica sinensis* (Oliv.) Diels (*dang gui* 当归) is widely used in CM for cardiovascular diseases, inflammation, headache, infection and fatigue. Volatile oils are the main constituents contained in *A. sinensis*, in addition to amino acids, sugars and sterols [2]. Anti-inflammatory and immunomodulatory actions of the chemical constituents have been shown in some laboratory research. Hydrosoluble fractions of *A. sinensis* including polysaccharide, oligosaccharide, sucrose, and *A. sinensis* total amino acids, dose-dependently increased cell proliferation of mouse peritoneal macrophages [337]. In the same study, these four fractions increased phagocytic and lysosomal activity compared to LPS, especially at higher concentrations. The production of peroxide (H₂O₂) was also seen, suggesting enhanced inflammatory response. In addition, these four fractions also increased the production of NO significantly in a time-dependent manner, and promoted the activity of iNOS.

Selenizing Chinese angelica polysaccharides (sCAPs) isolated from the water extraction of *A. sinensis*, showed immune-enhancing activity in the study by Qin et al. [338]. sCAPs were shown to promote lymphocyte proliferation and increase serum antibody titer significantly in
chicken vaccinated with Newcastle Disease vaccine. Polysaccharides from *A. sinensis* also showed promotion effect of cell proliferation in total spleen cell population, macrophage depleted cell population, peritoneal macrophages and macrophage/B cell depleted cell population from BALB/c mice [339]. An acidic *A. sinensis* polysaccharide showed dose-dependent promotion of lysosomal enzyme activity in murine peritoneal macrophages *in vitro*, and increased lysosomal activity and *in vivo* [340]. The production of NO was also increased in the same study, associated with the promoted expression of iNOS.

Other constituents of *A. sinensis* have shown potential benefit through anti-inflammatory actions, which may alleviate the acute symptoms of HZ. N-butylidene-2-naphthalide, a constituent derived from *A. sinensis*, significantly decreased the production of IL-6 and TNFα in LPS-stimulated murine dendritic 2.4 cells via NF-κB-dependent pathways [341]. The anti-inflammatory effects of ligustilide of *A. sinensis*, has been evaluated by Su et al. on LPS-induced RAW 264.7 macrophages cells [342]. Ligustilide has demonstrated strong inhibitory action against NO, PGE₂, and TNFα *in vitro*. The expression of iNOS was inhibited by ligustilide at protein and mRNA levels. Furthermore, pre-treatment of cells with ligustilide prior to LPS stimulation significantly inhibited NF-κB p65 expression and reduced the nuclear level of c-Jun (indicative of transcription of activator protein 1, AP1). Ligustilide appears to exert its effects through inhibiting nuclear factor kappaB (NF-κB) and AP-1 pathways.

8.4.7 Experimental evidence for *Alisma orientalis* (Sam.) Juzep. (*ze xie* 泽泻)

*Alisma orientalis* (Sam.) Juzep. (*ze xie* 泽泻) is a commonly used herb in CHM practice. In addition to being used for HZ, *A. orientalis* is often used as a diuretic to treat diabetes, hyperglycemia, hyperlipidemia, neuroprotection, and nephritis. The immunomodulatory and
anti-inflammatory effects of the chemical constituents from *A. orientalis* has been examined in several studies. Alismol and alisol B monoacetate, showed dose-dependent inhibition of NO production in IFN-γ plus LPS stimulated RAW 264.7 murine macrophage-like cells [343]. The inhibition may be due to the suppression of iNOS expression at mRNA levels. Some guaiane-type sesquiterpene, and protostane- and seco-protostane-types triterpenes were also found to have significant suppression of LPS-induced NO production [344]. In the same study, alismol and alisol F showed inhibition of iNOS induction.

Alisol B-23 monoacetate, which is a constituent of *Alisma Plantago-aquatica* (another species of *ze xie* 泽泻), showed immunomodulatory effect in inducing cell apoptosis and significantly reducing the mitochondrial cell membrane potential in A7r5 rat aortic smooth muscle cells and human acute lymphoblastic leukaemia cell line [345].

**8.4.8 Experimental evidence for *Isatis indigotica* Fort. (*ban lan gen* 板蓝根)**

*Isatis indigotica* Fort. (*ban lan gen* 板蓝根) is one of the most widely used herbs in CHM practice to treat influenza, bacterial infection, hepatitis, and fever. Alkaloids, nucleosides, amino acids, organic acids, flavonoids, volatile oils and polysaccharides are the main constituents of this herb. The antiviral action of the constituent isoquinoline derivatives from *I. indigotica*. has been explored, showing inhibitory effects against herpes simplex virus type 1 (HSV-1) in Vero cells by MTT assay [346].

The anti-inflammatory action in suppressing inflammatory cytokines and enzymes of the constituents of *I. indigotica* has been demonstrated in various studies. Indole alkaloids [347] and methanolic extracts [348] of *I. indigotica* inhibited NO production in LPS-stimulated
RAW 264.7 murine macrophage cells, and reduced expression of iNOS [348]. Chemical constituents from *I. indigotica* also showed suppression of PGE2 and pro-inflammatory cytokines PGE2, TNFα and IL-6 in LPS-stimulated RAW 264.7 cells [348, 349]. Methanolic extracts of *I. indigotica* also reduced inflammation in 12-O-Tetradecanoylphorbol 13-acetate (TPA) induced ear edema in mice [348], which may suggest its potential therapeutic efficacy in the management of skin conditions.

### 8.4.9 Experimental evidence for *Corydalis yanhusuo* W.T. Wang (*yan hu suo* 延胡索)

*Corydalis yanhusuo* W.T. Wang (*yan hu suo* 延胡索) is a widely used herb in CM for treating pain. Alkaloids are the main constituents isolated from *C. yanhusuo* [314], and their anti-inflammatory and analgesic mechanisms have been explored in some studies. Extract of *C. yanhusuo* demonstrated anti-nociceptive effect on acute and neuropathic pain in mice [350], which may be partially mediated through dopamine D2 receptor antagonism. Dehydrocorybulbine (DHCB), an alkaloid from *C. yanhusuo*, showed effective analgesic effect in managing thermally induced acute pain, inflammatory pain and injury-induced neuropathic pain in mice [351]. The anti-nociceptive effect was contributed to DHCB’s interaction with D2 receptors. Another alkaloid, DI-tetrahydropalmatine, showed dose-dependent analgesic action in acetic acid-induced writhing in mice [352].

Inhibitory action on the *in vivo* and *in vitro* production of interleukins were seen with dehydrocorydaline [353], and tetrahydropalmatine [354]. This suggests the anti-inflammatory mechanisms of *C. yanhusuo* may contribute to managing the acute symptoms of HZ. Another constituent, Berberine, found in many herbal products including *C. yanhusuo* [355], showed promotion of IL-12 production in both macrophages and dendritic cells. These experimental evidence suggest the potential therapeutic mechanism of *C. yanhusuo*. 

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8.4.10 Experimental evidence for *Plantago* species (*che qian zi* 车前子)

*Plantago asiatica* L., and *Plantago depressa* Willd. are the two species that CM herb *che qian zi* 车前子 is sourced from. Iridoid, phenylpropane glycosides, organic acids and other constituents (for example, β-sitosterol) have been isolated from *Plantago* species [314]. Antiviral and immunomodulatory actions of these constituents have been evaluated in some experimental studies, which may be relevant to HZ. Hot water extract of *Plantago asiatica* L. species was shown to have weak antiviral activity against the herpes simplex type 2 (HSV-2) virus [356]. In the same study, *Plantago asiatica* L. also demonstrated immunodulatory activity in promoting lymphocyte proliferation at low concentrations, but inhibited this effect at high concentration \((\geq 50 \ \mu\text{g/mL})\). In contrast, the secretion of IFN-γ increased at higher concentration. Seed extract of *Plantago asiatica* L. species was shown to induce the maturation of murine dendritic cells (DCs), which can directly stimulate naïve T lymphocytes and initiate primary immune responses [357].

Plantagoside, a chemical constituent identified from the seed extract of *Plantago asiatica* L., was identified as having dose-dependent inhibitory actions on jack bean α-mannosidase activity [358]. Plantagoside was shown to decrease the antigen forming ability against sheep red blood cells in spleen cells from mice. Plantagoside also demonstrated suppression of T-cell proliferation caused by concanavalin A in this study.

8.4.11 Experimental evidence for *Glycyrrhiza* species (*gan cao* 甘草)

*Glycyrrhiza* (gan cao 甘草) is one of the most frequently used herbs in CHM formulae. *Glycyrrhiza* is traditionally source from three species including *Glycyrrhiza uralensis* Fisch.
*Glycyrrhiza inflata* Bat., and *Glycyrrhiza glabra* L. Triterpenes, flavonoids and coumarin derivatives are the three main groups of chemical constituents isolated from *Glycyrrhiza* species [314]. *Glycyrrhiza* and its compounds have been widely used in both conventional and CM to treat skin conditions. Antiviral and analgesic properties of *Glycyrrhiza* and its compounds have been evaluated by various experimental studies that have highlighted mechanisms through which it may improve the symptoms of HZ.

Glycyrrhizin (GL), a key constituent of *Glycyrrhiza*, showed rapid pain alleviation in people with HZ [359]. In this study, GL appeared to decrease human leukocyte antigen-antigen D related (HLA-DR+) expression in CD8+ T-cells from peripheral blood of HZ patients. As cytolytic CD8+ T-cells contribute to controlling varicella zoster virus (VZV) replication in sensory ganglia during the acute state of HZ [360], evidence from this study suggest antiviral activity of GL.

The antiviral action on VZV of GL has also been evaluated *in vitro* [361]. GL demonstrated suppression action on VZV replication in pre-treated and post-treat VZV infected human embryonic fibroblast cells [361]. The authors postulated the mechanism may due to GL suppressing the penetration, uncoating or release of virus particles. GL was also shown to have antiviral actions in Vero cell cultured VZV from vesicular aspirates from children diagnosed with varicella [362]. In BALB/c mice, GL induced apoptotic cell death in mature splenic and thymic lymphocytes *in vitro*, suggesting it has an anti-inflammatory effect [363].

Glycyrrhetinic acid (GA) isolated from *Glycyrrhiza* exhibited analgesic effects in an inflamed rat model [364]. The compound dose-dependently suppressed the capsaicin-induced flinching behaviour. In this study, GA also effectively inhibited pain-related behaviours in the late
phase of the formalin test. Tachykinin receptor inhibition induced by GA may be the mechanism of its analgesic effects.

8.5 Chapter summary

Much of the experimental evidence for the most frequently used herbs has shown anti-inflammatory actions. Inhibition of inflammatory cytokines and pro-inflammatory enzymes have been demonstrated, with some studies showing actions at the mRNA level. The main mechanism of action appears to be through inhibition of NO [262, 325, 340, 344, 348], ILs [262, 319, 341, 348, 349], and tumour necrosis factor production [327, 330, 348, 349], and COX-2 [316, 324] and iNOS expression [316, 327]. This may contribute to relieving the acute inflammatory response in patients with HZ, which in turn may reduce sensory nerve necrosis.

Some constituents of the herbs have demonstrated antiviral actions, in which Glycyrrhizin isolated from Glycyrrhiza spp showed direct evidence of inhibition of VZV replication [360, 361]. The antiviral activity of other constituents from the most commonly used herbs remains unknown. The analgesic action of some constituents has also been demonstrated in the experimental evidence of C. yanhusuo [350-352] and Glycyrrhiza spp [364]. The evidence suggests their possible mechanisms of alleviating acute neuropathic pain of HZ.
In conclusion, anti-inflammatory, antiviral, and analgesic actions shown in the experimental evidence of these herbs may be the key mechanisms for symptom improvements seen in clinical studies. The mechanisms appeared to be consistent with the conventional medication of antiviral and analgesic therapies recommended by contemporary guidelines. More research is needed to confirm their mode of actions, including direct anti-inflammatory action on sensory ganglion, and immunomodulatory and antiviral action against the replication of VZV.
Chapter 9. Long dan xie gan tang plus antiviral therapy for herpes zoster: a trial protocol

9.1 Introduction

In this research, the classical literature evidence showed that Long dan xie gan tang 龙胆泻肝汤 (LDXGT) was the most commonly cited formula to treat herpes zoster (HZ) in ancient times (Chapter 4). From the modern literature evidence research, LDXGT was the most frequently evaluated formula in clinical studies (Chapter 6), while nine of the ten most frequently used herbs were the listed ingredients of LDXGT in the overview of Chinese herbal medicine (CHM) for HZ (Chapter 6). The experimental evidence showed that the herbs of LDXGT demonstrated anti-inflammatory, antiviral, and analgesic actions, which may contribute to relieving the acute inflammatory response and pain in patients with HZ (Chapter 8). The systematic review showed LDXGT was a well-tolerated and effective treatment for HZ. However, the evidence was limited by the methodological flaws (Chapter 6). A rigorous trial protocol is needed to confirm the clinical efficacy of LDXGT.

Systematic review of acupuncture combined with moxibustion in the management of HZ demonstrated promising benefits in pain alleviation and cutaneous improvement. Considering that conducting a trial of acupuncture therapies requires daily visit for participants according to acupuncture guideline recommends, this might not be feasible for older people. Accordingly, the formula LDXGT was selected considering factors such as efficacy, safety and convenience of use.

This chapter will detail the protocol for a randomised, double-blinded, placebo controlled
trial using LDXGT integrated with antiviral therapy in the management of HZ. The design of this study is guided by the findings from the previous systematic review of classical literature, clinical, and experimental evidence of Chinese herbal medicine. The trial will not be conducted as part of this PhD project. The protocol is made available for researchers who wish to conduct such a trial. Researchers would be responsible for obtaining funding and ensuring all regulatory requirements are met.

9.2 Aims

This trial protocol aims to:

1. To design a rigorous trial protocol for future using LDXGT as an intervention for HZ.
2. Incorporate data from the previous review to prepare a rigorously designed randomised controlled clinical trial (RCT) using LDXGT in the management of HZ.

9.3 Trial compliance

This protocol complies with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines that includes the following:

1. CPMP/ICH, Note for Guidance on Good Clinical Practice – Annotated with Therapeutic Goods Administration (TGA) comments (CPMP/ICH/135/95);
2. CPMP/ICH, General Considerations for Clinical Trial (CPMP/ICH/291/95);
3. CPMP/ICH, Statistical Principles for Clinical Trial (CPMP/ICH/363/96);
4. NHMRC, National Statement on Ethical Conduct in Research Involving Humans;
This protocol is developed in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement: defining standard protocol items for clinical trials [365].

9.4 Trial registration and ethical issues

The ethical issues of the trial protocol will be required to be assessed and approved by the relevant organisation prior to trial implementation (for example, Human Research Ethics Committee of RMIT University, Melbourne, Australia). The risks of the trial and the strategies proposed to manage the risks will need to be reviewed. The safety, the eligibility of target population, and patient informed consent form for the proposed research will need to be assessed to protect the participants from harm. Other ethical issues including the storage of the research data, dissemination of the research should also require review to protect the privacy of the individuals.

Prior to trial implementation, the protocol will also need to be registered with an official registry (for example, Australian and New Zealand Clinical Trials Registry, and Therapeutic Goods Administration).

9.5 Participants

This study targets people older than 50 years of age with acute stage HZ, as higher incidence rate of HZ is seen with increasing age [3, 34]. Postherpetic neuralgia (PHN) is an intractable and common chronic sequelae of HZ also increases with age [3]. As HZ is a self-limiting neurocutaneous disease, no specific antiviral therapy needs to be prescribed to young
individuals who are at low risk. For the patients beyond the age of 50 years, antiviral therapy is recommended in clinical practice guidelines as first line pharmacotherapy to shorten the healing process, reduce the incidence, duration and severity of PHN [7, 9].

In order to evaluate the effect of LDXGT plus antiviral therapy, people older than 50 years diagnosed with acute stage HZ will be recruited according to the inclusion/exclusion criteria listed below. Participants will be randomly assigned into either treatment or placebo groups. Informed consent or verbal assent will be obtained prior to trial participation.

9.5.1 Inclusion and exclusion criteria

Participants recruited for this trial will be required to meet all the following criteria:

1. Diagnosis of HZ: either based on clinical presentation or laboratory confirmed.
2. Acute stage HZ: acute stage HZ defined as less than 28 days from onset of rash [9].
3. Age: ≥50 years.
4. Immunocompetent patients.
5. Meet the CM diagnostic criteria for Stagnant heat in the Liver meridian (see Chapter 2.3 Syndrome differentiation).

People with any of the following criteria will be excluded for this trial:

1. Diagnosis other than HZ.
2. Diagnosed as PHN stage.
3. Age: <50 years.
4. Diagnosis of HZ oticus (Ramsay Hunt syndrome), HZ ophthalmicus, HZ encephalitis, zoster sine herpete, visceral HZ, or disseminated HZ.
5. Immunocompromised patients (for example, HIV, cancer, diabetes, pregnant, breastfeeding).
6. Individuals who have taken any Chinese herbal medicine product within the last three months.
7. Diagnosed with a serious illness such as cardiovascular, liver, or renal diseases.

### 9.5.2 Chinese medicine diagnostic criteria

According to Chinese medicine (CM) theory, LDXGT is prescribed for the CM syndrome of Stagnant heat in the Liver meridian [16, 18, 117]. Participants recruited in this study must be diagnosed as having Stagnant heat in the Liver meridian syndrome by a CM practitioner registered with the Chinese Medicine Board of Australia. People with syndromes other than Stagnant heat in the Liver meridian will not be eligible to participate.

Based on CM textbooks [16, 18, 117], the diagnostic criteria of Stagnant heat in the Liver meridian should include the following points:

1. Lesions: red lesion, tense blister walls, burning heat, and pricking pain.
2. Accompanying symptoms: irritability, dry throat and bitter taste in mouth, and dry stools with yellow urine.
3. Tongue: red tongue with thin or thick yellow coat.
4. Pulse: rapid, rolling and string-like pulse.
9.6 Procedure of recruitment

9.6.1 Setting

Future researchers should consider the setting of this trial. Hospitals and clinics (for example, the RMIT Traditional and Complementary Medicine Research Group Clinical Trial Clinic, RMIT University, Bundoora West Campus in Melbourne, Australia) can be considered to conduct this trial.

9.6.2 Advertising

Advertising is another issue to be considered by future researchers to recruit participants. For the clinical trial conducted in RMIT Traditional and Complementary Medicine Research Group Clinical Trial Clinic, the following advertising methods can be considered:

1. Internet: RMIT website, association websites (such as Australian Traditional Medicine Society, and Australian Acupuncture & CM Association)
2. Poster or flyers: posters or flyers will be placed in RMIT University Bundoora, City and Brunswick campuses, local medical centres, clinics of CM practitioners, and community libraries of surrounding suburbs in Melbourne. An example study recruitment poster is presented in Appendix 9. The poster is required to be approved by RMIT Human Research Ethics Committee before being released to the public.
3. Traditional media: radio and newspaper advertisements.
4. Referrals from local general practitioners (GPs) in Melbourne. Meetings will be organised to explain the study to the GPs and to answer their questions.
9.6.3 Screening

It is anticipated that participants will self-refer to the trial. Expression of interest will be by telephone or email. Contact details of interested participants will be recorded on the expression of interest form. Participant information and consent forms (PICF) will be sent out to potential participants after the telephone interview via email. Potential participants will undergo preliminary screening for eligibility over the phone by an investigator, which will include a registered CM practitioner. If deemed to be eligible according to the inclusion criteria, the first visit will be scheduled. Participant information and consent forms are required to be developed in accordance with the relevant ethics committee (for example, RMIT Human Research Ethics Committee) guidelines.

9.6.4 Informed consent

Informed consent will be sought during the initial assessment at the clinic prior to randomisation. Written information and verbal explanation concerning the study will be provided. Full explanation will be given to any questions that arise prior to the signing of the participant information and consent form. Written consent will be required from the participants with adequate fluency in English; verbal assent in the presence of a witness will be sought from participants who are unable to read and write in English. The witness will be someone who is not involved in the clinical trial and whose signature will be required as evidence of witnessing the informed consent process. The responsible investigator will record the date, time, and location of the provision of informed consent.
9.7 Trial design

9.7.1 Randomisation
Randomisation will be carried out using computer generated block randomised sequences, prepared by an independent researcher. Study numbers will be entered into sealed envelopes individually. Each participant will draw an envelope at the time of randomisation. The code inside each envelop will correspond with a package number that will contain seven days of either LDXGT granules plus valacyclovir, or placebo granules plus valacyclovir. An independent researcher who isn’t involved in this trial will keep the study numbers and treatment codes in a secure location (either locked filing cabinet or in a password protected electronic file). The participant’s treatment allocation can be retrieved in the event of medical emergency.

9.7.2 Blinding
This trial will be conducted in a double blinded design. The randomisation sequence and allocation will be unknown to all the researchers, participants, and outcome assessors involved in the trial.

9.7.3 Participant withdrawal/drop-outs
Participants are permitted to withdraw at will at any time during the trial with or without reason provided. When serious adverse event occurs, a participant may be withdrawn from the study by the researcher. When participants withdraw, they have two options. They can withdraw from the study altogether, in which case they should not be contacted further, or they can withdraw from treatment but still be contacted for outcome data assessment. For the participants who agree to be contacted after withdraw, they will be contacted four weeks
following withdrawal, at the follow-up period, to obtain information of visual analogue scale (VAS) pain scores.

9.8 Trial intervention

9.8.1 Long dan xie gan tang

The ingredients and the dosage of LDXGT are based on the CM textbooks [16-18, 101]:

- **Long dan cao** 龙胆草 (*Gentiana scabra* Bunge.) (6 g).
- **Zhi zi** 梓子 (*Gardenia jasminoides* Ellis.) (9 g).
- **Huang qin** 黄芩 (*Scutellaria baicalensis* Georgi.) (6 g).
- **Tong cao** 通草 (*Tetrapanax papyrifer* (Hook.) K.Koch) (6 g).
- **Ze xie** 活血 (*Alisma orientale* (Sam.) Juzep.) (12 g).
- **Che qian zi** 车前子 (*Plantago asiatica* L.) (9 g).
- **Chai hu** 柴胡 (*Bupleurum chinense* DC.) (6 g).
- **Gan cao** 甘草 (*Glycyrrhiza uralensis* Fisch.) (6 g).
- **Dang gui** 当归 (*Angelica sinensis* (Oliv.) Diels.) (3 g).
- **Sheng di** 生地 (*Rehmannia glutinosa* Libosch.) (6 g).

The granules of LDXGT and placebo will be produced by a manufactory that holds a Good Manufacturing Practice (GMP) manufacturing practice certificate. Each package will contain 25 gram concentrated herbal extract granules equivalent to the amount of raw herbs listed above. Each package will be labelled with instructions for administration. One package of LDXGT granules will be prescribed to the participants in the intervention group once daily for seven days. LDXGT administration will be limited to seven days to be consistent with
antiviral therapy administration. The granules should be dissolved in 200 ml warm water and taken orally after meals.

9.8.2 Placebo
The placebo granules will consist of starch with no active ingredients. It will be matched as closely as possible to the appearance, smell and taste of the LDXGT granules. Each package will contain 25 gram placebo granules and will be prescribed to the participants randomised to the control group. Granules should be dissolved in 200 ml warm water and taken orally after meals once a day for seven days.

9.8.3 Antiviral therapy
Oral antiviral therapy will be prescribed by a register medical practitioner involved in this study to both intervention and control groups using the guideline recommended medication: Valacyclovir (Product name: Valtrex ®), 1000 mg, three times daily for seven days [7, 9]. The tablet should be swallowed with a glass of water, once in the morning, afternoon and evening. The participants will be told to drink plenty of fluids while taking the tablets.

9.9 Trial procedure
After screening, eligible participants will undergo initial assessments for baseline data collection, which includes the VAS pain scores, Medical Outcomes Study Short-Form 36 (SF-36) assessment, measurement of vital signs (temperature, blood pressure and heart rate), and given their daily diary to record medication compliance, usage of any other therapies and occurrence of any adverse events.
After the initial assessments, participants will be randomly assigned to either the treatment (LDXGT and valacyclovir) group or the control (placebo and valacyclovir) group and the treatment period will commence immediately. During the first visit, participants will be given seven days’ worth of LDXGT or placebo granules, valacyclovir and daily diary. Participants will be asked to return their medication packages to enable the counting of left-over medication for trial medication adherence monitoring.

Throughout the treatment period, participants will not be permitted to use any complementary medicines, such as acupuncture or other herbal medicine. The use of conventional systemic therapies, such as analgesic therapy, will not be provided as part of the trial, but patients are free to use them. Concomitant medications will be recorded and accounted for in statistical analysis. To assist the monitoring of patient compliance and intervention acceptability, participants will be required to record their trial medication compliance, usage of any other therapies and occurrence of any adverse events in the daily diary.

After the seven day’s treatment period, the participants will be required to have a second visit to the clinic. VAS pain scores, and SF-36 assessment will be assessed during the second period.

During the follow-up period, VAS pain scores and SF-36 questionnaires will be sent out to the participants via post. Participants will be provided with pre-paid envelopes to return trial questionnaires. Follow-up assessment will be conducted at weeks four, 12 and 26. The outline of trial procedures is illustrated in Figure 9.1.
9.9.1 Early termination of the trial

According to the TGA [366], serious adverse events (SAEs) are defined as “Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is a medically-important event or reaction”. All ingredients of LDXGT are used in daily practice, and within the safe dosage. In the event of an SAE that is deemed by the study doctor to be related to the treatment, the trial medication will be discontinued.

9.9.2 Procedures for emergency unblinding

Emergency 24-hour access to the participant identification and treatment codes will be made
available to authorised personnel who has prepared the randomisation and holds the codes at the study site. Should the need to unmask the treatment code arise, the authorised personnel will have access to the treatment code upon request of the investigator and one of the supervisors. The details of adverse events and the unmasking of the treatment code will be documented by the investigator with endorsement from one of the supervisors. The code will not be revealed to participants or personnel involved in data entry and analysis.

9.10 Assessments and outcome measures

9.10.1 Primary outcome measurements

9.10.1.1 Pain severity

Zoster related pain is one of the characteristic symptoms of HZ. In many clinical trials, pain severity was the primary outcome in evaluating the efficacy of the intervention [367, 368]. One of the most frequently used methods of assessing the pain severity is through VAS pain scores, which has a scale 0 to 100 mm (or 0 to 10 cm), with 0 mm being no pain and 100 mm (or 10 cm) being the maximum imaginable pain (see Figure 9.2). In this trial, VAS pain scores will be assessed at the baseline assessment (before treatment), the time point when treatment finished (seventh day of treatment), and at the follow-up period (weeks four, 12, and 26) to observe the severity of pain. The change of VAS pain scores from baseline of each participant will also be recorded.

Figure 9.2 Visual analogue scale pain score assessment
9.10.2 Secondary outcome measurements

9.10.2.1 Quality of life questionnaires

The pain occurring in the HZ acute phase is always the most significant concern of patients, and can remarkably reduce the quality of life [15]. This impacts on four aspects of their life: physical health, psychological wellbeing, social functioning and activities of daily living [4-6]. The SF-36 is a general wellbeing questionnaire, but has also been used in HZ clinical trials [15]. The SF-36 covers eight domains, including vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. It also provides a summary of physical and mental health. In this trial, SF-36 assessment will be performed pre- and post-treatment (first and seventh days), and in the follow-up period.

9.10.2.2 Adverse events

All reactions, including adverse events, will be recorded by participants in the daily diary. The record of adverse events aims to evaluate the safety or tolerability of LDXGT in HZ patients. Safety will be monitored by a data safety and management board throughout this trial.

9.11 Data collection and analysis

9.11.1 Data identification

All data will be entered in the Case Report Form (CRF) by authorised personnel of this project. Training sessions for data entry will be provided to all personnel prior to the study commencement. All data entry will be personally initialled and dated by the responsible
personnel. Assessors, data collectors and personnel involved in data entry will be blinded to the treatment assignment until the study is completed. Standard operation procedures for data entry in the CRF will be developed as a guide to all personnel and will be used as a training tool.

9.11.2 Data confidentiality

Investigators, supervisors and consultants (study doctor and CM practitioner) will have access to the source data and outcomes of analysis of the data. Hard copies of the CRF will be stored in a locked filing cabinet in a secure location in the site of trial conduct. Electronic data will be stored in a password protected file on a secure server. Upon request of regulatory authority, the investigator will make available direct access to the source data and other trial-related records.

9.11.3 Data quality control and quality assurance

Quality control will be applied to each stage of data handling to ensure reliability and accuracy. Any corrections to the data will be documented and the database will be updated throughout the study. Double-checking will be performed to ensure accuracy of the data. The investigator will be available for agreed visits upon request of the regulatory authority during the study for quality assurance.

9.11.4 Data handling and record keeping

In all CRFs, participants will be identified only by their identification code. All information excluding identifiable information of the participants, including the administration of interventions, outcome measures, adverse events, and other relevant data will be recorded in
or attached to the CRF, signed and dated by the investigator and stored in a secure place. All corrections made to the CRF should be single line through, and correct information as near as possible, initialled and dated. All corrections must be personally signed and dated by the person responsible.

9.11.5 Sample size

Before the implementation of the full-scale trial, a pilot trial should be considered. The aim of the pilot study is to test the feasibility of the intervention, safety and trial design as opposed to gathering data on efficacy. Post-hoc power analysis via effect size estimation of the pilot study data should be used to determine sample size for the full-scale trial. There is no standard sample size calculation method for pilot trial. A convenience sample size of 30 participants, with 15 people assigned to the intervention group and 15 people assigned to the control group, would be considered appropriate.

9.11.6 Data analysis

The trial data will be processed and analysed by an independent statistician (for example, from the School of Mathematical and Geospatial Sciences at RMIT University), who will be blinded to subject allocation. Intention to treat (ITT) analysis will be applied to include all randomised participants, which means all patients who were enrolled and randomly allocated to treatment are included in the analysis and are analysed in the groups to which they were randomised. Last observation carried forward method will be used to account for missing data.

Descriptive statistics will be performed on each significant variable to detect unusual or
unexpected data. Codes will not be unmasked during descriptive analysis. Treatment codes will be broken only when the data validation and editing processes are completed for each individual using a code in the database.

Data will be summarised as means and standard deviations and analysed using the SPSS software, Windows Version 21.0. Analysis of between and within-groups differences will be calculated using t-tests. All P values will be 2-tailed and at α=0.05.

9.12 Dissemination of findings

No individual identifiable information of participants will be reported or published. Data will be published in group form and presented in such a way that no individual will be identified. The findings from the results will be published in an international scientific journal, and may be presented at national or international conferences.

9.13 Financing and insurance

The researchers who conduct this trial should seek for sufficient funding to ensure its completion. The study should be covered by relevant liability insurance (for example, Broadform Public and Product Liability Insurance).
Chapter 10. General discussion and summary

10.1 Introduction

Herpes zoster (HZ) is a characteristic neurocutaneous disease caused by the reactivation of the varicella zoster virus (VZV) [7]. The pain induced by the inflammatory response and necrosis of the sensory neurons in the acute stage of HZ significantly impacts patient quality of life, an aspect that remains the greatest concern of patients [15, 48]. The effectiveness of therapeutic approaches was highlighted as an unmet need for people with HZ according to a recent research [15].

Chinese medicine (CM) which consists of multiple treatment approaches including Chinese herbal medicine (CHM), acupuncture therapies may offer alternative and complementary treatment methods to conventional medicine. The systematic reviews which evaluated the efficacy and safety of CM therapies for HZ identified several gaps, including limited databases searched, study inclusion criteria, and statistical analyses. This thesis addressed these gaps by conducting more comprehensive search of databases, strict inclusion criteria and rigorous review methods guided by Cochrane Handbook for Systematic Reviews and Interventions [122]. A rigorous trial protocol evaluating the CM formula Long dan xie gan tang (LDXGT) 龙胆泻肝汤 for people with HZ has been designed to generate new clinical evidence data and inform future research.

The classical CM literature evidence for HZ had not been reviewed through previous databases search. This thesis also systematically evaluated the classical evidence by data mining and cluster analysis methods.
10.2 Summary of the research

The classical literature research was conducted in Zhong Hua Yi Dian (ZHYD) 中华医典 [104], one of the largest collections of CM classical literature in the world. Fifty-four possible HZ citations and 44 “most likely” to be HZ citations met the justification criteria based on the symptom descriptions in text, and were included for further analysis. The well recognised earliest citation of HZ in contemporary CM literature, which is from the Zhu Bing Yuan Hou Lun 诸病源候论 [100, 109, 110], was judged to be possible HZ citation due to the insufficient information on symptoms. The earliest citation judged to be “most likely” to be HZ from this research was from Zheng Zhi Zhun Sheng - Yang Yi 证治准绳・疡医. Symptoms described in this citation are consistent with the contemporary clinical and CM definition of HZ [7, 17, 18].

Various CM formulas, herbs, acupuncture therapies and other therapies were identified from the included citations. Chinese herbal medicine treatments for HZ in the classical literature were also consistent with contemporary CM textbooks [16-18]. The most frequently reported formula in classical literature, LDXGT, and another commonly reported formula, Chu shi wei ling tang 除湿胃苓汤, are both recommended by contemporary textbooks to treat HZ [16-18]. Likely due to the safety concern, some frequently used herbs and formula (for example, xiong huang 雄黄, and Bai ye san 柏叶散 which contains toxic ingredient qing fen 轻粉) are not included in contemporary textbooks and guideline.

Another finding of this thesis is the hypothetical symptom structure of HZ through the cluster analysis in the classical literature research. The results highlight that the symptoms cluster of
heat disease in CM theory is an important symptom classification of HZ. The symptoms included in this cluster are also typical manifestations of local signs of inflammation according to conventional medicine.

The comprehensive modern literature research was conducted through five English and four Chinese databases. Results from the overview of the CHM therapies for HZ showed a slight difference when comparing the top ten most frequently used herbs between classical and modern literature. Only two herbs *ban lan gen* 板蓝根 and *yan hu suo* 延胡索 were not identified in the classical citations. This may be caused by the larger number of formulae and herbal ingredients that were found in the modern literature compared with the smaller number seen in classical literature. *Ban lan gen* 板蓝根 is used for clearing heat and detoxifying and is typically used for HZ patients with heat in Liver meridian syndrome, while *yan hu suo* 延胡索 is for regular *qi* and managing pain, and is used for treating *qi* and Blood stasis syndrome in contemporary CM practice. Both *ban lan gen* 板蓝根 and *yan hu suo* 延胡索 could be used to resolve HZ symptoms.

A variety of CHM formulae were reported in this overview other than those recommended in the contemporary CM textbooks. The key function of the formulae, including “clearing heat, and/or detoxifying”, and “activating Blood, and/or dispelling stasis”, echoes the four main HZ syndromes seen in CM textbooks. The overview also showed that *Long dan xie gan tang* 龙胆泻肝汤 was the most commonly evaluated formula in modern literature. In addition, nine of the top ten frequently used herbs are listed ingredients of LDXGT. Evidence from both modern and classical literature highlights the importance of LDXGT in the CHM management of HZ.
This thesis reports on the results of a systematic review which was undertaken to evaluate the clinical effectiveness and safety of the LDXGT formula. Modified LDXGT formula was found to shorten the time to alleviate pain, reduce the incidence of postherpetic neuralgia (PHN) and improve cutaneous outcomes. Modified LDXGT was well tolerated by participants with few mild adverse events reported. However, the small number and poor quality of the included studies limits the ability to form reliable conclusions about the efficacy of LDXGT formula.

Although Izzo et al. reported herbal medicines to be better tolerated by patients than conventional medicine, the potential risk of harm to the public health and safety from serious adverse events remains a significant point of concern [369]. One ingredient of LDXGT formula, Mu tong has been sourced from multiple species. *Akebia quinata* and *A. trifoliata* (Thunb.) Decne. are considered the official species for *Mu tong* 木通, while *Clematis armandii* Franch. and *C. montana* Buch. Ham. are the official species for *Chuan mu tong* 川木通. However, in the past, Aristolochia species, which contain the toxin aristolochic acid, were used as *Mu tong* 木通 substitutes or adulterants and this led to cases of renal failure [116, 117, 370]. In the 1990s, concerns about aristolochic acid containing species led to increased pharmacovigilance of CMs and the prohibition of Aristolochia species in CMs [371]. This highlights the critical importance of quality assurance of herbal medicine use including authentication of species in clinical studies and clinical practice.

This thesis also has reviewed the acupuncture therapies evaluated in modern literature of randomised controlled trials. Findings from the general overview showed that the acupuncture approaches and the acupuncture points selection in the included studies were
consistent with the contemporary acupuncture guideline [12]. Many studies combined two or more acupuncture therapies, and/or pharmacotherapies as intervention, which may inform the CM practitioner to consider in the management of HZ.

When comparing the modern and classical evidence of acupuncture therapies for HZ, a significant development has been seen in the modern literature. For the classical literature, only moxibustion and pricking needling therapies were reported to manage HZ, while multiple acupuncture approaches has been reported in modern literature and recommended by CM textbooks and guidelines [12, 16-18]. Reasons for the improvement may be due to developments in technology (that is, electro-acupuncture) and special acupuncture techniques (that is, surrounding acupuncture).

Similar to the systematic review of LDXGT, acupuncture and moxibustion showed benefits in reducing pain intensity, reducing time to resolution of rash, and reducing the incidence of PHN according to meta-analysis. Mild adverse events were reported which related to needles puncturing the capillary vessels. Acupuncture and moxibustion were well tolerated by participants. However, the clinical evidence was limited by the poor quality of the studies. The anti-inflammatory action of acupuncture has been researched in several experimental studies, which may contribute to the analgesic effect of acupuncture seen in the clinical studies.

The modern literature evidence of this thesis showed CM therapies of both CHM and acupuncture were well tolerated by people with HZ and may benefit in hastening pain relief, improving cutaneous outcomes, and decreasing the incidence of PHN. As the effectiveness of conventional medications are not meeting the needs of people with HZ [15], CM therapies
may be complementary or alternative treatments in the management of HZ. More rigorous clinical studies are needed to confirm the safety and efficacy of CM therapies.

This thesis provided an overview of the experimental evidence of the most frequently used herbs for HZ identified in modern literature research. Much of the evidence has shown anti-inflammatory actions via inhibition of inflammatory cytokines and pro-inflammatory enzymes of the constituents, which may contribute to alleviating acute inflammatory response in patients with HZ. This evidence suggests the possible mechanisms of reducing pain severity, and improving cutaneous outcomes seen in the clinical evidence of this research.

The modern clinical and experimental literature evidence suggests anti-inflammatory action might be the key mechanism of CM therapies (that is, CHM and acupuncture) in managing the symptoms of HZ. Not surprisingly, the “whole evidence” of modern and classical literature research in this thesis shows “anti-inflammation” is the keyword common throughout all components of this thesis.

10.3 Limitations of this thesis

Classical literature research

The evidence from the classical literature in this research was sourced from ZHYD. Future research using the Chinese materia medica 中华本草全书, which contains more than 6,000 classical CM books, may help to provide further information and evaluation of CM therapies used in ancient times. The results of cluster analysis in data mining of this research might be limited by the sample size of the HZ symptoms dataset, similarity measurement and statistical tests available for cluster analysis. Future data mining using other statistical software (for
Modern literature research

The modern literature research was conducted in the major Chinese and English databases in this thesis. To acquire more comprehensive clinical evidence, future literature search conducted in other language databases, particularly the Korean and Japanese databases where herbal medicine research is commonly published, would broaden our understanding of the clinical benefits of CM for HZ.

The findings from the systematic reviews of CHM and acupuncture were limited by the methodological quality of the included studies. In the risk of bias assessment, few studies detailed the sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors in texts, which may contribute to bias and heterogeneity, and influence the reliability of the clinical outcomes. Another limitation of the included studies in these systematic reviews was the dosage of the pharmacotherapies in the control groups. Very few studies used doses of antivirals which matched those recommended in clinical practice guidelines. Other studies used dosages lower than that recommended in guidelines, which may exaggerate the efficacy of CM therapies in the clinical research.

Some outcome measurements of the included studies were not validated (for example, therapeutic effective rate), and none of the included studies reported on the outcome health-related quality of life. The clinical evidence of CM therapies in this research should be interpreted with caution. Rigorously designed randomised controlled trials are needed to provide evidence regarding the efficacy and safety of the CM therapies. To address this gap, as part of this thesis a trial protocol using LDXGT integrated with antiviral therapy was
developed to inform future research.

This thesis has reviewed the most frequently used herbs in the modern literature search. The mechanisms of other less commonly used, but potentially active, CHMs in the management of HZ need to be examined further. A comprehensive network medicine research including protein-protein interaction and metabolic pathways of the constituents of the herbs may also contribute to detail the mechanisms that related to the management of HZ.

10.4 Conclusion

This thesis applied a systematic approach to summarise classical and modern literature evidence of CM therapies in the management of HZ. The whole evidence in this thesis shows “anti-inflammation” is the keyword common throughout classical and modern literature research of CM for HZ. Data mining results from the classical literature demonstrated that the inflammation symptoms cluster was one of components of the HZ symptoms structure. Modern literature research showed CM therapies of both CHM and acupuncture were well tolerated and may benefit in hastening pain relief, improving cutaneous outcomes, and decreasing the incidence of PHN. The clinical evidence of the CM therapies shows that Chinese herbal medicine and acupuncture may be alternative and complementary approaches in the management of HZ, as there exits unmet satisfaction with the effectiveness of conventional medicine. While the clinical evidence was limited by the methodological flaws in the included studies of this research, a rigorous trial protocol using LDXGT formula as intervention for HZ was designed to inform future research. The anti-inflammatory action of the most commonly used herbs and acupuncture from the experimental evidence may be a mechanism to explain clinical benefit of CM therapies.
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## Appendix 1: Search terms for Zhong Hua Yi Dian

<table>
<thead>
<tr>
<th>Pinyin</th>
<th>Chinese Characters</th>
<th>English Translation (direct translation)</th>
<th>English Translation (translation from the meaning of Chinese characters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bai she chan yao</td>
<td>白蛇缠腰</td>
<td>A white snake encircling waist</td>
<td>Snake (or belt) shape rashes encircling waist</td>
</tr>
<tr>
<td>Chan yao</td>
<td>缠腰</td>
<td>Encircling waist</td>
<td>Encircling waist</td>
</tr>
<tr>
<td>Chan yao chuang</td>
<td>缠腰疮</td>
<td>Rashes encircling waist</td>
<td>Rashes encircling waist</td>
</tr>
<tr>
<td>Chan yao dan</td>
<td>缠腰丹</td>
<td>Pellets encircling waist</td>
<td>Rashes encircling waist</td>
</tr>
<tr>
<td>Chan yao huo dan</td>
<td>缠腰火丹</td>
<td>Fire pellets encircling waist</td>
<td>Red rashes encircling waist</td>
</tr>
<tr>
<td>Chan yao huo long</td>
<td>缠腰火龙</td>
<td>Fire dragon encircling waist</td>
<td>Red rashes encircling waist</td>
</tr>
<tr>
<td>Chan yao long</td>
<td>缠腰龙</td>
<td>Dragon encircling waist</td>
<td>Rashes encircling waist</td>
</tr>
<tr>
<td>Chuan yao long</td>
<td>串腰龙</td>
<td>Dragon encircling waist</td>
<td>Rashes encircling waist</td>
</tr>
<tr>
<td>Feng chi chuang qi</td>
<td>风赤疮痍</td>
<td>Red rashes and wind</td>
<td>Red rashes and wind</td>
</tr>
<tr>
<td>Fu xing zhen</td>
<td>爬行疹</td>
<td>Rashes creeping forward</td>
<td>Rashes extending</td>
</tr>
<tr>
<td>Huo dai chuang</td>
<td>火带疮</td>
<td>Fire rashes shape like a belt</td>
<td>Belt shape red rashes</td>
</tr>
<tr>
<td>Huo dan</td>
<td>火丹</td>
<td>Fire pellets</td>
<td>Red rashes</td>
</tr>
<tr>
<td>Huo dan chuang</td>
<td>火丹疮</td>
<td>Fire pellets</td>
<td>Red rashes</td>
</tr>
<tr>
<td>Huo liao chuang</td>
<td>火燎疮</td>
<td>Fire rashes</td>
<td>Red rashes</td>
</tr>
<tr>
<td>Huo yao dai</td>
<td>火腰带</td>
<td>Fire encircling waist</td>
<td>Rashes encircling waist</td>
</tr>
<tr>
<td>Huo yao dai du</td>
<td>火腰带毒</td>
<td>Fire and toxin encircling waist</td>
<td>Rashes encircling waist</td>
</tr>
<tr>
<td>Pao zhen</td>
<td>疱疹</td>
<td>Blisters and papules</td>
<td>Blisters and papules</td>
</tr>
<tr>
<td>She chan chuang</td>
<td>蛇缠疮</td>
<td>Rashes shape like a snake twining</td>
<td>Snake (or belt) shape rashes twining</td>
</tr>
<tr>
<td>She chan dan</td>
<td>蛇缠丹</td>
<td>Pellets shape like a snake twining</td>
<td>Snake (or belt) shape rashes twining</td>
</tr>
<tr>
<td>She chan hua dai</td>
<td>蛇缠虎带</td>
<td>Snake and tiger stripe twining like a belt</td>
<td>Snake (or belt) shape rashes twining</td>
</tr>
<tr>
<td>She chuan chuang</td>
<td>蛇串疮</td>
<td>Rashes shape like a snake or necklace</td>
<td>Rashes shape like a snake</td>
</tr>
<tr>
<td>She dan</td>
<td>蛇丹</td>
<td>Snake pellets</td>
<td>Snake (or belt) shape rashes</td>
</tr>
<tr>
<td>Pinyin</td>
<td>Chinese Characters</td>
<td>English Translation (direct translation)</td>
<td>English Translation (translation from the meaning of Chinese characters)</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------------------</td>
<td>---------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>She dan yu hou tong</td>
<td>蛇丹愈后痛</td>
<td>Pain after snake pellets healed</td>
<td>Pain after resolution of rashes</td>
</tr>
<tr>
<td>She ke chuang</td>
<td>蛇窠疮</td>
<td>Rashes shape like a snake</td>
<td>Rashes shape like a snake</td>
</tr>
<tr>
<td>She pan chuang</td>
<td>蛇盘疮</td>
<td>Rashes shape like a snake encircling</td>
<td>Rashes shape like a snake</td>
</tr>
<tr>
<td>She xing dan 1</td>
<td>蛇型丹</td>
<td>Rashes shape like a snake</td>
<td>Rashes shape like a snake</td>
</tr>
<tr>
<td>She xing dan 2</td>
<td>蛇形丹</td>
<td>Rashes shape like a snake</td>
<td>Rashes shape like a snake</td>
</tr>
<tr>
<td>Sheng she</td>
<td>生蛇</td>
<td>Onset of snake shape rashes</td>
<td>Onset of snake shape rashes</td>
</tr>
<tr>
<td>Zeng dai chuang</td>
<td>甑带疮</td>
<td>Rashes like a belt</td>
<td>Rashes like a belt</td>
</tr>
<tr>
<td>Zhi zhu chuang</td>
<td>蜘蛛疮</td>
<td>Rashes like spiders</td>
<td>Rashes like spiders</td>
</tr>
</tbody>
</table>
Appendix 2: Hits of search terms in *Zhong Hua Yi Dian*

<table>
<thead>
<tr>
<th>Pinyin</th>
<th>Chinese Characters</th>
<th>Title/Heading Hits</th>
<th>Full Text Hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bai she chan yao</td>
<td>白蛇缠腰</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Chan yao</td>
<td>缠腰</td>
<td>16</td>
<td>106</td>
</tr>
<tr>
<td>Chan yao chuang</td>
<td>缠腰疮</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Chan yao dan</td>
<td>缠腰丹</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Chan yao huo dan</td>
<td>缠腰火丹</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Chan yao huo long</td>
<td>缠腰火龙</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chan yao long</td>
<td>缠腰龙</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Chuan yao long</td>
<td>串腰龙</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Feng chi chuang qi</td>
<td>风赤疮痍</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Fu xing zhen</td>
<td>匍行疹</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Huo dai chuang</td>
<td>火带疮</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Huo dan</td>
<td>火丹</td>
<td>145</td>
<td>1047</td>
</tr>
<tr>
<td>Huo dan chuang</td>
<td>火丹疮</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Huo liao chuang</td>
<td>火燎疮</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Huo yao dai</td>
<td>火腰带</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Huo yao dai du</td>
<td>火腰带毒</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pao zhen</td>
<td>疱疹</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>She chan chuang</td>
<td>蛇缠疮</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>She chan dan</td>
<td>蛇缠丹</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>She chan hu dai</td>
<td>蛇缠虎带</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>She chuan chuang</td>
<td>蛇串疮</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>She dan</td>
<td>蛇丹</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>She dan yu hou tong</td>
<td>蛇丹愈后痛</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>She ke chuang</td>
<td>蛇窠疮</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>She pan chuang</td>
<td>蛇盘疮</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>She xing dan 1</td>
<td>蛇型丹</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>She xing dan 2</td>
<td>蛇形丹</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sheng she</td>
<td>生蛇</td>
<td>5</td>
<td>71</td>
</tr>
<tr>
<td>Zeng dai chuang</td>
<td>颖带疮</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Zhi zhu chuang</td>
<td>蜘蛛疮</td>
<td>8</td>
<td>25</td>
</tr>
</tbody>
</table>
### Appendix 3: Possibly herpes zoster citations

<table>
<thead>
<tr>
<th>Citation Number</th>
<th>Full Texts</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>又有腰间红肿一道名缠腰丹亦名缠蛇疮。缠腰丹遍身起泡如蛇缠有赤白缠。</td>
</tr>
<tr>
<td>182</td>
<td>雄黄（八两）朱砂（一两）蜗牛（二两）冰片（一钱）麝香（五分）共为细末，蟾酥为锭，银朱为衣。盖谓痈疽者皆因气血凝滞，阴阳相搏而成也，今诚修合此药，能治一切痈疽发背，无名肿毒，对口疔疮，诸般恶疮，疼痛肿硬及一切蝎螫蛇咬，夏月毒虫蜈蚣咬伤，湿气疼痛，蛇带火丹等疼痛不止者，俱用凉水磨化，重者用陈醋磨化，涂搽患处，立见奇效。</td>
</tr>
<tr>
<td>197</td>
<td>其疱色白，或赤如火丹，疮头瘜浆白脓者轻，若紫色作根，隐隐在肌肉者甚重。</td>
</tr>
<tr>
<td>218</td>
<td>（蟾酥锭 雄黄 240 克 朱砂 30 克 麝香 1.5 克 冰片 3 克 蜗牛 60 克 共研细末，蟾酥为锭，银朱为衣。）盖谓痈疽者皆因气血凝滞，阴阳相搏而成也，今诚修合此药，能治一切痈疽发背，无名肿毒，对口疔疮，诸般恶疮，疼痛肿硬及一切蝎螫蛇咬，夏月毒虫蜈蚣咬伤，湿气疼痛，蛇带火丹等疼痛不止者，俱用凉水磨化，重者用陈醋磨化，涂搽患处，立见奇效。</td>
</tr>
<tr>
<td>227</td>
<td>医宗金鉴治缠腰火丹加连翘，便秘加生大黄。</td>
</tr>
<tr>
<td>232</td>
<td>（案 14）缠腰火丹已经泡溃，延漫未止，加之忍痛，气滞脉络不舒，清蕴兼理气。</td>
</tr>
<tr>
<td>233</td>
<td>香白芷 西赤芍 淡黄芩 杜霍香 金银花 建连翘 左秦艽 六一散 土贝母 地丁草（案 112）暑风入肺，始由腰间发泡，形如火丹，继则四肢遍满，痛痒并作，即丹毒之重候也。</td>
</tr>
<tr>
<td>516</td>
<td>龙胆泻肝汤见腰部缠腰火丹。</td>
</tr>
<tr>
<td>517</td>
<td>龙胆泻肝汤见腰部缠腰火丹(丹)</td>
</tr>
<tr>
<td>518</td>
<td>龙胆泻肝汤见腰部缠腰火丹(丹)</td>
</tr>
<tr>
<td>519</td>
<td>龙胆泻肝汤见腰部缠腰火丹(丹)</td>
</tr>
<tr>
<td>521</td>
<td>龙胆泻肝汤见腰部缠腰火丹(丹)</td>
</tr>
</tbody>
</table>
柏叶散见腰部缠腰火丹

火丹者，心火妄动，三焦风热乘之，故发于肌肤之表，有干湿不同，红白之异。
化斑解毒汤
化斑解毒汤石膏 玄参知母共连翘
黄连升麻蒡子等 甘草人中黄更甚
治三焦风热上攻，致生火丹，延及遍身痒痛者。

除湿胃苓汤
除湿胃苓汤草朴 陈皮二术泽猪苓
防风滑石山栀等 木通薄桂赤芩名
治脾、肺二经湿热壅遏，致生火丹作烂疼痛者。

柏叶散
柏叶散中蚯蚓粪 赤豆大黄君莫混
加上黄柏轻粉霜 水调敷上何须问
治三焦火甚致生火丹，作痒或作痛，延及遍身。

缠腰火丹，方用宝钞一张，烧化存性，研为细末，用米醋调稀，鸡翎蘸涂患上，一日三次即愈。
如意金黄散见肿疡门
治火丹不论新久痒痛，用新汲水调敷，靛汁亦好。

{方歌}除湿胃苓火丹疮，脾肺湿热疱自黄，胃苓汤用通栀子，滑石防风共作汤。
白鳝泥（敷火带疮。）剪春罗（敷火带疮。)
<table>
<thead>
<tr>
<th>Citation Number</th>
<th>Full Texts</th>
</tr>
</thead>
<tbody>
<tr>
<td>583</td>
<td>(《纲目》)</td>
</tr>
<tr>
<td></td>
<td>{主治}火带疮，水洗取泥炒研，香油调敷（时珍）。</td>
</tr>
<tr>
<td>585</td>
<td>带状匐行疹 汉名火带疮。其名火带疮。</td>
</tr>
<tr>
<td>586</td>
<td>《多能鄙事》</td>
</tr>
<tr>
<td></td>
<td>火带疮，绕腰生者。</td>
</tr>
<tr>
<td>587</td>
<td>火带疮。</td>
</tr>
<tr>
<td>591</td>
<td>(《理例》)</td>
</tr>
<tr>
<td></td>
<td>窦汉卿曰：火腰带毒，乃心肝二经热毒，流滞于膀胱不行，壅于皮肤，此风毒也。（《全书》）</td>
</tr>
<tr>
<td></td>
<td>薛立斋曰：火腰带生系带之处，初起如桃，渐渐红肿，宜用断毒截腰法敷之。</td>
</tr>
<tr>
<td>592</td>
<td>甑带疮者，绕腰生。</td>
</tr>
<tr>
<td>699</td>
<td>生腰下，长一二寸，或碎如饭，或红腰坚硬。以：</td>
</tr>
<tr>
<td></td>
<td>雄黄</td>
</tr>
<tr>
<td></td>
<td>研末，醋调敷，极效。</td>
</tr>
<tr>
<td>701</td>
<td>此丹毒也。生腰下，长一二寸，或碎如粟，或红肿坚硬，有灯火向两头烧五次，并用雄黄外敷内服，极效。</td>
</tr>
<tr>
<td></td>
<td>又方：陈石灰，麻油调敷即愈。</td>
</tr>
<tr>
<td></td>
<td>又方：旧粪桶烧灰，麻油调敷，其效尤速。或照游风丹毒各方治之。</td>
</tr>
<tr>
<td>710</td>
<td>拔除处出齐匀朗红润，而腰间稠密灰滞作痛者，名缠腰，此毒滞千阴，不能成浆，九日危，迟则不过十一日也。</td>
</tr>
<tr>
<td>711</td>
<td>治缠腰丹 急救方：用旧伞纸烧存性为末，香油调敷。</td>
</tr>
<tr>
<td>720</td>
<td>蛇丹验方 治小儿大人缠腰丹，其色红赤，形如蛇有头有尾。</td>
</tr>
<tr>
<td>729</td>
<td>痱科之流传久矣，自昔遵用鼻苗，由肺传肝及脾肾，相攻相伐，逆传命门，攻出先天伏毒，毒因逆攻而出，发无定处，设遇蒙头、锁项、缠腰，以致变症丛生，调治不善，在在惊其险巇。</td>
</tr>
<tr>
<td>731</td>
<td>又有腰间红肿一道，名缠腰丹，又名缠蛇疮（方见痛毒诸方门），又有鸡冠丹、茱萸丹两种。</td>
</tr>
<tr>
<td>740</td>
<td>又有腰间红肿一圈，名缠腰，甚毒火甚更炽，是心包及内肾有毒热感风邪而成，其发甚速，顷刻伤生，无法救治也。</td>
</tr>
<tr>
<td>744</td>
<td>若连珠环绕，名曰缠腰，此毒伏于肾也。缠</td>
</tr>
<tr>
<td>Citation Number</td>
<td>Full Texts</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------</td>
</tr>
<tr>
<td>755</td>
<td>（《启玄》）白蛇缠腰，乃腰里起一红泡圈子，若不早治，被其缠到者不救。缠腰者如裤腰样也。</td>
</tr>
<tr>
<td>756</td>
<td>腰胁生之，肝火妄动，又名缠腰丹，柴胡清肝汤主之。）缠腰丹腰生一红蕾，两边生红筋，缠至脐必死，（金墨磨浓和雄黄末涂之。</td>
</tr>
<tr>
<td>767</td>
<td>（日上下胞属脾、脾有风湿，则虫生弦烂，又新瓦炙为末，少加雄黄、麻油调敷。治蛇串疮，有人食乌梢蛇，浑身变黑，渐生鳞甲，见者惊缩。郑翁一令服晚蚕砂五钱、尽一二斗，久之乃退。</td>
</tr>
<tr>
<td>771</td>
<td>一方柿油搽之，并搽蛇串疮。</td>
</tr>
<tr>
<td>779</td>
<td>（遍身瘙痒 身上无故一孔出血 半身不遂 两胁痛 腰疼 两腋狐臭 汗斑 黄肿 嗜茶 自汗 盗汗 雀斑 酒刺 白屑风皮等症 串蛇丹 点痣 背心寒 治癤 贴骨疮极痛人身救急便方，诸汗 诸汗涂脐法 坐板疮）</td>
</tr>
<tr>
<td>780</td>
<td>（《秘方摘要》）蜘蛛疮（生颈上）蛇丹疮（生腰上，多生于夏秋之间）雄黄末调熟猪油，多敷疮上，以愈为度。</td>
</tr>
<tr>
<td>792</td>
<td>又串蛇丹 先于七寸处灯火三灸，用苋菜根烧灰，存性，麻油调搽。</td>
</tr>
<tr>
<td>795</td>
<td>治蛇串疮 灸心土干研，青油调涂。</td>
</tr>
<tr>
<td>801</td>
<td>治蛇串疮，灶心土干研，青油调涂。</td>
</tr>
<tr>
<td>807</td>
<td>蛇窠疮，生于身体脐腹之上下左右，本无定处，其形象宛如蛇也。治蛇窠疮，兼治蛇咬伤成疮，俱神。（蜈蚣十条，为末，不可经火，白芷三钱，为末，白者佳，雄黄三钱，为末，生甘草末，三钱，香油二两，将三味（注：此处言三味，上文只说以雄黄、白芷佐治，故恐无甘草也。原注说“三”应为“四”。）浸之三日，或随浸调搽，皆能建功也。）</td>
</tr>
<tr>
<td>808</td>
<td>解蛇油 治蛇窠疮，生于皮毛作痛，并治诸恶疮。</td>
</tr>
<tr>
<td>811</td>
<td>糯米粉合盐嚼涂之。或龙胆草研末，柿漆调搽。</td>
</tr>
<tr>
<td>812</td>
<td>糯米粉和盐嚼涂之。</td>
</tr>
<tr>
<td>Citation Number</td>
<td>Full Texts</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>813</td>
<td>蛇缠丹毒 糯米粉和盐嚼涂之。</td>
</tr>
<tr>
<td>815</td>
<td>又蛇缠丹毒，糯米粉合盐嚼涂，或龙胆草研末，柿漆调涂。</td>
</tr>
<tr>
<td>817</td>
<td>蛇缠丹毒，糯米粉合盐嚼涂，或龙胆草研末，柿漆调涂。</td>
</tr>
</tbody>
</table>
| 819             | 王师禁土鬼丹及蛇缠丹  
一气念二十一遍，吹在病处，自立东南方上，令病人在西北，以大指掐中指节文，以第二指掐大指中节，两手皆然，吹时即放手，持咒四十九日，于五更初向北受持可用。 |
| 820             | 治蛇缠丹、匝腰则死。 |
| 823             | 王师禁土鬼丹及蛇缠丹  
一气念二十一遍，吹在病处，自立东南方上，令病人在西北，以大指掐中指节文，以第二指掐大指中节，两手皆然，吹时即放手，持咒四十九日，于五更初向北受持可用。 |
| 824             | 治蛇缠丹，旧破草席人睡过有汗者，烧灰香油调敷。 |
| 827             | 嘉庆癸亥，予寓西溪吴氏家，次子年十五，忽腹背患起红瘰，蔓延及腰如带，或云蛇缠疮，或云丹毒，乃风火所结，血凝滞而成。 |
| 828             | 蛇缠疮，用雄黄为末，醋调涂。 |
| 830             | 蛇缠疮出危氏方）  
以雄黄为末。 |
<p>| 833             | （案 109）蛇缠疮化势非定，红晕开大，势将腐烂。 |</p>
<table>
<thead>
<tr>
<th>Citation Number</th>
<th>Full Texts</th>
</tr>
</thead>
<tbody>
<tr>
<td>836</td>
<td>白蛇缠疮，有头尾，俨似蛇形。</td>
</tr>
</tbody>
</table>
| 840             | 治蛇缠疮  
|                 | 上用雄黄研为末，以醋调涂，仍用酒调服。 |
| 862             | 蜘蛛疮生于皮肤之上，如水窠仿佛，其色淡红，微痛，三三两两，或群攒聚，宛似蜘蛛，故以蜘蛛名之。  
|                 | 解蛛丹 治蜘蛛疮。 |
Appendix 4: “Most likely” to be herpes zoster citations

<table>
<thead>
<tr>
<th>Citation Number</th>
<th>Full Texts</th>
</tr>
</thead>
</table>
| 35              | 生腰肋间，累累如珠形，有干湿不同，红黄之异。干者色红赤，形如云片，上起风粟，作痒发热，属肝胆风热，宜服龙胆泻肝汤。湿者色黄，或起白水泡，大小不等，作热，烂流水，较干者更疼，属肝脾湿热，宜服胃苓汤加山栀、防风、石膏，其小泡用线针穿破。外俱用粪桶箱，炭火烧存性研末，香油调敷。或用蛇蜕（煅）、毛厕蹲板上泥，等分，麻油调敷俱效。此证不速治，缠腰已遍，毒气入脐，令人膨胀闷呕者危险，须急治之。胃苓汤
苍术 陈皮 泽泻 厚朴 猪苓 生甘草
上水煎，温服。
除湿逐丹汤治蛇串白泡。
防风（五钱） 苍术（三钱） 赤苓（五钱） 陈皮（一钱） 厚朴（一钱） 山栀（三钱） 甘草（三分） 白术（三钱） 薄桂（三钱）
水煎服，连服数剂，丹退而愈。
龙胆泻肝汤通用九。 |
<p>| 250             | 又 缠腰火丹，凡腰间起红泡一圈，若不早治，缠转者，不救。 |
| 263             | 又，缠腰火丹，如带围住发红，用龙胆草研末，柿漆调敷。 |
| 342             | 缠腰火丹者，即火带疮，由心肾不交，肝火内炽，流入膀胱，缠于带脉，故腰间生疮，累累如珠，如束带者然，急宜服药以解之（宜仙方活命饮），壮实者下之（宜内疏黄连汤），外用清热解毒药敷之，不早治，毒由脐入，亦膨胀死也。 |
| 514             | 龙胆泻肝汤见腰部缠腰火丹 |</p>
<table>
<thead>
<tr>
<th>Citation Number</th>
<th>Full Texts</th>
</tr>
</thead>
<tbody>
<tr>
<td>524</td>
<td>缠腰火丹蛇串名，干湿红黄似珠形，肝心脾肺风热湿，缠腰已遍不能生。</td>
</tr>
<tr>
<td></td>
<td>缠腰火丹图</td>
</tr>
<tr>
<td></td>
<td>龙胆泻肝汤</td>
</tr>
<tr>
<td></td>
<td>龙胆草 连翘（去心） 生地 泽泻（各一钱） 车前子 木通 黄芩 黄连 当归 槟子（生研） 甘草（生，各五分） 生军（便秘加之，二钱）</td>
</tr>
<tr>
<td></td>
<td>水二盅，煎八分，食前服。</td>
</tr>
<tr>
<td></td>
<td>{方歌} 龙胆泻肝火丹生，形如云片粟多红，芩连栀胆车归尾，生地军翘泻木通。</td>
</tr>
<tr>
<td></td>
<td>{方歌} 除湿胃苓火丹疮，脾肺湿热疱白黄，胃苓汤用通栀子，滑石防风共作汤。</td>
</tr>
<tr>
<td></td>
<td>{方歌} 柏叶散扑火丹方，大黄赤豆柏雄黄，柏叶轻粉蚯蚓粪，研末香油调更良。</td>
</tr>
<tr>
<td>527</td>
<td>缠腰火丹方 挑瞎蛇头上眼。</td>
</tr>
<tr>
<td>531</td>
<td>于腰为肾俞发，为蛇串、缠腰火丹。为疮鼓，为天火丹毒，为瘭疽，为痛风，为痒风，为毒气攻心，为疮口误入毒水，为诸疮生蛆蛆，为暑令病毒小疖，为体气，为黑子痣。</td>
</tr>
<tr>
<td>555</td>
<td>缠腰火丹蛇串名，红黄干湿各分形。</td>
</tr>
<tr>
<td>556</td>
<td>柏叶散 见缠腰火丹。</td>
</tr>
<tr>
<td>557</td>
<td>解毒泻心汤 松叶散 见缠腰火丹。</td>
</tr>
<tr>
<td>579</td>
<td>即缠腰火丹。见该条。</td>
</tr>
<tr>
<td>696</td>
<td>此疮生于腰间系带之处，初起红肿，痛如火烧而不可忍，约三日间破皮出水，但不成脓，乃急症也。治法内服中九丸解毒，外用青黛敷于患处，以止其痛，看其所敷之物干了又换；至红肿消退而不作热时，再以麻凉膏敷之（加倍子末一两于膏内），如恐其干燥，可滴入少许清油以调剂之，水干即愈。</td>
</tr>
<tr>
<td>697</td>
<td>此症，绕腰生疮，累累如珠。由心肾不交，肝火内炽，流入膀胱，环于带脉，形如束带，俗呼蛇蛋疮。须急用化斑解毒汤，迟则毒由脐入，膨胀不食。</td>
</tr>
<tr>
<td></td>
<td>化斑解毒汤</td>
</tr>
<tr>
<td></td>
<td>治三焦风热，致生火丹，遍身痒痛。兼治漆疮。元参 知母 石膏 人中黄 黄连 升麻 连翘 牛子（各一钱） 甘草（五分） 淡竹叶（廿片 水煎服。</td>
</tr>
</tbody>
</table>

279
白蛇缠腰 腰起红泡一圈，若不早治，被其缠到，不救。

若腰胁生之，乃肝火妄动，名曰缠腰丹，用柴胡清肝散，以慈婴散敷之。

（蛇窠疮）即缠腰火丹。千百缠腰如蛇形。

又 缠腰火丹，凡腰间起红泡一圈，若不早治，缠转者，不救。

缠腰疮 腰生红瘤，两边生红筋，围至脐即死。

又，缠腰火丹，如带围住发红，用龙胆草研末，柿漆调敷。

缠腰火丹
俗名蛇串疮，有干湿不同，红黄之异，皆如累累珠形。若单生腰肋，系肝火妄动，宜服柴胡清肝汤（元），其丹上小疱，用线针穿破，外用柏叶散（李）敷之；若不急治，缠腰已遍，毒气入脐，令人膨闷，毒气入心令人呕哕，急服清心散、护心丸（为）救之。

缠腰火丹 一名火带疮。

则缠腰已遍。

缠腰火丹蛇串名，干湿红黄似珠形，肝心脾肺风热湿，缠腰已遍不能生。若腰肋生之，系肝火妄动，宜用柴胡清肝汤治之；其间小疱，用线针穿破，外用柏叶散敷之；若不速治，缠腰已遍，毒气入脐，令人膨胀、闷呕者逆。

龙胆泻肝汤
龙胆草 连翘（去心） 生地 泽泻（各一钱） 车前子 木通 黄芩 黄连 当归 桑子（生研） 甘草（生，各五分） 生军（便秘加之，二钱）

水二盅，煎八分，食前服。

缠腰火丹
俗名蛇串疮，有干湿红黄之别。湿者色黄，串起水泡大小不等，溃流黄水，较前多疼，此属脾肺湿热，治宜除湿胃苓汤（见五卷往字号）；若单一腰胁生肝火妄动，宜服柴胡清肝汤（见五卷元字号）。
<table>
<thead>
<tr>
<th>Citation Number</th>
<th>Full Texts</th>
</tr>
</thead>
<tbody>
<tr>
<td>758</td>
<td>或问：绕腰生疮，累累如珠何如？曰：是名火带疮，亦名缠腰火丹。此证若不早治，缠腰已遍，则毒由脐入，膨胀不食而死。</td>
</tr>
<tr>
<td>764</td>
<td>缠腰火丹，方用宝钞一张，烧化存性，研为细末，用米醋调稀，鸡翎蘸涂患上，一日三次即愈。</td>
</tr>
<tr>
<td>765</td>
<td>又，缠腰疮，腰生红瘤，两边生红筋，围至脐不救。</td>
</tr>
<tr>
<td>766</td>
<td>即缠腰火丹。见该条。</td>
</tr>
<tr>
<td>768</td>
<td>又新瓦炙，为末，少加雄黄，麻油调敷，治蛇串疮。</td>
</tr>
<tr>
<td>769</td>
<td>又，缠腰火丹，如带围住发红，用龙胆草研末，柿漆调敷。</td>
</tr>
<tr>
<td>770</td>
<td>俗名蛇串疮，有干、温不同，红、黄之异，如累累珠形；干者，色红形如云片上起风粟，作痒发热，此心肝二经风火，治宜龙胆泻肝汤，外敷如意金黄散（见二十四卷）；湿者，色黄白，串起小泡，大小不等，溃流黄水，较干者多疼，此脾肺二经湿热，治宜除湿胃苓汤。</td>
</tr>
<tr>
<td>772</td>
<td>俗名蛇串疮。</td>
</tr>
<tr>
<td>838</td>
<td>蛇缠疮亦往往生腰间，如蛇盘之状（宜醋调雄黄末涂之，仍酒调服）。</td>
</tr>
</tbody>
</table>
Appendix 5: Cluster analysis of likely erysipelas citations

Figure appendix 5.1 Single linkage dendrogram: Jaccard coefficient
Figure appendix 5.2 Complete linkage dendrogram: Jaccard coefficient
Figure appendix 5.3 Average linkage (between groups) dendrogram: Jaccard coefficient
Figure appendix 5.4 Average linkage (within groups) dendrogram: Jaccard coefficient
Figure appendix 5.5 Single linkage dendrogram: Sneath and Sokal measurement
Figure appendix 5.6 Complete linkage dendrogram: Sneath and Sokal Measurement
Figure appendix 5.7 Average linkage (between groups) dendrogram: Sneath and Sokal measurement
Figure appendix 5.8 Average linkage (within groups) dendrogram: Sneath and Sokal measurement
Appendix 6: Search terms for Chinese language databases:

Interventions:

Chinese Herbal Medicine: 中医 OR 中西医 OR 中医疗法 OR 辨病论治 OR 辨证 OR 辨证论治 OR 辨症施治 OR 汉方 OR 祖国医学 OR 传统医学 OR 传统治疗 OR 替代医学 OR 替代治疗 OR 中国传统医学 OR 民族医药 OR 草药 OR 中草药 OR 中药 OR 中药疗法 OR 中西医 OR 传统医药 OR 中成药 OR 植物药 OR 中医治法 OR 煎洗 OR 药浴 OR 沐足 OR 足浴 OR 灌肠 OR 灸法 OR 药灸 OR 灸药 OR 热灸 OR 热敷 OR 敷脐 OR 药枕 OR 药烘

Acupuncture: 针刺 OR 灸 OR 针法 OR 刺法 OR 体针 OR 腹 OR 温针 OR 火针 OR 电针 OR 电磁针 OR 梅花针 OR 水针 穴位注射 OR 经络注射 OR 穴位按压 OR 穴位按摩 OR 指压穴位 耳压 OR 耳针 OR 耳穴 OR 耳豆 OR 埋藏疗法 OR 埋线

Other Chinese Medicine Therapies: 外治 OR 推拿 OR 按摩 OR 拔罐 OR 药罐 OR 推罐 OR 闪罐 OR 电罐 OR 火罐 OR 砭石 OR 砭术 OR 砭法 OR 刮痧 OR 刮搓 OR 挑治 OR 割治 OR 发泡 OR 导引 OR 吐纳 OR 气功 OR 太极 OR 八段锦 OR 刺经 OR 刺血 OR 放血 OR 三棱针

Study designs: 系统评价 OR meta OR 荟萃分析 OR 系统分析 OR 综述 OR 进展 OR 概况 OR 现状 OR 近况 OR 临床观察 OR 临床评估 OR 临床试验 OR 临床效果 OR 临床研究 OR 疗效 OR 评价研究 OR 前瞻性 OR 随访 OR 对比研究 OR 多中心 OR 随机 OR 对照 OR 病例报告 OR 病例研究 OR 病例分析 OR 病例报道

Search Terms for English language databases:

Interventions:

Chinese Herbal Medicine: 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 Phytotherapy OR Herbs, OR Plants, Medicine OR Materia Medica OR Single Prescription OR Herbs OR Chinese Medicine Herb OR Herbal Medicine

Acupuncture: Acupuncture OR Meridians OR Electroacupuncture OR Moxibustion OR Auriculotherapy OR plum blossom OR acupressure OR ear acupuncture OR ear acupressure OR acupuncture, ear OR acupuncture therapy OR moxa OR laser acupuncture OR seven star needle OR acupuncture analgesia OR acupuncture points OR electro-acupuncture OR electroacupuncture 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

Other Chinese Medicine Therapies: 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

Study designs:

Randomized Controlled Trial: randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups

Reviews articles: Systematic

Other Studies: 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
### Formulae for clearing heat and detoxifying (38 formulae)

<table>
<thead>
<tr>
<th>Formula Name (Pinyin or translation, Chinese)</th>
<th>Herbs Ingredients (Pinyin, Chinese)</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long dan xie gan tang 龙胆泻肝汤</td>
<td>Variant 1: Long dan cao 龙胆草, huang qin 黄芩, lian qiao 连翘, zhi zi 栀子, jin yin hua 金银花, mian yin chen 绵茵陈, ze xie 泽泻, che qian zi 车前子, ban lan gen 板蓝根, tong cao 通草, sheng di 生地, chai hu 柴胡, gan cao 甘草</td>
<td>25 studies [139, 144, 161, 163, 166, 177, 178, 180, 182, 186, 200, 201, 205, 210, 212, 216, 218, 219, 223, 229, 231, 232, 372-374]</td>
</tr>
<tr>
<td></td>
<td>Variant 2: Ban lan gen 板蓝根, da qing ye 大青叶, zi cao 紫草, ze xie 泽泻, yan hu suo 延胡索, jin yin hua 金银花, ju hua 菊花, ling xiao hua 凌霄花, yi yi ren 薏苡仁, chi shao 赤芍</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Variant 3: Long dan cao 龙胆草, chai hu 柴胡, mu tong 木通, zhi zi 栀子, ban lan gen 板蓝根, ze xie 泽泻, fu ling 茯苓, huang qin 黄芩, sheng di 生地, gan cao 甘草</td>
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<td>Variant 4: Long dan cao 龙胆草, huang qin 黄芩, zhi zi 栀子, ze xie 泽泻, mu tong 木通, che qian zi 车前子, dang gui 当归, sheng di 生地, chai hu 柴胡, gan cao 甘草</td>
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<td>Variant 5: Long dan cao 龙胆草, huang qin 黄芩, sheng di 生地, ze xie 泽泻, mu dan pi 牡丹皮, chi shao 赤芍, che qian zi 车前子, dang gui 当归, zhi zi 栀子, zao cao 紫草, ban lan gen 板蓝根, gan cao 甘草</td>
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<td>Variant 6: Long dan cao 龙胆草, huang qin 黄芩, mu tong 木通, zhi zi 栀子, dang gui 当归, chuan lian zi 川楝子, chai hu 柴胡, ze xie 泽泻, mo yao 没药, ru xiang 乳香, sheng di 生地, che qian zi 车前子, yan hu suo 延胡索, zhi ke 枳壳</td>
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<td>Variant 7: Long dan cao 龙胆草, chai hu 柴胡, zhi zi 栀子, ze xie 泽泻, ku shen 苦参, da qing ye 大青叶, huang qin 黄芩, dang gui 当归</td>
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<td>Herbs Ingredients (Pinyin, Chinese)</td>
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<td>Variant 8: Long dan cao 龙胆草, zhi zi 栀子, huang qin 黄芩, chai hu 柴胡, che qian cao 车前草, ze xie 泽泻, mu tong 木通, sheng di 生地, dang gui 当归, chuan xiong 川芎, jing jie 荆芥, fang feng 防风, qiang huo 羌活, bai zhi 白芷, xi xin 细辛, bo he 薄荷, gan cao 甘草</td>
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<td>Variant 9: Long dan cao 龙胆草, ze xie 泽泻, che qian zi 车前子, dang gui 当归, zhi zi 栀子, huang qin 黄芩, chai hu 柴胡, sheng di 生地, tong cao 通草, gan cao 甘草</td>
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<td>Variant 10: Long dan cao 龙胆草, mu tong 木通, huang qin 黄芩, sheng di 生地, dang gui 当归, zhi zi 栀子, chai hu 柴胡, chuan lian zi 川楝子, che qian zi 车前子, ze xie 泽泻, zhi ke 枇杷, yan hu suo 延胡索, ru xiang 乳香, mo yao 没药</td>
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<td>Variant 11: Long dan cao 龙胆草, huang qin 黄芩, zhi zi 栀子, ze xie 泽泻, mu tong 木通, che qian zi 车前子, dang gui 当归, sheng di 生地, chai hu 柴胡, gan cao 甘草</td>
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<td>Variant 12: Long dan cao 龙胆草, huang qin 黄芩, zhi zi 栀子, ze xie 泽泻, mu tong 木通, dang gui 当归, sheng di 生地, chai hu 柴胡, huang lian 黄连, huang qi 黄芪, gan cao 甘草</td>
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<td>Variant 13: Long dan cao 龙胆草, chai hu 柴胡, ze xie 泽泻, che qian zi 车前子, mu tong 木通, sheng di 生地, dang gui 当归, zhi zi 栀子, huang qin 黄芩, gan cao 甘草, ban lan gen 板蓝根, guan zhong 贯众, zi cao 紫草, fu ling 茯苓, bai zhu 白术</td>
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<td>Variant 14: Long dan cao 龙胆草, huang qin 黄芩, zhi zi 栀子, ze xie 泽泻, dang gui 当归, chai hu 柴胡, gan cao 甘草, che qian zi 车前子</td>
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<td>Variant 15: Long dan cao 龙胆草, lian qiao 连翘, sheng di 生地, ze xie 泽泻, che qian zi 车前子, huang qin 黄芩, zhi zi 梔子, mu dan pi 牡丹皮, zao xiu 蚤休, ban lan gen 板蓝根, da qing ye 大青叶, tian hua fen 天花粉, gan cao 甘草</td>
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<td>Variant 16: Long dan cao 龙胆草, zhi zi 梔子, huang qin 黄芩, ban lan gen 板蓝根, da qing ye 大青叶, che qian zi 车前子, sheng di 生地, chuan lian zi 川楝子, dang gui 当归, chai hu 柴胡, mu dan pi 牡丹皮, ye ju hua 野菊花, yan hu suo 延胡索, gan cao 甘草</td>
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<td>Variant 17: Long dan cao 龙胆草, zhi zi 梔子, huang qin 黄芩, chai hu 柴胡, dang gui 当归, sheng di 生地, ze xie 泽泻, che qian cao 车前草, mu tong 木通, gan cao 甘草, ban lan gen 板蓝根, fu ling 茯苓, cang zhu 苍术</td>
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<td>Variant 18: Long dan cao 龙胆草, che qian zi 车前子, sheng di 生地, ze xie 泽泻, huang qin 黄芩, zhi zi 梔子, chai hu 柴胡, dang gui 当归, mu tong 木通, gan cao 甘草</td>
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<td>Variant 19: Long dan cao 龙胆草, huang qin 黄芩, zhi zi 梔子, mu dan pi 牡丹皮, mu tong 木通, gan cao 甘草, lian qiao 连翘, sheng di 生地, ze xie 泽泻, che qian zi 车前子, dan shen 丹参, dang gui 当归, chi shao 赤芍, ru xiang 乳香, mo yao 没药</td>
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<td>Variant 20: Chai hu 柴胡, bai shao 白芍, chi shao 赤芍, zhi zi 梔子, huang qin 黄芩, sheng di 生地, che qian zi 车前子, ze xie 泽泻, chuan xiong 川芎, dang gui 当归, chen pi 陈皮, zhi ke 枳壳, fu ling 茯苓, xiang fu 香附, yu jin 郁金, yan hu suo 延胡索, gan cao 甘草</td>
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<tr>
<td>Variant 21: Long dan cao 龙胆草, zhi zi 梔子, huang qin 黄芩, chai hu 柴胡, ze xie 泽泻, sheng di 生地, ban lan gen 板蓝根, da qing ye 大青叶, mian yin chen 绵茵陈, yu jin 郁金, che qian zi 车前子, gan cao 甘草</td>
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<td>Variant 22: NS</td>
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<tr>
<td><strong>Huang lian jie du tang combined with long dan xie gan tang 黄连解毒汤合龙胆泻肝汤</strong></td>
<td>Long dan cao 龙胆草, huang lian 黄连, huang qin 黄芩, huang bo 黄柏, zhi zi 桂子, che qian zi 车前子, ze xie 泽泻, sheng di 生地, dang gui 当归, chai hu 柴胡</td>
<td>1 study [169]</td>
</tr>
<tr>
<td><strong>Yin guan he ji 银贯合剂</strong></td>
<td>Jin yin hua 金银花, lian qiao 连翘, guan zhong 贯众, chi shao 赤芍, long dan cao 龙胆草, huang qin 黄芩, jiang can 僵蚕</td>
<td>1 study [225]</td>
</tr>
<tr>
<td><strong>Tui re jie du ling ke li (granule) 退热解毒灵颗粒</strong></td>
<td>NS</td>
<td>1 study [190]</td>
</tr>
<tr>
<td><strong>Ku shen jie du tang 苦参解毒汤</strong></td>
<td>Ku shen 苦参, jin yin hua 金银花, lian qiao 连翘, da qing ye 大青叶, bai xian pi 白鲜皮, huang qin 黄芩, huang lian 黄连, huang bo 黄柏, long dan cao 龙胆草, mu dan pi 牡丹皮, sheng di 生地, chi shao 赤芍, zi cao 紫草, fang feng 防风, gan cao 甘草</td>
<td>1 study [167]</td>
</tr>
<tr>
<td><strong>Dan cao jie du tang 胆草解毒汤</strong></td>
<td>Long dan cao 龙胆草, huang qin 黄芩, sheng di 生地, mu dan pi 牡丹皮, lian qiao 连翘, ban lan gen 板蓝根, ze xie 泽泻, tu fu ling 土茯苓, quan xie 全蝎, gan cao 甘草</td>
<td>1 study [203]</td>
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<tr>
<td><strong>Zi cao xiao zhen tang 紫草消疹汤</strong></td>
<td>Zi cao 紫草, chai hu 柴胡, long dan cao 龙胆草, ban lan gen 板蓝根, huang qin 黄芩, chi shao 赤芍, dan shen 丹参, yan hu suo 延胡索, che qian zi 车前子, zao xiu 蚤休, si gua luo 丝瓜络</td>
<td>1 study [224]</td>
</tr>
<tr>
<td><strong>Bai xuan xia ta re pian (tablet) 百癣夏塔热片</strong></td>
<td>NS</td>
<td>1 study [192]</td>
</tr>
<tr>
<td><strong>Shu feng jie du jiao nang (capsule) 疏风解毒胶囊</strong></td>
<td>NS</td>
<td>1 study [154]</td>
</tr>
<tr>
<td><strong>Huo dan fen (powder) 火丹粉</strong></td>
<td>Da huang 大黄, huang bo 黄柏, qing dai 青黛, hua shi 滑石, gan cao 甘草, bing pian 冰片</td>
<td>1 study [222]</td>
</tr>
<tr>
<td><strong>Qing jie hua yu zu fang 清解化瘀组方</strong></td>
<td>Ku shen 苦参, jing jie 荆芥, she chuang zi 蛇床子, long dan cao 龙胆草, zhi zi 桂子, chi shao 赤芍, dang gui 当归, wu gong 蜈蚣, ji li 蒺藜, sheng di 生地, ban lan gen 板蓝根</td>
<td>1 study [209]</td>
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<tr>
<td>Qing kai ling fen san pian (tablet) 清开灵分散片</td>
<td>NS</td>
<td>1 study [170]</td>
</tr>
<tr>
<td>Xiao zhen zhi tong tang 消疹止痛汤</td>
<td>Chai hu 柴胡, jin yin hua 金银花, ban lan gen 板蓝根, long dan cao 龙胆草, huang qin 黄芩, zhi zi 柴胡, zi cao 紫草, mu dan pi 牡丹皮, yi yi ren 薏苡仁, che qian zi 车前子, yan hu suo 延胡索, chuan xiong 川芎, bai zhi 白芷, xi xin 细辛, gan cao 甘草</td>
<td>1 study [220]</td>
</tr>
<tr>
<td>Chai hu gong xie tang 柴虎蜈蝎汤</td>
<td>Chai hu 柴胡, shan ci gu 山慈菇, ban lan gen 板蓝根, hu zhang 虎杖, fu ling 土茯苓, ling xiao hua 凌霄花, chi shao 赤芍, dang gui 当归, bai shao 白芍, lu feng fang 露蜂房, wu gong 蜈蚣, quan xie 全蝎</td>
<td>1 study [207]</td>
</tr>
<tr>
<td>Xin huang pian (tablet) 新癀片</td>
<td>Variant 1: NS</td>
<td>2 studies [146, 188]</td>
</tr>
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<td>Variant 2: Jiu jie cha 九节茶, tian qi 田七, niu huang 牛黄, shui niu jiao 水牛角, zhen zhu ceng fen 珍珠层粉</td>
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<tr>
<td>Dai pao jie du tang 带疱解毒汤</td>
<td>Jin yin hua 金银花,lian qiao 连翘, niu bang zi 牛蒡子, huang qin 黄芩, fu ling 伏苓, ze xie 滑石, che qian zi 车前子, sheng di 生地, dan shen 丹参, gua lou 瓜蒌, hong hua 红花, cao guo 草果, tian zhu huang 天竺黄, mu xiang 木香, chen xiang 沉香</td>
<td>1 study [185]</td>
</tr>
<tr>
<td>Ru yi zhen bao wan (pill) 如意珍宝丸</td>
<td>Zhen zhu 珍珠, niu huang 牛黄, shui niu jiao 水牛角, jin meng shi 金礞石, he zi 诃子, jue ming zi 决明子, pang xie 蟾蜍, hong hua 红花, cao guo 草果, tian zhu huang 天竺黄, mu xiang 木香, chen xiang 沉香</td>
<td>1 study [215]</td>
</tr>
<tr>
<td>Li shi jie du tang 利湿解毒汤</td>
<td>Jin yin hua 金银花, ban lan gen 板蓝根, tu fu ling 伏苓, sheng di 生地, hua shi 滑石, huang bo 黄柏, chen pi 陈皮, zhi ke 枳壳, zi cao 紫草, bai hua she she cao 白花蛇舌草, chi shao 赤芍, gan cao 甘草</td>
<td>1 study [231]</td>
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<tr>
<td>Chuang yu ye (topical solution) 创愈液</td>
<td>Hu zhang 虎杖, di yu 地榆, ren dong teng 忍冬藤, bai ji 白及, da huang 大黄, bing pian 冰片</td>
<td>1 study [181]</td>
</tr>
<tr>
<td>Yuan tong he ji (oral solution) 元痛合剂</td>
<td>Long dan cao 龙胆草, chai hu 柴胡, huang qin 黄芩, zhi zi 柴胡, ze xie 滑石, che qian zi 车前子, mu tong 木通, ban lan gen 板蓝根, yan hu suo 延胡索, dang gui 当归, sheng di 生地</td>
<td>1 study [211]</td>
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<tr>
<td>Fu qing zhu huo dan shen fang 傅青主火丹神方</td>
<td>Si gua zi 丝瓜子, xuan shen 玄参, dang gui 当归, sheng ma 升麻, chai hu 柴胡</td>
<td>1 study [145]</td>
</tr>
<tr>
<td>Wu wei xiao du yin 五味消毒饮</td>
<td>Si gua zi 丝瓜子, xuan shen 玄参, dang gui 当归, dan zhu ye 淡竹叶, chan tui 蝉蜕, shan dou gen 山豆根, jiang can 姜蚕, xue jie 血竭, pu gong ying 蒲公英, zi hua di ding 紫花地丁, ku shen 苦参, huang qi 黄芪, gan cao 甘草, fu ling 茯苓, wu gong 蜈蚣</td>
<td>2 studies [165, 193]</td>
</tr>
<tr>
<td>San huang fen (powder) 三黄粉</td>
<td>Da huang 大黄, huang bo 黄柏, huang lian 黄连, ru xiang 乳香, mo yao 没药</td>
<td>1 study [182]</td>
</tr>
<tr>
<td>San huang san (powder) 三黄散</td>
<td>Da huang 大黄, huang bo 黄柏, huang lian 黄连, fu pen ye 覆盆叶</td>
<td>1 study [173]</td>
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<tr>
<td>Qing dan hu (cataplasm) 清丹糊</td>
<td>Huang bo 黄柏, huang lian 黄连, qing dai 青黛, cang shu 苍术, bing pian 冰片</td>
<td>1 study [205]</td>
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<tr>
<td>She xian tang 蛇苋汤</td>
<td>Nan she le 南蛇簕, ma chi xian 马齿苋</td>
<td>1 study [158]</td>
</tr>
<tr>
<td>Ji de sheng she yao pian (tablet) 季德胜蛇药片</td>
<td>NS</td>
<td>1 study [165]</td>
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<tr>
<td>Self-designed formula 1</td>
<td>Ku shen 苦参, long dan cao 龙胆草, huang qin 黄芩, zhi zi 梔子, jie xue teng 鸡血藤, ren dong teng 忍冬藤, zi cao 紫草, yan hu suo 延胡索, chai hu 柴胡, mu tong 木通, bing pian 冰片</td>
<td>1 study [168]</td>
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<tr>
<td>Self-designed formula 2</td>
<td>Chai hu 柴胡, huang qin 黄芩, che qian zi 车前子, ze xie 泽泻, mu tong 木通, zhi zi 梔子, long dan cao 龙胆草, di long 地龙, yan hu suo 延胡索, sheng di 生地, dang gui 当归, pu gong ying 蒲公英, zi hua di ding 紫花地丁, tu fu ling 土茯苓, zi cao 紫草, bai xian pi 白鲜皮, da qing ye 大青叶, ban lan gen 板蓝根, gan cao 甘草</td>
<td>1 study [187]</td>
</tr>
<tr>
<td>Self-designed formula 3</td>
<td>Da huang 大黄, huang bo 黄柏, huang lian 黄连, ma chi xian 马齿苋</td>
<td>1 study [174]</td>
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<tr>
<td>Self-designed formula 4</td>
<td>Chai hu 柴胡, long dan cao 龙胆草, chuan lian zi 川楝子, bai zhi 白芷, huang qin 黄芩, ban lan gen 板蓝根, xi xin 细辛, xia gu cao 夏枯草, xuan shen 玄参, pu gong ying 蒲公英, mu dan pi 牡丹皮, quan xie 全蝎, bai hua she cao 白花蛇舌草, gan cao 甘草, bai xian pi 白鲜皮, dang gui 当归, chi shao 赤芍, chuan xiong 川芎</td>
<td>1 study [191]</td>
</tr>
<tr>
<td>Self-designed formula 5</td>
<td>Long dan cao 龙胆草, huang qin 黄芩, zhi zi 梔子, che qian zi 车前子, dang gui 当归, sheng di 生地, ban lan gen 板蓝根, tian hua fen 天花粉, hu zhang 虎杖, yan hu su 延胡索, gan cao 甘草</td>
<td>1 study [222]</td>
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<tr>
<td>Self-designed formula 6</td>
<td>Bai jiang cao 败酱草, ma chi xian 马齿苋, ban lan gen 板蓝根, zi cao 紫草, jin yin hua 金银花, lian qiao 连翘, huang qin 黄芩, zhi zi 梔子, yan hu su 延胡索, chuan lian zi 川楝子, sheng di 生地, dang gui 当归, chi shao 赤芍, da huang 大黄</td>
<td>1 study [143]</td>
</tr>
<tr>
<td>Self-designed formula 7</td>
<td>Da huang 大黄, huang bo 黄柏, huang lian 黄连, qing dai 青黛, wu bei zi 五倍子, mang xiao 茯苓, ru xiang 乳香, mo yao 没药, bing pian 冰片</td>
<td>1 study [151]</td>
</tr>
<tr>
<td>Self-designed formula 8</td>
<td>Jin yin hua 金银花, pu gong ying 蒲公英, zi hua di ding 紫花地丁, yi yi ren 薏苡仁, ban lan gen 板蓝根, xiang fu 香附, hong hua 红花, huang lian 黄连, huang bo 黄柏, huang qin 黄芩, lian qiao 连翘</td>
<td>1 study [199]</td>
</tr>
<tr>
<td>Self-designed formula 9</td>
<td>Huang lian 黄连, huang qin 黄芩, ren zhong huang 人中黄, jin yin hua 金银花, lian qiao 连翘, zi cao 紫草, da qing ye 大青叶, mu dan pi 牡丹皮, yan hu su 延胡索</td>
<td>1 study [142]</td>
</tr>
<tr>
<td>Self-designed formula 10</td>
<td>Ban lan gen 板蓝根</td>
<td>1 study [162]</td>
</tr>
</tbody>
</table>

**Formulæ for clearing heat, detoxifying and resolving dampness (2 formulæ)**

<table>
<thead>
<tr>
<th>Formula Name</th>
<th>Herbs Ingredients</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Yi yi zhu ye san 薏苡竹叶散加味</td>
<td>Yi yi ren 薏苡仁, dan zhu ye 淡竹叶, hua shi 滑石, bai kou ren 白蔻仁, fu ling 茯苓, lian qiao 连翘, tong cao 通草</td>
<td>1 study [233]</td>
</tr>
<tr>
<td>Yi ren chi dou tang 薏仁赤豆汤</td>
<td>Yi yi ren 薏苡仁, chi xiao dou 赤小豆, che qian zi 车前子, cang shu 苍术, chen pi 陈皮, bai zhu 白术</td>
<td>1 study [216]</td>
</tr>
<tr>
<td>Formula Name (Pinyin or translation, Chinese)</td>
<td>Herbs Ingredients (Pinyin, Chinese)</td>
<td>Number of Studies</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Formulae for clearing heat, detoxifying and activating Blood and dispelling stasis (4 formulae)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jie du huo xue tang 解毒活血汤</td>
<td>Long dan cao 龙胆草, chi shao 赤芍, huang qin 黄芩, da qing ye 大青叶, bai shao 白芍, chai hu 柴胡, gan cao 甘草, zhi zi 桂子, huang bo 黄柏, ku shen 苦参, sheng di 生地, dang gui 当归, chuan xiong 川芎, chuan lian zi 川楝子, ban lan gen 板蓝根, fu ling 茯苓</td>
<td>1 study [146]</td>
</tr>
<tr>
<td>Pao zhen ke li ji (granule) 疱疹颗粒剂</td>
<td>Chai hu 柴胡, long dan cao 龙胆草, yan hu suo 延胡索, chuan lian zi 川楝子, yu jin 郁金, ban lan gen 板蓝根, jiang huang 姜黄, jin yin hua 金银花, quan xie 全蝎, di long 地龙, wu gong 蛇蜈蚣, gan cao 甘草</td>
<td>1 study [202]</td>
</tr>
<tr>
<td>Du yu bing jie fang 毒瘤并解方</td>
<td>Huang qin 黄芩, zhi zi 桂子, er zhu 茺术, yan hu suo 延胡索, zhu ling 猪苓, mu tong 木通, rou gui 肉桂, gan cao 甘草</td>
<td>1 study [153]</td>
</tr>
<tr>
<td>Self-designed formula 11</td>
<td>Jin yin hua 金银花, lian qiao 连翘, ye ju hua 野菊, dan shen 丹参, hong hua 红花, mo yao 多药, ru xiang 乳香, yan hu suo 延胡索, ren dong teng 忍冬藤, chi shao 赤芍, chai hu 柴胡, yu jin 郁金, shui zhi 水蛭, gan cao 甘草</td>
<td>1 study [156]</td>
</tr>
<tr>
<td><strong>Formulae for resolving dampness (3 formulae)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>San ren tang 三仁汤</td>
<td>Yi yi ren 藿苡仁, hai kou ren 白蔻仁, xing ren 杏仁, dan zhu ye 淡竹叶, hua shi 滑石, tong cao 通草, hou po 厚朴, fu ling 茯苓, pu gong ying 蒲公英, lian qiao 连翘</td>
<td>1 study [164]</td>
</tr>
<tr>
<td>Chu shi wei ling tang 除湿胃苓汤</td>
<td>Variant 1: Cang shu 苍术, hou po 厚朴, chen pi 陈皮, zhu ling 猪苓, ze xie 泽泻, fu ling 茯苓, bai zhu 白术, hua shi 滑石, fang feng 防风, zhi zi 桂子, mu tong 木通, rou gui 肉桂, gan cao 甘草</td>
<td>4 studies [139, 161, 201, 218]</td>
</tr>
<tr>
<td></td>
<td>Variant 2: Bai zhu 白术, cang shu 苍术, hou po 厚朴, chen pi 陈皮, yan hu suo 延胡索, fu ling 茯苓, che qian zi 车前子, ze xie 泽泻, ban lan gen 板蓝根, yi yi ren 藿苡仁, gan cao 甘草</td>
<td></td>
</tr>
<tr>
<td>Formula Name (Pinyin or translation, Chinese)</td>
<td>Herbs Ingredients (Pinyin, Chinese)</td>
<td>Number of Studies</td>
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<tr>
<td>---------------------------------------------</td>
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<tr>
<td>Variant 3: Cang shu 苍术, chen pi 陈皮, hou po 厚朴, zhu ling 猪苓, ze xie 泽泻, bai zhu 白术, hua shi 滑石, yi yi ren 薏苡仁, ban lan gen 板蓝根, da qing ye 大青叶, yan hu suo 延胡索, lian qiao 连翘, zhi cao 紫草, gan cai 甘草</td>
<td>NS</td>
<td>1 study [175]</td>
</tr>
<tr>
<td>Shen ling bai zhu san 参苓白术散</td>
<td>NS</td>
<td>1 study [175]</td>
</tr>
</tbody>
</table>

**Formulae for activating Blood and dispelling stasis (16 formulae and 1 single herb)**

<table>
<thead>
<tr>
<th>Formula Name (Pinyin or translation, Chinese)</th>
<th>Herbs Ingredients (Pinyin, Chinese)</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qing jie hua yu zu fang 清解化瘀组方</td>
<td>Ku shen 苦参, jing jie 荆芥, she chuang zi 蛇床子, long dan cai 龙胆草, zhi zi 梔子, chi shao 赤芍, dang gui 当归, wu gong 蜈蚣, ji li 荆芥, sheng di 生地, ban lan gen 板蓝根</td>
<td>1 study [150]</td>
</tr>
<tr>
<td>Du yi wei jiao nang (capsule) 独一味胶囊</td>
<td>NS</td>
<td>1 study [160]</td>
</tr>
<tr>
<td>Zhi tong tang 止痛汤</td>
<td>Huang qi 黄芪, dan shen 丹参, bai shao 白芍, chuan shan jia 穿山甲, bai zhi 白芷, ge gen 葛根, gan cai 甘草</td>
<td>1 study [230]</td>
</tr>
<tr>
<td>Long xie jie chang rong pian (tablet) 龙血竭肠溶片</td>
<td>NS</td>
<td>1 study [184]</td>
</tr>
<tr>
<td>Huo xue hua yu tang 活血化瘀汤</td>
<td>NS</td>
<td>1 study [175]</td>
</tr>
<tr>
<td>Tong luo liang xue jie du tang 通络凉血解毒汤</td>
<td>Sheng di 生地, dang gui 当归, chuan xiong 川芎, mu dan pi 牡丹皮, chi shao 赤芍, tian qi 田七, dan shen 丹参, yu jin 郁金</td>
<td>1 study [206]</td>
</tr>
<tr>
<td>Xing qi qu yu tang (self-designed formula) 行气祛瘀汤</td>
<td>Huang qi 黄芪, yan hu suo 延胡索, chuan lian zi 川楝子, chai hu 柴胡, dang gui 当归, chi shao 赤芍, ru xiang 乳香, mo yao 没药, mu dan pi 牡丹皮, ban lan gen 板蓝根, qing dai 青黛, zhi cao 紫草</td>
<td>1 study [227]</td>
</tr>
<tr>
<td>Long xue jie jiao nang (capsule) 龙血竭胶囊</td>
<td>NS</td>
<td>1 study [159]</td>
</tr>
<tr>
<td>Formula Name (Pinyin or translation, Chinese)</td>
<td>Herbs Ingredients (Pinyin, Chinese)</td>
<td>Number of Studies</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Formulae for cooling Blood and detoxifying (1 formula)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-designed formula 11</td>
<td>Di yu地榆, bing pian冰片</td>
<td>1 study [171]</td>
</tr>
<tr>
<td>Xie cao qing yu tang 缬草清郁汤</td>
<td>Xie cao 缬草, hong teng 红藤, luo shi teng 络石藤, ren dong teng 忍冬藤, li zhi he 荔枝核, sheng di 生地, chuan xiong 川芎, ze xie 泽泻, mu dan pi 牡丹皮, zhi ke 枳壳, yan hu suo 延胡索, fu shen 茯神, huang qi 黄芪</td>
<td>1 study [179]</td>
</tr>
<tr>
<td>Shang ke jie gu pian (tablet) 伤科接骨片</td>
<td>NS</td>
<td>1 study [196]</td>
</tr>
<tr>
<td>Shang ke ling pen wu ji (spray) 伤科灵喷雾剂</td>
<td>NS</td>
<td>1 study [198]</td>
</tr>
<tr>
<td>Tao hong si wu tang 桃红四物汤</td>
<td>Variant 1: Shu di 熟地, dang gui 当归, bai shao 白芍, chuan xiong 川芎, tao ren 桃仁, hong hua 红花</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Variant 2: Tao ren 桃仁, hong hua 红花, dang gui 当归, chuan xiong 川芎, chi shao 赤芍, zhi ke 枳壳, zi cao 紫草, ban lan gen 板蓝根, dan shen 丹参, ru xiang 乳香, mo yao 没药, mu dan pi 牡丹皮, xuan shen 玄参, gan cao 甘草</td>
<td>2 studies [161, 218]</td>
</tr>
<tr>
<td>Huo xue san yu tang 活血散瘀汤</td>
<td>Tao ren 桃仁, hong hua 红花, ji xue teng 鸡血藤, yan hu suo 延胡索, xiang fu 香附, chen pi 陈皮, chai hu 柴胡, yu jin 郁金, sheng di 生地, bai shao 白芍, mu dan pi 牡丹皮, gan cao 甘草</td>
<td>1 study [231]</td>
</tr>
<tr>
<td>Shi run shao shang gao (ointment) 湿润烧伤膏</td>
<td>NS</td>
<td>1 study [229]</td>
</tr>
<tr>
<td>Yun nan bai yao (powder) 云南白药</td>
<td>NS</td>
<td>1 study [220]</td>
</tr>
<tr>
<td>Single herb</td>
<td>Xi nan wen shu lan 西南文殊兰</td>
<td>1 study [159]</td>
</tr>
<tr>
<td>Formula Name (Pinyin or translation, Chinese)</td>
<td>Herbs Ingredients (Pinyin, Chinese)</td>
<td>Number of Studies</td>
</tr>
<tr>
<td>---------------------------------------------</td>
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</tr>
<tr>
<td><strong>Formulae for treating abscess, ulcer and detoxifying (11 formulae)</strong></td>
<td></td>
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</tr>
<tr>
<td>Ba du gao (ointment) 拔毒膏</td>
<td>Xiong huang 雄黄, ming fan 明矾, bing pian 冰片</td>
<td>1 study [157]</td>
</tr>
<tr>
<td>Qing zhen zhi tong gao (ointment) 消疹止痛膏</td>
<td>Xiong huang 雄黄, bai fan 白矾, ru xiang 乳香, mo yao 没药, bing pian 冰片</td>
<td>1 study [172]</td>
</tr>
<tr>
<td>San fen ca ji (liniment) 三粉擦剂</td>
<td>Xiong huang 雄黄, ming fan 明矾, hu po 琥珀</td>
<td>1 study [194]</td>
</tr>
<tr>
<td>Liu shen wan (pill) 六神丸</td>
<td>Niu huang 牛黄, zhen zhu 珍珠, xiong huang 雄黄, chan su 蟾酥, she xiang 麝香, bing pian 冰片</td>
<td>1 study [226]</td>
</tr>
<tr>
<td>Ba du tu mo ji (film coating agent) 拔毒涂膜剂</td>
<td>Xiong huang 雄黄, bai fan 白矾</td>
<td>1 study [213]</td>
</tr>
<tr>
<td>Ba du san (powder) 拔毒散</td>
<td>Xiong huang 雄黄, bai fan 白矾</td>
<td>1 study [213]</td>
</tr>
<tr>
<td>Pao zhen san (powder) 疱疹散</td>
<td>Xiong huang 雄黄, bing pian 冰片, qing dai 青黛, shi gao 石膏, bai zhi 白芷, guan zhong 贯众, ma chi xian 马齿苋, gan cao 甘草</td>
<td>1 study [230]</td>
</tr>
<tr>
<td>Lu huang san (powder) 芦黄散</td>
<td>Xiong huang 雄黄, wu gong 蜈蚣, bai zhi 白芷, bing pian 冰片, lu hui 芦荟</td>
<td>1 study [146]</td>
</tr>
<tr>
<td>Pao zhen gao (ointment) 疱疹膏</td>
<td>Da huang 大黄, huang bo 黄柏, bai zhi 白芷, xiong huang 雄黄, dan nan xing 胆南星, zhang nao 樟脑, bing pian 冰片</td>
<td>1 study [222]</td>
</tr>
<tr>
<td>Liu shen wan (pill) 六神丸</td>
<td>NS</td>
<td>1 study [229]</td>
</tr>
<tr>
<td>Zi jin ding (pill) 紫金锭</td>
<td>Zi jin ding 紫金锭, qing dai 青黛</td>
<td>1 study [204]</td>
</tr>
<tr>
<td><strong>Formulae for clearing heat, activating Blood and regulating qi (5 formulae)</strong></td>
<td></td>
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</tr>
<tr>
<td>Modified Xiao chai hu tang 加味小柴胡汤/小柴胡汤化裁</td>
<td>Variant 1: Chai hu 柴胡, huang qin 黄芩, zhi zi 柘子, fa ban xia 法半夏, jin yin hua 金银花, zi hua di ding 紫花地丁, chuan xiong 川芎, bai shao 白芍, chen pi 陈皮, yan hu suo 延胡索, gan cao 甘草</td>
<td>3 studies [197, 208, 221]</td>
</tr>
<tr>
<td></td>
<td>Variant 2: Chai hu 柴胡, ban xia 半夏, gan cao 甘草, huang qin 黄芩, zhi zi 柘子, lian qiao 连翘, fang feng 防风, jing jie 荆芥, chuan xiong 川芎, bai shao 白芍, chen pi 陈皮</td>
<td></td>
</tr>
<tr>
<td>Formula Name (Pinyin or translation, Chinese)</td>
<td>Herbs Ingredients (Pinyin, Chinese)</td>
<td>Number of Studies</td>
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<tr>
<td>---------------------------------------------</td>
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</tr>
<tr>
<td>Chai hu shu gan san 柴胡疏肝散</td>
<td>Variant 1: Chai hu 柴胡, bai shao 白芍, chi shao 赤芍, chuan xiong 川芎, dang gui 当归, chen pi 陈皮, zhi ge 枳壳, xiang fu 香附, yu jin 郁金, long dan cao 龙胆草, ye ju hua 野菊花, jin qian cao 金钱草, gan cao 甘草</td>
<td>2 study [183, 201]</td>
</tr>
<tr>
<td></td>
<td>Variant 2: Chai hu 柴胡, sheng di 生地, dang gui 当归, bai shao 白芍, chi shao 赤芍, zhi ge 枳壳, xiang fu 香附, chuan lian zi 川楝子, hong hua 红花, chen pi 陈皮, chuan xiong 川芎, yu jin 郁金, san leng 三棱, er zhu 茵术, gan cao 甘草</td>
<td></td>
</tr>
<tr>
<td>Fu yuan huo xue tang combined with Chai hu shu gan san 复元活血汤合柴胡疏肝散</td>
<td>Chai hu 柴胡, xiang fu 香附, chi shao 赤芍, hong hua 红花, tao ren 桃仁, ren dong teng 忍冬藤, si gua luo 丝瓜络, dang gui 当归, chuan xiong 川芎, zhi ke 枳壳, ru xiang 乳香, mo yao 没药</td>
<td>1 study [216]</td>
</tr>
<tr>
<td>Xiao yao san 逍遥散</td>
<td>NS</td>
<td>1 study [139]</td>
</tr>
<tr>
<td>Self-designed formula 12</td>
<td>Jin yin hua 金银花, da qing ye 大青叶, pu gong ying 蒲公英, ma chi xian 马齿苋, huang qin 黄芩, zhi zi 桑子, long dan cao 龙胆草, yi yi ren 薏苡仁, ze xie 泽泻, che qian cao 车前草, dan shen 丹参, chai hu 柴胡, yan hu suo 延胡索, gan cao 甘草</td>
<td>1 study [175]</td>
</tr>
</tbody>
</table>

**Formulae for clearing heat and tonifying qi (2 formulae)**

<table>
<thead>
<tr>
<th>Formula Name</th>
<th>Herbs Ingredients (Pinyin, Chinese)</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yi qing qu pao tang 益清祛疱汤</td>
<td>Huang qi 黄芪, wu wei zi 五味子, dang gui 当归身, mai dong 麦冬, da qing ye 大青叶, long dan cao 龙胆草, jie geng 桔梗, bo he 薄荷, hong hua 红花, yan hu suo 延胡索, mu dan pi 牡丹皮, gan cao 甘草</td>
<td>1 study [195]</td>
</tr>
<tr>
<td>Qi shen tang 芪参汤</td>
<td>Huang qi 黄芪, xuan shen 玄参, dan shen 丹参, jin yin hua 金银花, dang gui 当归, tu fu ling 土茯苓, gan cao 甘草</td>
<td>1 study [158]</td>
</tr>
<tr>
<td>Formula Name (Pinyin or translation, Chinese)</td>
<td>Herbs Ingredients (Pinyin, Chinese)</td>
<td>Number of Studies</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>------------------------------------</td>
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</tr>
<tr>
<td><strong>Formulae for resolving dampness and regulating qi (1 formula)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wei ling tang combined with Chai hu shu gan san 胃苓汤合并柴胡疏肝散</td>
<td>Zhu ling 猪苓, ze xie 泽泻, fu ling 茯苓, gu i zhi 桂枝, hou po 厚朴, cang zhu 苍术, chai hu 柴胡, chuan xiong 川芎, zhi ke 枳壳, bai shao 白芍, long dan cao 龙胆草, huang qin 黄芩, huang qi 黄芪, gan cao 甘草</td>
<td>1 study [217]</td>
</tr>
<tr>
<td><strong>Formulae for moistening dryness and resolving itch (1 formula)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Run zao zhi yang jiao nang (capsule) 润燥止痒胶囊</td>
<td>Sheng di 生地, he shou wu 何首乌, ku shen 苦参, sang ye 桑叶, hong huo ma 红活麻</td>
<td>1 study [228]</td>
</tr>
<tr>
<td><strong>Chemical compounds extracted from the herbs (2 chemical compounds from single herbs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound Glycyrrhizin tablet 复方甘草酸苷片</td>
<td>Gan cao 甘草</td>
<td>1 studies [176]</td>
</tr>
<tr>
<td>Dan shen tong jiao nang (capsule) 丹参酮胶囊</td>
<td>Dan shen 丹参</td>
<td>1 study [141]</td>
</tr>
<tr>
<td><strong>Not Specified formula (1 formula)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>She bu guo zhi (topical solution) 无固膏 (topical solution)</td>
<td>NS</td>
<td>1 study [165]</td>
</tr>
<tr>
<td><strong>Single herb treatment (1 single herb)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single herb</td>
<td>Qi she hua 七色花</td>
<td>1 study [149]</td>
</tr>
<tr>
<td><strong>Note:</strong> Ingredient chuan shan jia 穿山甲 is on the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) list in Australia (Appendix II). The trading of chuan shan jia 穿山甲 is strictly restricted in Australia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix 8: Search terms for experimental evidence

<table>
<thead>
<tr>
<th>Herb Name (Pinyin, Chinese)</th>
<th>Scientific Name</th>
<th>Key Chemical Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhi zi 柘子</td>
<td>1. <em>Gardenia jasminoides</em> Ellis</td>
<td>Iridoid and flavonoid glycosides: gardenoside, geniposide, genipin-1-gentiobioside, shanzhiside, gardoside, jasminoidin</td>
</tr>
<tr>
<td>Huang qin 黄芩</td>
<td>1. <em>Scutellaria baicalensis</em> Georgi</td>
<td>Flavonoids: baicalein, wogonin, norwogonin</td>
</tr>
<tr>
<td>Dang gui 当归</td>
<td>1. <em>Angelica sinensis</em> (Oliv.) Diels</td>
<td>Volatole oil: humulene, guaiacol, ethylresorcinol, isoeugenol, vanillin, ligustilide, butylideneaphthalide, angelicide&lt;br&gt;Other constituents: angelicin</td>
</tr>
<tr>
<td>Herb Name (Pinyin, Chinese)</td>
<td>Scientific Name</td>
<td>Key Chemical Compounds</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------</td>
<td>------------------------</td>
</tr>
</tbody>
</table>
| Ban lan gen 板蓝根          | 1. *Isatis indigotica* Fort. | **Alkaloids**: indgotin (indigo), indirubin  
**Amino acids, glycosides**  
**Other constituents**: epigoitrin, tryptanthrine |
| Ze xie 泽泻                  | 1. *Alisma orientalis* (Sam.) Juzep. | **Tetracyclic triterpenes**: alisol  
**Sesquiterpenes**: alismol, alismoxide  
**Amino acids, fatty acids** |
| Yan hu suo 延胡索            | 1. *Corydalis yanhusuo* W.T. Wang | **Alkaloids**: dehydrocorydaline, tetrahydropalmatine, berberine  
**Other constituents**: mucilage, volatile oil |
| Che qian zi 车前子           | 1. *Plantago asiatica* L.  
2. *Plantago depressa* Willd. | **Iridoid glycosides**: aucubin,  
**Phenylpropane glycosides**: plantainoside, plantamajoside,  
**Organic acids** |
Appendix 9: Study recruitment poster example

Shingles is biting you, and Chinese medicine may help.

If you are 50 years or older and suffering from shingles (herpes zoster), you may be eligible to participate in our study conducted by RMIT University. We are investigating a Chinese herbal medicine formula combined with conventional medicine to treat this disease.

If you are interested, please contact one of our researchers for further information:

Kaiyi Wang Ph: email: