



**CHINESE HERBAL MEDICINES AS AN
ADJUNCT MANAGEMENT FOR
FATIGUE AND MUSCLE WEAKNESS IN
CANCER PATIENTS RECEIVING
CHEMOTHERAPY**



DISCLAIMER

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organizations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

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Published by

Malaysian Health Technology Assessment Section, (MaHTAS)

Medical Development Division, Ministry of Health Malaysia

Level 4, Block E1, Complex E, Precinct 1

Federal Government Administrative Centre

62590, Putrajaya, Malaysia

Tel: 603 88831246

Fax: 603 8883 1230

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ISBN (Print):

Available on the MOH website: <http://www.moh.gov.my/v/hta>

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DISCLOSURE

The authors of this report have no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health Malaysia.

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ACKNOWLEDGEMENT

The authors for this Health Technology Assessment Report would like to express their gratitude and appreciation to the following for their contribution and assistance:

- Health Technology Assessment and Clinical Practice Guidelines Council.
- Technical Advisory Committee for Health Technology Assessment.

DISCLOSURE

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EXECUTIVE SUMMARY

A National Health & Morbidity Survey was conducted in year 2015 to study the prevalence usage of traditional & complementary medicine (T&CM) in Malaysia. From the survey, the overall prevalence of ever used T&CM with consultation was 29.25% (95% CI: 27.66%, 30.89%). The prevalence of T&CM use within the last twelve months was 21.51% (95% CI: 20.11%, 22.98%). T&CM practices are mainly used to maintain wellness. Chinese herbal medicines originated in ancient China and have evolved over thousands of years. The basic concept of traditional Chinese medicines is to help patients achieve balance with the application of essence-*qi*-spirit theory, *yin-yang* theory and five elements theory. Throughout the years, large number of Chinese herbal medicines was used to treat different health conditions. Studies have been done on the effectiveness of single herbs entity, multiple herbs entity which are used separately or concurrently with mainstream medicines to treat selected diseases.

Currently in Malaysia, Chinese herbal medicines treatments are available at four Ministry of Health hospitals namely National Cancer Institute, Hospital Kepala Batas (Pulau Pinang), Hospital Sultan Ismail (Johor Bahru) and Hospital Wanita & Kanak-kanak Sabah. A guideline was developed to document the practice of using traditional and complementary medicine on herbal therapy as an adjunct treatment for cancer.² In the guideline, it was mentioned that an adjunct is define as a supporting treatment for chemotherapy and radiotherapy. The aim of herbal treatment is usually to improve well being. There are four categories of patients that will be referred for the herbal therapy. i.) Newly diagnosed cancer patients on radiotherapy or chemotherapy or surgery. ii.) Patients completed chemotherapy with recurrence. iii.) Advanced stage cancer on palliative treatment. iv.) Cancer patients who refused medical treatment. As a standard of practice, the guideline outlined that all cancer patients seeking for adjunct treatment at T&CM Unit should be referred by medical oncologist, properly investigated and a precise diagnosis has been made. A qualified herbal practitioner will provide consultation and prescribe herbal treatment. Then, the patients will receive concentrated extract granule (which are prepared and packed in the form of sachet).

With the development of herbal therapy as an adjunct for the cancer patients during or after chemotherapy, there are always issues that need to be discussed and considered regarding the treatment effectiveness.

This Health Technology Assessment (HTA) focuses on the study of Chinese herbal medicines concept in management of the fatigue and muscle weakness in cancer patients receiving chemotherapy. For example, herbs such as ren shen, dang shen huang qi, bai zhu, fu ling, gan cao huang jing and hong zao, have been used to address the fatigue and muscle weakness which are caused by syndrome of Qi.

This HTA was requested by Senior Principal Assistant Director from Traditional and Complementary medicine Division, Ministry of Health to assess the effectiveness of Chinese herbal medicines in the management of fatigue and muscle weakness in cancer patients receiving chemotherapy.

Technical Features

In Traditional and Complementary Medicine (T&CM), herbs are used in combinations to enhance their medical benefit and/or to reduce their side effects. In fact, low dose of multiple pharmacological agents are being administered synergistically. As a branch of T&CM,

Chinese herbs or herbal products may have been ingested (as in a tea), inhaled or applied to the body and may have been used singly or in combination with other herbs. A (non-exhaustive) list includes ren shen (ginseng), huang qi (astragalus root), shan yao (dioscorea rhizome), fu ling (poria), common curculigo, gan cao (glycyrrhiza root), bai zhu (atractylodes rhizome), and Chinese jujube. Herbs that have been recently studied through clinical research for chronic fatigue syndrome (CFS) and related symptoms include single herbs such as ren shen (ginseng root), fu ling (poria), gan cao (glycyrrhiza root), dang gui (angelica root), and bai shao (peony root), as well as established formulations.

Many patients have symptoms of general weakness, thirst, and fatigue during or after chemotherapy or radiotherapy. These symptoms are similar to the syndrome of Qi and Yin deficiency in Traditional Chinese medicine theory. Usually for these symptoms, the patients were given Chinese herbal medicines recipes that will benefit the Qi or Yin. In recent decades, cancer patients around the world and especially in China have used a large number of herbal medicines including single herbs, traditional herbal formulations, and Chinese medicine preparations.

Policy Question

Should Chinese herbal medicine be used as an adjunct in the management for fatigue and muscle weakness in cancer patients receiving chemotherapy?

Objectives

- a) To assess the efficacy/effectiveness of using Chinese herbal medicines as an adjunct management for fatigue and muscle weakness in cancer patients receiving chemotherapy.
- b) To assess the safety of using Chinese herbal medicines as an adjunct management for fatigue and muscle weakness in cancer patients receiving chemotherapy.
- c) To assess the economic implications of using Chinese herbal medicines as an adjunct management for fatigue and muscle weakness in cancer patients receiving chemotherapy.
- d) To assess the organizational issues related to the use of certain Chinese herbal medicines as an adjunct management for fatigue and muscle weakness in cancer patients receiving chemotherapy.

Methods

Major electronic databases such as Medline, Embase, Pubmed, EBM reviews, HTA databases, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Review, Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) databases were searched until November 2016. Studies were reviewed separately according to the research questions. Retrieved records were screened for relevance. The search was limited to publication year from 2000-2016. Additional articles were identified by reviewing the bibliographies of retrieved articles and hand searching of journals. Potentially relevant papers were retrieved and independently checked against predefined criteria for inclusion by two reviewers. Included reviews and primary papers were critically appraised using the Critical Appraisal Skills Programme (CASP), evidence was graded based on guidelines from U.S./Canadian Preventive Services Task Force, and data were extracted and narratively presented.

Results and conclusion

Six studies were included in this review: one systematic review, four randomized controlled trial (RCT's), and one pre and post interventional study. All the six studies reported on efficacy/effectiveness, while only five of the six studies reported on safety/side effects. We found two chinese papers with abstracts in English and full text in Chinese. However due to lack of funds, it was not translated by a professional translator (expensive payment fee required). The article on Systematic review by Wu X et al, had most of the articles included in the study from the Chinese database (Wan Fang Digital Journals, Chinese Biomedical Databases, and Taiwan Periodical Literature Databases). All papers were from China and studies were done on the chinese population.

a) Management of fatigue

Study	Types of preparation	Herbs used	Effectiveness	Treatment given
Wu X et al. 2016. Systematic reviews consisting of 61 RCTs. (n=4247)	Decoction, injection, tablet	Yi-fei-bai-du decoction, Fei-liu-ping extract, Hai-shen-su, Fu-zheng-jie-du decoction Kang-la-te injection, Shen-qi-fu-zheng injection, Compound ku-shen injection, Kang-ai injection, Zi-jin-long tablet, Xiao-ai-ping injection, Shen-fu injection	beneficial effect on QoL among NSCLC patients when used with chemotherapy	CHM given during chemotherapy
Barton DL et al. 2013. RCT, (n=364)	Capsule	2000 mg of American ginseng	Improvement in fatigue	CHM given during chemotherapy, but those who had completed chemotherapy were given after
Xu Y et al. 2015. Phase I/II open label trial, (n=33)	As package to make a decoction	Ren Shen Yangrong Tang (RSYRT) consist of Dangshen (<i>Radix codonopsis pilosulae</i>), Huanqi (<i>Astragalus mongholicus</i>), Baizhu (<i>Rhizoma Atractylodes macrocephala</i> ; white rhizome of largehead atractylodes); Fuling (<i>Poria cocos</i> ; Indian bread), Chenpi (<i>Pericarpium citri reticulatae</i> , dried tangerine peel), Shengdi (<i>Radix rehmanniae</i> ; root of rehmannia), Baishao (<i>Radix paeoniae alba</i> ; white peony root), Danggui (<i>Angelica sinensis</i> ; root of Chinese Angelica), Wuweizi (<i>Fructus schisandrae</i> ; shizandra berry), Yuanzhi (<i>Radix polygalae</i> ; polygala root), Rougui (<i>Cortex cinnamomi</i> ; cinnamon), Gancao (<i>Radix glycyrrhizae</i> ; licorice).	Fatigue severity decreased	CHM given after completed chemotherapy
Xue D et al. 2015. RCT, (n=24)	Not mentioned but Include decoction	Chinese herbal medicines : Type of herbs not mentioned	For function-dependent patients, the symptoms of fatigue and cough were alleviated	CHM given during chemotherapy
Jeong JS et al.2010. RCT, (n=40)	Granules (given orally)	Bojungikki-tang	improvements in fatigue level	CHM given after completed chemotherapy
Yennurajalingam S et al. 2015. Intervention study, (n=30)	Capsule	800 mg. Panax Ginseng	improved cancer related fatigue (CRF)	CHM given during chemotherapy

There was limited fair to low level of evidence to suggest that Chinese herbal medicines was effective in improving the QoL such as fatigue symptoms severity when used as an adjunct management for fatigue in cancer patients receiving chemotherapy. Most of the side effects of the Chinese herbal medicine in these studies were mild such as agitation, anxiety, insomnia, nausea, and vomiting. There were no morbidity and severe adverse events reported. There was no retrievable evidence on cost-effectiveness. However, the retail price of certain Chinese herbal medicine in Malaysia ranges from RM 26 to RM 151 per 100 gm. However, small number of subjects limited most of the studies and most studies did not report on allocation concealment as well as blinding. The studies included invovled the use of

many different types of Chinese herbal medicines and many different types of assessment tools were used to measure the efficacy / effectiveness of the Chinese herbal medicines for the management of fatigue in cancer patients receiving chemotherapy.

b) Management of muscle weakness

There was no retrievable evidence on effectiveness, safety and cost effective of Chinese herbal medicine as an adjunct management of muscle weakness for cancer patients receiving chemotherapy.

Recommendation

Based on the above review, most of the studies suggested that Chinese herbal medicines such as Yi-fei-bai-du decoction, Fei-liu-ping extract, Hai-shen-su, Fu-zheng-jie-du decoction Kang-la-te injection, Shen-qi-fu-zheng injection, compound ku-shen injection, Kang-ai injection, Zi-jin-long tablet, Xiao-ai-ping injection, Shen-fu injection, American ginseng, Ren Shen Yangrong Tang (RSYRT), Bojungikki-tang and Panax Ginseng may have potential benefit for the management of fatigue in cancer patients receiving chemotherapy. However, the evidence retrieved was limited and had biases. More rigorous and well-designed clinical trials investigating the effects of Chinese herbs on relieving the fatigue and muscle weakness effect in cancer patients receiving chemotherapy is warranted. Hence, Chinese herbal medicines may be used for the management of fatigue in cancer patients receiving chemotherapy in a research environment by a certified and registered practitioner.

TABLE OF CONTENTS

DISCLAIMER	i
AUTHORS	ii
EXPERT COMMITTEE	iii
EXTERNAL REVIEWERS	iv
ACKNOWLEDGEMENT AND DISCLOSURE	v
EXECUTIVE SUMMARY	vi
ABBREVIATION	xi
CHAPTER 1: BACKGROUND	1
Description of Health Problem	1
Current service provision	2
Technical features	2
CHAPTER 2: DEFINITION OF POLICY QUESTION AND OBJECTIVES	4
Policy Question	4
Overall aims and objectives of the assessment	4
CHAPTER 3: METHODS	5
Search Strategy	5
Inclusion and exclusion criteria	6
Critical Appraisal of Literature	6
Analysis and Synthesis of evidence	7
Data extraction strategy	7
Data synthesis	7
CHAPTER 4: OVERALL SEARCH RESULTS	8
CHAPTER 5: CHINESE HERBAL MEDICINES AS AN ADJUNCT MANAGEMENT OF FATIGUE AND MUSCLE WEAKNESS IN CANCER PATIENTS RECEIVING CHEMOTHERAPY	12
CHINESE HERBAL MEDICINE AS AN ADJUNCT MANAGEMENT OF FATIGUE	12
Efficacy / Effectiveness	12
Safety	15
Cost/cost effectiveness	17
Organizational Issues	19
CHINESE HERBAL MEDICINE AS AN ADJUNCT MANAGEMENT OF MUSCLE WEAKNESS	19
Efficacy / Effectiveness	19
Safety	19
Cost/cost effectiveness	19
Organizational Issues	19
Limitations	19
Discussion	20
Conclusion	20
Recommendation	21
REFERENCES	22
APPENDICES	25
Appendix 1- Health Technology Assessment Protocol	26
Appendix 2- Electronic databases searched	29
Appendix 3 - Hierarchy of evidence for effectiveness studies	31
Appendix 4- Evidence Table (Included studies)	32
Appendix 5- List of excluded studies	44

Abbreviations

ADL	Activities of daily life
CFS	Chronic fatigue syndrome
CGA	Comprehensive geriatric assessment
CHM	Chinese herbal medicine
CNS	Central nervous system
CRF	Cancer related fatigue
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern cooperative oncology group
EORTC QLQ-C30 core scale	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 scale
ESAS	Edmonton Symptom Assessment Scale
FACT-F	Functional Assessment of Cancer Therapy-fatigue
FACT-G	Functional Assessment of Cancer Therapy-general
GSE	Global Symptom Evaluation
HADS	Hospital Anxiety And Depression Scale
IADL	Instrumental Activities Of Daily Life
LC13 scale	Lung Cancer 13 scale
MFSI-SF	Multidimensional Fatigue Symptom Inventory–Short Form
MDASI–TCM scale	M.D. Anderson Symptom Inventory–Traditional Chinese Medicine scale
NMA	Network meta-analysis
NSCLC	Nonsmall Cell Lung Cancer
NCCN	National Comprehensive Cancer Network
PG	Panax Ginseng
RCT	Randomised Controlled Trial
RSYRT	Ren Shen Yangrong Tang
SD	Standard Deviation
SR	Systematic Reviews
T&CM	Traditional and Complementary Medicine
TOI-F	Trial Outcome Index-fatigue
QoL	Quality of Life
VAS	Visual Analogue Scale
VAS-F	Visual Analogue Scale Of Global Fatigue

HEALTH TECHNOLOGY ASSESSMENT

THE EFFECT OF CHINESE HERBAL MEDICINES AS AN ADJUNCT MANAGEMENT OF FATIGUE AND MUSCLE WEAKNESS IN CANCER PATIENTS RECEIVING CHEMOTHERAPY

Chapter 1: Background

Description of health problem

A National Health & Morbidity Survey was conducted in year 2015 to study the prevalence usage of Traditional & Complementary Medicine (T&CM) in Malaysia. From the survey, the overall prevalence of ever used T&CM with consultation was 29.25% (95% CI: 27.66%, 30.89%). The prevalence of T&CM use within the last twelve months was 21.51% (95% CI: 20.11%, 22.98%). T&CM which are practiced in Malaysia include Chinese herbal medicines, acupuncture, malay massage, Ayurveda, etc. and are mainly used to maintain wellness.¹ Chinese herbal medicines originated in ancient China and have evolved over thousands of years. The basic concept of traditional Chinese medicines is to help patients achieve balance with the application of essence-qi-spirit theory, *yin-yang* theory and five elements theory. Throughout the years, large number of Chinese herbal medicines was used to treat different health conditions.

Traditional Chinese Medicines has been applied in cancer patient's care in recent decades. The different types of deficiency syndrome in Traditional Chinese Medicines is an important concept to categorize the patients lacking of specific element [(such as qi, blood, yin, yang) (氣 qì, 血 xuè, 陰 yīn, 陽 yáng)]. In brief, qi (氣 qì) refers to the vital energy of the body. It maintains blood circulation, warms the body, and fights diseases. The blood nourishes the body, moistens body tissues, and ensures they do not dry out. Yin (陰 yīn) and yang (陽 yáng) are complementary opposites that interact within a greater whole, as part of a dynamic system. Generally, anything that is moving, ascending, bright, progressing, hyperactive, including functional diseases of the body, pertains to yang (陽 yáng). The characteristics of stillness, descending, darkness, degeneration, hypo-activity, including organic disease, pertain to yin (陰 yīn). Patients with any type of deficiency syndrome may also have the symptoms of weakness, low energy, anemia etc., which are roughly described as fatigue-like sensations in western medicine.² Fatigue is a common and distressing problem for cancer patients. In contrast to everyday or normal fatigue, cancer related fatigue (CRF) is characterized by feelings of tiredness and weakness despite adequate amounts of sleep and rest. Furthermore, quality of life (QoL) is a significant concern for cancer patients, whereby symptoms such as fatigue, insomnia, and psychological distress often disrupt cancer patients' QoL. Several studies have focused on CRF and QoL in cancer patients, although there is limited data on the association of CRF with Traditional Chinese Medicines deficiency syndrome. Patients with Traditional Chinese Medicines deficiency syndromes had poorer QoL and experienced CRF, which may need to be managed early, especially the qi deficiency (氣虛 qì xū) groups. The "qi" (氣 qì) may play an important role in the health balance of cancer patients. Therefore, qi (氣 qì) supply treatment may have a promising role in palliating the cancer related symptoms and improving the QoL. Qi (氣 qì) and yin (陰 yīn), are closely related to each other and need to be treated at the same time. Further research in this field would be of great help in T&CM development of cancer patients' care.²⁻⁹

Current service provision

Currently in Malaysia, Chinese herbal medicines treatments are available at four Ministry of Health hospitals namely National Cancer Institute, Hospital Kepala Batas (Pulau Pinang), Hospital Sultan Ismail (Johor Bahru) and Hospital Wanita & Kanak-kanak Sabah. A guideline was developed to document the practice of using traditional and complementary medicine on herbal therapy as an adjunct treatment for cancer.¹⁰ In the guideline, it was mentioned that an adjunct is define as a supporting treatment for chemotherapy and radiotherapy. The aim of herbal treatment is usually to improve well being. There are four categories of patients that will be referred for the herbal therapy. i.) Newly diagnosed cancer patients on radiotherapy or chemotherapy or surgery. ii.) Patients completed chemotherapy with recurrence. iii.) Advanced stage cancer on palliative treatment. iv.) Cancer patients who refused medical treatment. As a standard of practice, the guideline outlined that all cancer patients seeking for adjunct treatment at T&CM Unit should be referred by medical oncologist, properly investigated and a precise diagnosis has been made. A qualified herbal practitioner will provide consultation and prescribe herbal treatment. Then, the patients will receive concentrated extract granule (which are prepared and packed in the form of sachet).

With the development of herbal therapy as an adjunct for the cancer patients during or after chemotherapy, there are always issues that need to be discussed and considered regarding the treatment effectiveness.¹¹

This Health Technology Assessment (HTA) focuses on the study of Chinese herbal medicines concept in management of the fatigue and muscle weakness in cancer patients receiving chemotherapy. For example, herbs such as ren shen, dang shen huang qi, bai zhu, fu ling, gan cao huang jing and hong zao, have been used to address the fatigue and muscle weakness, which are caused by syndrome of Qi.

This HTA was requested by Senior Principal Assistant Director from Traditional and Complementary medicine Division, Ministry of Health to assess the effectiveness of Chinese herbal medicines in the management of fatigue and muscle weakness in cancer patients receiving chemotherapy.

Technical Features

In Traditional and Complementary Medicine (T&CM), herbs are used in combinations to enhance their medicinal benefits and/or to reduce their side effects. In fact, low doses of multiple pharmacological agents are being administered synergistically. Traditional Chinese Medicines (TCM) and herbal medicines in particular have been used cancer treatment for thousands of years in China, Japan, and other Asian countries. Integration of Traditional Chinese Medicines combined with conventional Western medicine (chemotherapy and radiotherapy) may provide effective supportive care for cancer patients. Traditional Chinese Medicines may increase the sensitivity of chemo- and radio-therapeutics, reduce the side effects and complications associated with chemotherapy and radiotherapy, and improving patients' QoL. Herbs may have been ingested (as in a tea), inhaled or applied to the body (as in a lotion), and may have been used singly or in combination with other herbs. A (non-exhaustive) list includes ren shen (ginseng), huang qi (astragalus root), shan yao (dioscorea rhizome), fu ling (poria), common curculigo, gan cao (glycyrrhiza root), bai zhu (atractylodes

rhizome), and Chinese jujube. Herbs that have been recently studied through clinical research for chronic fatigue syndrome (CFS) and related symptoms include single herbs such as ren shen (ginseng root), fu ling (poria), gan cao (glycyrrhiza root), dang gui (angelica root), and bai shao (peony root), as well as established formulations.¹²⁻¹⁷

Many patients have symptoms of general weakness, thirst, and fatigue during or after chemotherapy or radiotherapy. These symptoms are similar to the syndrome of Qi and Yin deficiency in Traditional Chinese medicine theory. Usually for these symptoms, the patients were given Chinese herbal medicines recipes that will benefit the Qi or Yin. In recent decades, cancer patients around the world and especially in China have used a large number of herbal medicines including single herbs, traditional herbal formulations, and Chinese medicine preparations. Several herbal medicines have been found to have potentially beneficial effects on cancer progression and may ameliorate chemotherapy- or radiotherapy-induced complications and side effects.¹²⁻¹⁷ Some examples of Chinese herbal medicine that are usually used to improve the quality of life or reduce the side effects of chemotherapy or radiotherapy such as fatigue are as in the table below:

Table 2: Examples of Chinese herbal medicines used to improve the quality of life or reduce the side effects of chemotherapy or radiotherapy such as fatigue or muscle weakness

Radix Astragali (<i>Astragalus propinquus</i> , huangqi)
Panax Ginseng
Spore powder of <i>Ganoderma lucidum</i> (<i>G. lucidum</i>)
Shen-Mai-San (SMS) is composed of: Ginseng radis, Liriope spicata, and Schizandrae fructus.
TJ-41 (Bu-Zhong-Yi-Qi-Tang in Chinese, Hochuekki-to in Japanese or Bojungikki-Tang in Korean). It contains 7 herbs including <i>Pinellia tuber</i> , <i>Scutellaria baicalensis</i> , <i>Zingiberis rhizoma</i> , <i>Zizyphi fructus</i> , <i>Coptidis rhizoma</i> , <i>Glycyrrhiza radix</i> , and <i>Panax ginseng</i>
Shu Gan Jian Pi (SGJP) is composed of six herbs including Radix astragali (Huang Qi), Radix bupleuri (Chai Hu), Radix angelicae alba (Dang Gui), and three other herbs.
LCS101 is composed of: <i>Astragalus membranaceus</i> ; <i>Atractylodes macrocephala</i> ; <i>Citrus reticulate</i> ; <i>Glehnia littoralis</i> ; <i>Ligustrum lucidum</i> ; <i>Lycium chinense</i> ; <i>Milletia reticulata</i> ; <i>Oldenlandia diffusa</i> ; <i>Ophiopogon japonicus</i> ; <i>Paeonia lactiflora</i> ; <i>Paeonia obovata</i> ; <i>Poriae cocos</i> ; <i>Prunella vulgaris</i> ; and <i>Scutellaria barbata</i> .
Kanglaite injection
Huachansu injection
Turmeric (<i>Curcuma longa</i> , jianghuang)
XPYS-HEG (10 g Radix Astragali, 2 g Radix Ginseng, 6 g Pericarpium Citri Reticulatae, 6 g Rhizoma Cyperi, 6 g Radix Angelicae, and 6 g Fructus Lycii)
TJ-48 (Shi-Quan-Da-Bu-Tang in Chinese and Juzentaiho-to in Japanese). It contains 10 herbs including <i>Angelica sinensis</i> , <i>Paeonia lactiflora</i> , <i>Atractylodes macrocephala</i> , <i>Poria cocos</i> , <i>Cinnamomum cassia</i> , <i>Astragalus membranaceus</i> , <i>Ligusticum wallichii</i> , <i>Glycyrrhiza inflata</i> , and <i>Rehmannia glutinosa</i>
YSJG granules (for musculoskeletal symptoms) are composed of: 12 herbs, including Radix rehmanniae Preparata (ShuDiHuang), Semen cuscatae (TuSiZi), Rhizoma cyperi (XiangFu), Rhizoma chuanxiong (ChuanXiong), Rhizoma corydalis (YanHuSuo), Caulis trachelospermi (LuoShiTeng)

Chapter 2: Policy Question and Objectives

Policy Question

Should Chinese herbal medicine be used as an adjunct in the management of fatigue and muscle weakness in cancer patients receiving chemotherapy?

Overall aims and objectives of the assessment

The objectives were:

- a. To assess the efficacy/effectiveness of using Chinese herbal medicines as an adjunct management for fatigue and muscle weakness in cancer patients receiving chemotherapy.
- b. To assess the safety of using Chinese herbal medicines as an adjunct management for fatigue and muscle weakness in cancer patients receiving chemotherapy.
- c. To assess the economic implications of using Chinese herbal medicines as an adjunct management for fatigue and muscle weakness in cancer patients receiving chemotherapy.
- d. To assess the organizational issues related to the use of Chinese herbal medicines as an adjunct management for fatigue and muscle weakness in cancer patients receiving chemotherapy.

Research questions:

- i. How safe is Chinese herbal medicines as an adjunct in the management of fatigue and muscle weakness in cancer patients receiving chemotherapy?
- ii. What are the benefits of using Chinese herbal medicines as an adjunct in the management of fatigue and muscle weakness in cancer patients receiving chemotherapy?
- iii. What is the economic implication of using Chinese herbal medicines as an adjunct in the management of fatigue and muscle weakness in cancer patients receiving chemotherapy?
- iv. What are the organisational issues related to the use of Chinese herbal medicines as an adjunct in the management of fatigue and muscle weakness in cancer patients receiving chemotherapy?

Chapter 3: Methods

Methods of the review, analysis and inclusion criteria has been specified in advance and documented in the previous protocol.

Search Strategy

The search aimed to systematically identify all literature related to the questions in this review. The last search was conducted in November 2016.

Eight electronic databases were searched from inception: MEDLINE including MEDLINE In-Process & Other Non-Indexed Citations (Ovid); PubMed; The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) databases and Embase.

In addition to the database searches, articles were identified from reviewing the references of retrieved articles.

Search terms

A combination of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords free text. Search strategies used in MEDLINE are included in Appendix 2 (these were adapted for use in other databases such as PubMed, Embase). The search was limited by including search filters for 'human studies'. The search was also limited to publication year from 2000-2016.

Inclusion and exclusion criteria

Two reviewers conducted eligibility assessment in an unblinded standardised manner independently using these prespecified inclusion and exclusion criteria.

Inclusion criteria

After discussion with the expert committee, it was agreed that articles were selected for inclusion in this systematic review based on the following criteria:

Study design

For systematic review on clinical effectiveness, systematic reviews, meta-analysis, randomized controlled trials, non-randomized comparative studies and trials with surrogate end points will be included. Additional studies such as cohort, case control, cross sectional will also be taken into consideration especially if the studies are related to safety or adverse events.

Population

Cancer patients suffering from fatigue and muscle weakness after chemotherapy

Intervention

Chinese herbal medicine

Comparators

Placebo

Outcome

One or more of the following outcome measures were assessed

- effectiveness/efficacy of chinese herbals as an adjunct for the management of fatigue and muscle weakness after chemotherapy
- safety / adverse events of chinese herbals as an adjunct for the management of fatigue fatigue and muscle weakness after chemotherapy
- cost effectiveness of chinese herbals as an adjunct for the management of fatigue fatigue and muscle weakness after chemotherapy
- organizational issues of using chinese herbals as an adjunct for the management of fatigue fatigue and muscle weakness after chemotherapy

Publication

Full text articles published in English

Exclusion criteria

- i. Animal study
- ii. Narrative review
- iii. Laboratory study
- iv. Non English full text articles

Critical Appraisal of Literature

Two reviewers independently using prespecified criteria assessed the validity of the eligible studies. For systematic reviews and meta- analysis the Cochrane checklist was used. The criteria assessed include unbiased selection of articles, heterogeneity of the included studies and publication bias. For RCTs, Critical Appraisal Skill Programs (CASP) checklist was used. The criteria assessed were sequence generation, allocation concealment, blinding, explanation on loss to follow up, intention to treat analysis and other potential sources of bias such as funding. For non-randomised studies with comparison, the criteria assessed were random selection of participants, prospective or retrospective study, blinding, and explanation on loss to follow up, control of confounding factors and other potential sources of bias. For economic evaluation, we used two steps to evaluate the risk of bias. First, we used the same criteria as RCTs and non-RCTS, then we appraised following Critical Appraisal Skill Programs checklist for economic evaluation.¹⁸

The evidence was later graded according to US/Canadian Preventive Services Task Force grading system (see Appendix 5).

Analysis and Synthesis of Evidence

Data extraction strategy

Data from included studies were extracted by a reviewer and checked by a second reviewer using a pre-tested data extraction form. Disagreements were resolved through discussion. A third person, whose decision is final, was consulted if disagreements persist after discussion.

Information was extracted from each included trial on (1) characteristics of trial participants (2) type of intervention (3) type of control used (4) outcome measures.

Methods of Data synthesis

All the data extracted were summarized in evidence table. The evidence was presented to a multidisciplinary expert committee member. Data were assessed for suitability for pooling with regards to the intervention, study design, populations, comparators and outcome. Due to methodological and clinical heterogeneity of the studies, a narrative synthesis was used.

The overall search results were presented in Chapter 4. The detailed results were presented in Chapter 5 according to the research questions.

Chapter 4: Overall Search Results

The electronic searches identified 913 titles. Out of these 913 titles, 704 titles were duplicates / not relevant. Two reviewers screened 209 titles and abstracts. Twenty-three full text articles were retrieved for assessment. Six articles met our inclusion and exclusion criteria. We found two Chinese papers with abstracts in English and full text in Chinese. However due to lack of funds, it was not translated by a professional translator (expensive payment fee required). The article on Systematic review by Wu X et al, had most of the articles included in the study from the Chinese database (Wan Fang Digital Journals, Chinese Biomedical Databases, and Taiwan Periodical Literature Databases). All papers were from China and the studies were done on the Chinese population.

For efficacy/effectiveness, six articles were included. For safety, five articles were included (same articles from efficacy/effectiveness).

A systematic review study published in Cochrane by Adams et al. to assess the effectiveness of traditional Chinese herbal medicine in treating chronic fatigue syndrome after chemotherapy or radiotherapy from thirteen databases found methodologic limitations of the randomised controlled trials whereby no studies that met the inclusion criteria were identified and hence no papers were reported for this study. Therefore, the authors concluded that although studies examining the use of traditional Chinese medicine herbal products for chronic fatigue were located, methodologic limitations resulted in the exclusion of all studies. Of note, many of the studies labelled as RCTs and conducted in China did not utilize rigorous randomization procedures.¹⁹

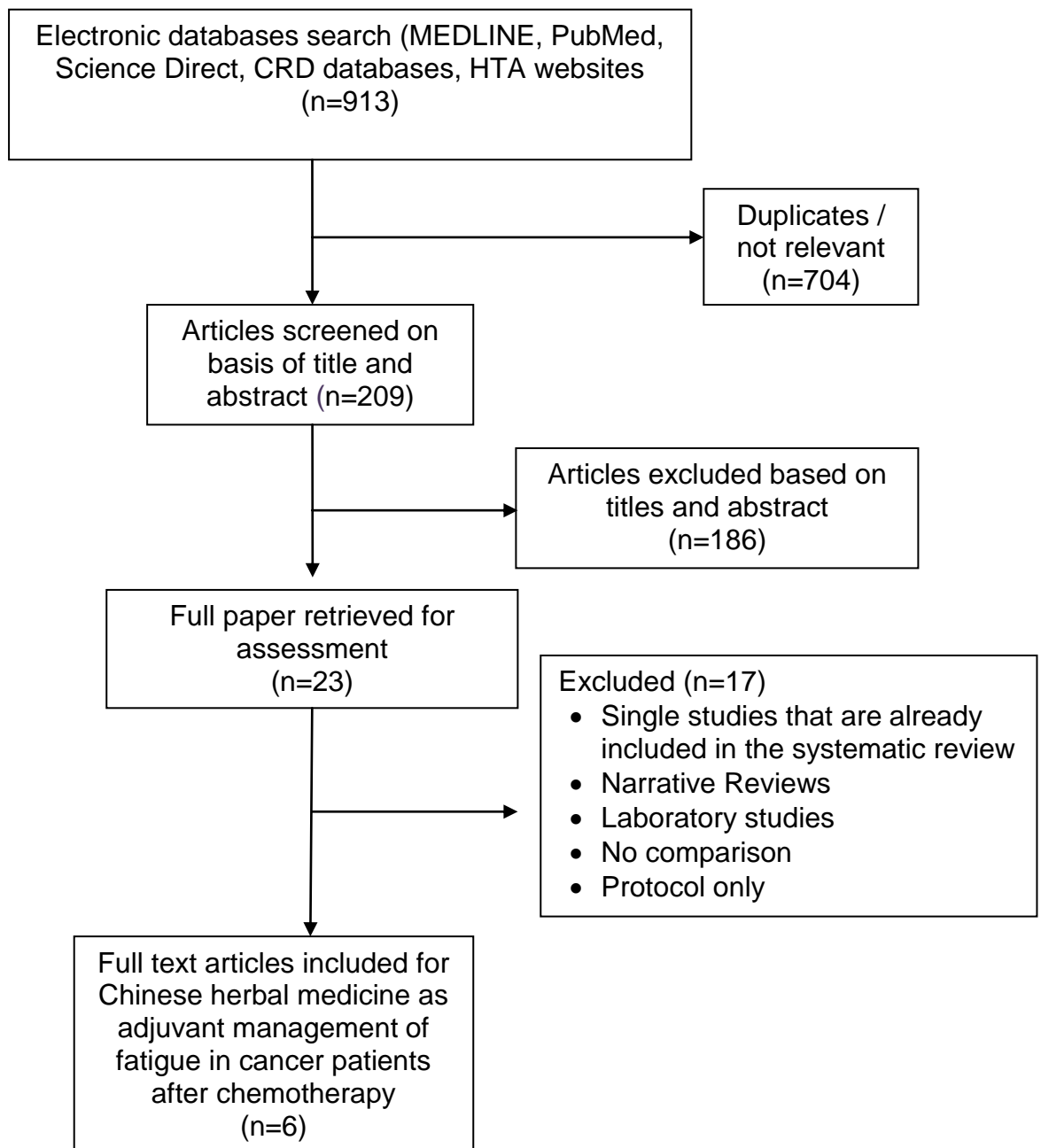
Five study protocols using randomised controlled trial methodology by Li C et al. (2015), Lo LC et al. (2012), Xu L et al. (2012), Peng N et al. (2014), and Xu L et al. (2012) using several types of Chinese herbal products to treat cancer-related fatigue (CRF) were found, and seems to be on going. The findings later may contribute to the development of an effective intervention for CRF.^{12, 13,20,21,22}

A flow diagram showing the number of articles identified, retrieved and included in the review is presented in Figure 1.

The evidence tables of these studies were presented in Appendix 4. The excluded studies were listed in Appendix 5.

The characteristics of included studies are discussed in the relevant chapters.

Figure 1. Flow chart of study selection



Characteristics of included studies

Study Design

Six studies were included in this review. Out of these, one study was an overview of systematic reviews and network Meta analysis, four randomised controlled trials (RCT) and one pre and post intervention study.

The four RCTs included in this review were Barton DL et al. 2013 (Comparing the Efficacy and Safety of American Ginseng versus placebo) study, Xu Y et al. 2015 (Comparing the Efficacy and Safety of Ren Shen Yangrong versus placebo), Xue D et al. 2015 (Comparing the Efficacy and Safety of traditional Chinese medicine versus no Chinese herbal medicine) and Jeong JS et al. 2010 (Comparing the Efficacy and Safety of Bojungikkintang versus placebo).

Participants

All the RCTs included patients aged more than 18 years old with cancer who had received radiotherapy or chemotherapy and reported moderate to severe fatigue.

Intervention

Chinese herbal medicine

Comparators

Placebo or no Chinese herbal medicine

Outcome measure

The outcome measures assessed include reduction of fatigue, quality of life and side effects of using the chinese herbal medicine.

Risk of bias assessment

We used Cochrane Risk of Bias Assessment tool to assess the risk of bias of the RCTs included in this review.²³ The sequence generation in the RCTs by Barton et al, Xu D et al and Jeong JS et al was clearly explained. Xu Y et al was an open label study, the allocation concealment was not clearly explained. The risk of bias for blinding was high. All the RCT's had small sample size. Overall, all the RCTs have a moderate to high risk of bias. The summary risk of bias assessment of the RCTs is as shown in Figure 2.

Figure 2. Risk of bias assessment of randomised controlled trials

	Adequate sequence generation	Allocation concealment	Blinding (Subjective Outcomes)	Incomplete outcome data addressed	Free of Selective reporting	Free of other bias
Barton et al						
Xu Y et al						
Xu D et al						
Jeong et al						

LEGEND	Yes low risk	Unclear risk of bias	No, High risk of bias
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CHAPTER 5: THE EFFECT OF CHINESE HERBAL MEDICINES AS AN ADJUNCT MANAGEMENT OF FATIGUE AND MUSCLE WEAKNESS IN CANCER PATIENTS RECEIVING CHEMOTHERAPY

I) CHINESE HERBAL MEDICINE AS AN ADJUNCT MANAGEMENT OF FATIGUE

A) EFFICACY/ EFFECTIVENESS

Clinical Effectiveness

Wu X et al. did an overview of systematic reviews (SRs) and network meta-analyses (NMA) to evaluate the comparative effectiveness of different Chinese herbal medicine (CHM) for patients with nonsmall cell lung cancer (NSCLC) receiving chemotherapy, in improving quality of life (QoL) including fatigue which was a major cause of poor QoL of these patients. Seven electronic databases including both international databases and Chinese databases were searched. Systematic Reviews focus on randomized controlled trials (RCTs) with comparison of CHM plus chemotherapy against chemotherapy alone on QoL among NSCLC patients were considered eligible. For retrieved RCTs, their risk of bias were assessed with the Cochrane risk of bias assessment tool. Six risk of bias domains were assessed, including sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting. Each domain was judged as having low, unclear, or high risk of bias according to information provided by the publication or its protocol (if available). Data from RCTs were extracted for random effect pairwise metaanalyses. Pooled relative risk (RR) with 95% confidence interval (CI) was used to quantify the impact of CHM on QoL. Network meta-analyses (NMA) was used to explore the most effective CHM for improving QoL when used with chemotherapy. Among all the included trials, only seventeen (28%) provided details on sequence generation, of which sixteen of them (26%) used appropriate methods and thus judged as having low risk of bias. Forty-four (72%) trials did not provide information on sequence generation and fifty eight (95%) RCTs did not describe allocation concealment and were judged as having unclear risk of bias. Only two (3%) trials reported using sequentially numbered, sealed, and opaque envelopes to ensure allocation concealment. For blinding, fifty eight (95%) RCTs were judged as having high risk of bias for blinding of participants and study personnel to intervention assignment, as well as blinding of outcome assessment. The included RCTs generally performed well in incomplete outcome data and selective reporting, with 95% and 100% judged as having low risk of bias, respectively.^{24 level 1} The results were as follows:

- From 14 SRs, 61 RCTs (n=4247) assessing eleven different CHM were included (Yi-fei-bai-du decoction, Fei-liu-ping extract, Hai-shen-su, Fu-zheng-jie-du decoction Kang-la-te injection, Shen-qi-fu-zheng injection, Compound kushen injection, Kang-ai injection, Zi-jin-long tablet, Xiao-ai-ping injection, Shen-fu injection).
- Result from pairwise meta-analyses showed six CHM (Kang-lai-te injection, Shei-qi-fu-zheng injection, Compound kushen injection, Kang-ai injection, Zi-jin-long tablet, and Shen-fu injection) has significant beneficial effect on QoL among NSCLC patients when used with chemotherapy, even after adjustment for publication bias. Pooled RR varied from 1.38 (95% CI: 1.11, 1.72).
- One trial comparing Hai-shen-su (a protein extract from *Tegillarca granosa* L.) plus chemotherapy compared with chemotherapy alone also demonstrated beneficial effect of combined treatment (RR=3.13, 95% CI: 1.41, 6.98).

- Results from NMA showed no differences on the comparative effectiveness among CHM, but Hai-shen-su plus chemotherapy has the highest probability (62.3%) of being the best option for improving QoL.

According to the authors, use of CHM on top of chemotherapy can significantly improve QoL including fatigue in NSCLC patients especially Hai-shen-su. However, rigorous placebo controlled trials with proper blinding are needed to confirm the effectiveness of CHM.

Barton DL et al. conducted a double-blind randomised trial on fatigued cancer survivors. Eligible participants included adult men and women with cancer-related fatigue (CRF) defined as a score of four or more on an eleven point scale where 0 is “no fatigue” and ten is “as bad as it can be.” Participants with all cancers, other than brain or CNS lymphoma, undergoing or having undergone curative intent treatment, were eligible, but participants had to have been diagnosed within the past two years. Participants could be getting cancer treatment or have completed treatment, but they could not be scheduled to change treatment status during the eight week trial whereby 364 patients were enrolled from forty different sites, mostly community cancer centers. The treatment group (n=183) was given 2000 mg of American ginseng while as the control group (181) was given placebo for eight weeks. The primary endpoint was the general subscale of the Multidimensional Fatigue Symptom Inventory–Short Form (MFSI-SF) at four weeks. Changes from baseline at four and eight weeks were evaluated between arms by a two-sided, two-sample *t* test.^{25 level II-I}

The results were as below:

- Changes from baseline in the general subscale of the MFSI-SF were 14.4 (standard deviation [SD] = 27.1) in the ginseng arm versus 8.2 (SD = 24.8) in the placebo arm at four weeks ($P = 0.07$).
- A statistically significant difference was seen at eight weeks with a change score of 20 (SD = 27) for the ginseng group and 10.3 (SD = 26.1) for the placebo group ($P = .003$).
- Greater benefit was reported in patients receiving active cancer treatment vs those who had completed treatment.
- More participants had a positive response to the ginseng and more had a strong clinical benefit ($\geq 30\%$ improvement) from ginseng compared with placebo.

There may be some risk of bias in the above study. Allocation concealment, blinding of outcome assessment, blinding of participants and study personnel was unclear. The authors also suggested more studies to be done to increase knowledge to guide the role of ginseng to improve CRF in cancer patients.

Xu Y et al. conducted an open-label, prospective, phase I/II trial to establish the safety and efficacy of Traditional Chinese Medicine (TCM) herbal products for treating non–anemia-related fatigue in patients with cancer. Thirty-three patients, who visited a TCM clinic in a tertiary cancer hospital in Beijing between June 2006 and October 2008, who had completed cancer treatment (surgery, radiotherapy, or chemotherapy), had stable disease and no anemia, and reported moderate to severe fatigue (rated ≥ 4 on a 0–10 scale) were enrolled in a TCM outpatient clinic. Patients took Ren Shen Yangrong Tang (RSYRT) decoction, a soup containing twelve TCM herbs of which ginseng (often replaced by dangshen in current TCM practice) and huangqi are the backbone components, twice a day for six weeks. Components of RSYRT consist of Dangshen (*Radix codonopsis pilosulae*), Huanqi (*Astragalus mongholicus*), Baizhu (*Rhizoma Atractylodes macrocephala*; white rhizome of largehead atractylodes); Fuling (*Poria cocos*; Indian bread), Chenpi (*Pericarpium citri reticulatae*, dried tangerine peel), Shengdi (*Radix rehmanniae*; root of rehmannia), Baishao (*Radix paeoniae alba*; white peony root), Danggui (*Angelica sinensis*; root of Chinese Angelica), Wuweizi (*Fructus schisandrae*; shizandra berry), Yuanzhi (*Radix*

polygalae; polygala root), Rougui (Cortex cinnamomi; cinnamon), Gancao (Radix glycyrrhizae; licorice). RSYRT aimed to correct qi deficiency. Fatigue was assessed before and after RSYRT therapy, which all patients completed. No discomfort or toxicity was observed. Before the study, all patients had fatigue for at least four months.^{26 level II-2} The result showed that:

- Fatigue severity decreased significantly from before therapy to six weeks after therapy: from 7.06 to 3.30 on a 0–10 scale ($p < 0.001$).
- Fatigue category (mild, moderate, severe) shifted significantly ($p = 0.024$): Of 22 patients with severe fatigue (rated ≥ 7) before therapy, 11 had mild fatigue and 11 had moderate fatigue after TCM treatment.
- The time-to-fatigue-alleviation was two to three weeks.

This study was an open label non-controlled phase I/II study. There was no control, no blinding of participants and study personnel, no blinding of outcome assessments and may have a high risk of bias. The authors concluded that RSYRT therapy was safe and was associated with fatigue improvement in nonanemic cancer survivors. However, decoction RSYRT warrants further study in randomized clinical trials to confirm its effectiveness for managing moderate to severe fatigue.

Xue D et al. conducted a RCT to observe the symptom improvement and clinical benefit in elderly patients with advanced non-small cell lung cancer (NSCLC) stratified on the basis of Comprehensive geriatric assessment (CGA) findings after treatment with a combination of traditional Chinese medicine and Western medicine. Patients hospitalised in the Department of Integrative Medicine and Geriatric Oncology, Peking University Cancer Hospital, from August 2012 to March 2013 were selected ($n=24$) for this study. On the basis of Comprehensive geriatric assessment (CGA) results, the patients were categorised into: a) function independent ($n=10$): without instrumental activities of daily life (IADL) dependence and activities of daily life (ADL) dependence, and with good nutritional status (given standardized therapy); b) mildly function impaired ($n=6$): with at least one item of IADL dependence, without ADL dependence, and at risk of malnutrition (given individualized therapy); and c) function dependent ($n=8$): ≥ 85 years old, with at least one item of ADL dependence, and with malnutrition (given best supportive care and Chinese medicine). The patients receiving standardised therapy and individualised therapy were randomised into two groups, with or without traditional Chinese medicine for symptom control, while for all the patients receiving best supportive care, traditional Chinese medicine was administered. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 scale (EORTC QLQ-C30 core scale), Lung Cancer 13 scale (LC13 scale), and M.D. Anderson Symptom Inventory–Traditional Chinese Medicine scale (MDASI–TCM scale) were used to assess relevant symptoms before and after treatment. Nine non-elderly NSCLC patients (65 years old) were enrolled as control and treated in accordance with National Comprehensive Cancer Network Non-small cell lung cancer NCCN NSCLC treatment guidelines.^{27 level II-I}

- After treatment for three weeks, function-dependent patients:
 - it was shown by QLQ-C30+LC13 scales, that the physical and role performances and the global health status were improved and the symptoms of fatigue and cough were alleviated $P < 0.05$.
 - by MDASI–TCM scale, the symptoms of fatigue, cough, and expectoration were improved.
- In function-independent and mildly function-impaired elderly patients,
 - there were no significant changes in functional status and symptoms $P < 0.05$

According to the author, traditional Chinese medicine may be beneficial to symptom control of function-dependent patients.

Jeong JS et al. conducted a pilot randomized clinical trial on forty patients (a) 18 years of age or older diagnosed with a malignancy; (b) had fatigue after cancer diagnosis due to cancer therapy or cancer itself with baseline global fatigue level 40 mm or above as measured by 100-mm Visual Analogue Scale (VAS); (c) Eastern Cooperative Oncology Group (ECOG) scale 2 or below; (d) at least two months must have elapsed since the last chemotherapy or radiotherapy. The treatment group (n=20) were given Bojungikki-tang while the control group (n=20) consisted of the patients with no intervention.^{28 level II-1} The results were as follows:

- The experimental group showed statistically significant improvements in fatigue level assessed by the Visual Analogue Scale of Global Fatigue (VAS-F) measuring the severity of fatigue (experimental vs control: -1.1 ± 2.1 in the experimental group versus 0.1 ± 0.9 in the control group, $P < .05$).
- Results of Functional Assessment of Cancer Therapy–General (FACT-G), Functional Assessment of Cancer Therapy–Fatigue (FACT-F), and Trial Outcome Index–Fatigue (TOI-F) also showed significant improvements
 - (FACT-G, 3.7 ± 9.9 in the experimental group versus -2.4 ± 9.5 in the control group, $P < .05$;
 - FACT-F, 8.0 ± 13.6 in the experimental group versus -2.2 ± 14.1 in the control group, $P < .05$;
 - TOI-F, 6.5 ± 9.2 in the experimental group versus -0.5 ± 10.9 in the control group, $P < .05$).

The authors suggested that the results of this study indicated that Bojungikki-tang might have beneficial effects on cancer-related fatigue and quality of lives in cancer patients. Trials that are more rigorous are needed to confirm the efficacy of Bojungikki-tang.

Yennurajalingam S et al. conducted a pre and post interventional study on thirty patients at the MD Anderson Cancer Center in Houston, Texas. The patients have been diagnosed with cancer and were undergoing outpatient chemotherapy at the cancer center, and experiencing cancer-related fatigue (CRF) with an average intensity of ≥ 4 on the Edmonton Symptom Assessment Scale (ESAS; a 0-10 scale) during the 24 hours prior to enrolling in the study. Patients received high-dose Panax Ginseng (PG) at 800 mg orally daily for 29 days. Scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale, Edmonton Symptom Assessment System (ESAS), and Hospital Anxiety and Depression Scale (HADS) were assessed at baseline, day 15, and day 29. Global Symptom Evaluation (GSE) was assessed at day 29.^{29 level II-2} The results showed that:

- Of the 30 patients enrolled, 24 (80%) were evaluable. The median age was 58 years; 50% were females, and 84% were white.
- Of the 24 evaluable patients, 21 (87%) had an improved (by ≥ 3 points) FACIT-F score by day 15.
- The mean ESAS score (standard deviation) for well-being improved from 4.67 (2.04) to 3.50 (2.34) ($P = 0.01374$).
- GSE score of Panax Ginseng (PG) for fatigue was ≥ 3 in 15/24 patients (63%) with median improvement of 5.

The authors suggested that PG was safe and improved CRF fatigue in these cancer patients.

B) SAFETY

Barton et al mentioned in his double-blind randomised trial on fatigued cancer survivors, who were given 2000 mg of American Ginseng whereby the results on toxicities and side effects were as follows:^{25 level II-I}

- Toxicities per self-report and Common Terminology Criteria for Adverse Events (CTCAE) grading did not differ statistically significantly between arms.
- Only five adverse events greater than 1% incidence were attributed to treatment, arm, and these were not statistically significantly different between arms. Study personal grade the adverse events as per CTCAE grading. The reported adverse events were agitation, anxiety, insomnia, nausea, and vomiting, $p > 0.05$.
- Patient-reported toxicities, were also not statistically significantly different between the arms, over the eight weeks of treatment.
- Scores changed little over the course of the study (no more than 5 points out of 100) for nausea, vomiting, nervousness, anxiety, trouble sleeping, and loose stools.
- Only loose stools at four weeks (-0.8) and pain at eight weeks (-0.3) were worse than baseline, and these occurred in the placebo group.
- All other symptoms improved over the course of the study.

Xu Y et al. in their open-label, prospective, phase I/II trial to establish the safety and efficacy of Traditional Chinese Medicine (TCM) herbal products for treating non-anemia-related fatigue in patients with cancer used Ren Shen Yangrong Tang (RSYRT) decoction for the intervention whereby the results on toxicities and side effects were as follows:^{26 level II-2}

- During the trial, no patient reported an uncomfortable event.
- Clinicians documented no gastrointestinal upset, insomnia, diarrhea, headache, sweating, rash, or other symptoms.
- Adherence to the TCM trial agent was excellent, with all patients reporting that they used the RSYRT decoction twice a day. No patients required a dose reduction or dose interruption because of poor tolerance of the decoction, nor did any patient withdraw from the study.
- Laboratory results showed no abnormal routine blood chemistry values or liver or kidney function results, either before or after traditional Chinese medicine.

Xue D et al. in their RCT to observe the symptom improvement and clinical benefit in elderly patients with advanced non-small cell lung cancer (NSCLC) after treatment with a combination of traditional Chinese medicine and Western medicine reported that after treatment for three weeks, in non-elderly patients:^{27 level II-1}

- the physical and social performances were lowered, and the symptoms of fatigue, constipation, and poor appetite were aggravated.
- Using the EORTC QLQ-C30 core scale
 - the scores of fatigue and constipation were increased, indicating that these symptoms were aggravated.
- Using MDASI-TCM scale
 - the scores of fatigue, sleep disturbance, and poor appetite were increased than before, indicating these symptoms were aggravated.

Jeong JS et al in their pilot randomized clinical trial using Bojungikki-tang for cancer-related fatigue reported the results on toxicities and serious side effects as follows:^{28 level 1}

- No serious adverse effects occurred during the study.
- However, one patient who had taken antihypertensive medication for three years with baseline serum creatinine at cut-off level showed slightly increased blood urea nitrogen (BUN) and creatinine level above the reference range. Further analysis using Wilcoxon signed-rank test on liver and renal toxicity revealed no significant change between baseline and week-2 test results.

- Two patients reported minor adverse effects including increased flatulence and dyspepsia

Yennurajalingam S et al. in their pre and post intervention study using high-dose Panax Ginseng 800 mg orally daily for 29 days reported the results on toxicities and side effects as follows: ^{29 level II-2}

- No grade 3 or higher adverse events related to the study drug were reported (such as pain, nausea, constipation, diarrhea, gastrointestinal pain)
- The results of this preliminary study showed that high-dose PG was safe and tolerable, and no severe adverse events related to the study drug were reported
- The study also showed that CRF and other symptoms including pain, appetite, and overall QOL improved with PG treatment for four weeks

C) COST/ COST- EFFECTIVENESS

There was no retrievable scientific evidence on the cost/ cost-effectiveness of Chinese herbal medicines in the management of side effects of fatigue in cancer patients receiving chemotherapy. Below in table 1 are listed the retail prices of Chinese herbal medicine used in the management of side effects of fatigue and muscle weakness in cancer patients receiving chemotherapy.

Table 1: Malaysian retail price of Chinese herbal medicine:

No	Herbs	Content	Price for herbal granule (RM)	SKU
1.	Xi Yang Shen (<i>Panax quinquefolius</i>)	--	151	100gm
2.	Bu Zhong Yi Qi Tang Granule = Bujongikki-tang	Huang Qi, Ren Shen, Zhi Gan Cao, Bai Zhu, Chen Pi, Dang Gui, Chai Hu, Sheng Ma, Sheng Jiang, Da Zao	118	200gm
3.	Huang Qi (<i>Astragalus membranaceus</i>)	--	42	100gm
4.	Bai Zhu (<i>Atractylodes macrocephala</i>)	--	50	100gm
5.	Chen Pi (<i>Citrus reticulata</i>)	--	26	100gm
6.	Bei Sha Shen (<i>Glehnia littoralis</i>)	--	50	100gm
7.	Nu Zhen Zi (<i>Ligustrum lucidum</i>)	--	26	100gm
8.	Gou Qi Zi (<i>Lycium chinense</i>)	--	35	100gm
9.	Ji Xue Teng (<i>Milletia reticulata</i>)	--	26	100gm
10.	Bai Hua She She Cao (<i>Oldenlandia diffusa</i>)	--	30	100gm
11.	Mai Men Dong (<i>Ophiopogon japonicus</i>)	--	68	100gm
12.	Bai Shao Yao (<i>Paenia lactiflora</i>)	--	42	100gm
13.	(<i>Paenia obovata</i>)	N/A		
14.	Fu Ling (<i>Poriae cocos</i>)	--	38	100gm
15.	Xia Ku Cao (<i>Prunella vulgaris</i>)	--	30	100gm
16.	Ban Zhi Lian (<i>Scutellaria barbata</i>)	--	26	100gm
17.	Jin Long She Granule	N/A		
18.	Yi Fei Bai Du	N/A		
	Fei Liu Ping			
	Hai Sheng Su			
	Fu Zheng Jie Du			
	Zi Jin Long			
19.	Ren Shen (<i>Radix Panax Ginseng</i>)	--	150	100gm
20.	Ren Shen Yangrong Tang	Ren She, Bai Zhu, Fu Ling, Zhi Gan Cao, Huang Qi, Chen Pi, Dang Gui, Bai Shao, Shu Di Huang, Wu Wei Zi, Yuan Zhi, Gui Xin, Sheng Jiang, Da Zao	92	200gm

D) ORGANIZATIONAL ISSUES

There was no retrievable scientific evidence on organizational issues of Chinese herbal medicines in the management of side effects of fatigue in cancer patients receiving chemotherapy. Those prescribing Chinese herbal medicine must be registered with the local T&CM practitioner body as stated under the T&CM Act implemented in 2016 under the Ministry of Health Malaysia and registration of local T&CM practitioners with the T&CM Council will be conducted in phases which will commence on a date to be determined in due course. Hence, it is important that those treating these patients be well trained in the clinical benefits of Chinese herbal medicine for the specific purposes. Also, it may be reasonable to offer Chinese herbal medicine within the hospital environment so its use can be monitored and patients can receive more evidence-based care.

II) CHINESE HERBAL MEDICINE AS AN ADJUNCT MANAGEMENT OF MUSCLE WEAKNESS

A) EFFICACY/ EFFECTIVENESS

There was no retrievable scientific evidence on the efficacy/ effectiveness of Chinese herbal medicines in the management of muscle weakness in cancer patients receiving chemotherapy.

B) SAFETY

There was no retrievable scientific evidence on the safety of Chinese herbal medicines in the management of muscle weakness in cancer patients receiving chemotherapy.

C) COST EFFECTIVENESS

There was no retrievable scientific evidence on the cost/ cost-effectiveness of Chinese herbal medicines in the management of muscle weakness in cancer patients receiving chemotherapy.

D) ORGANIZATIONAL ISSUES

There was no retrievable scientific evidence on organizational issues of Chinese herbal medicines in the management of muscle weakness in cancer patients receiving chemotherapy.

LIMITATIONS

Our study has several limitations. We had included RCTs as well as pre and post-intervention study for effectiveness and for adverse events. Our study also lacks local data as well as local economic evaluation studies. Although there was no restriction in language during the search but only English full text articles were included in the report. Articles of other languages including Chinese, which may have quality evidence in Chinese literature, were not able to be included in this review. Most published articles included in this HTA involved Chinese herbal medicine as an adjunct management for fatigue for cancer patients receiving chemotherapy. There was lack of retrievable full text

published articles on Chinese herbal medicine as an adjunct management for muscle weakness for cancer patients receiving chemotherapy.

DISCUSSION

A systematic review study published in Cochrane by Adams et al. to assess the effectiveness of traditional Chinese herbal medicine in treating chronic fatigue syndrome after chemotherapy or radiotherapy from thirteen databases found methodologic limitations of the randomised controlled trials whereby no studies that met the inclusion criteria were identified and hence no papers were reported for this study. Therefore, the authors concluded that although studies examining the use of traditional Chinese medicine herbal products for chronic fatigue were located, methodologic limitations resulted in the exclusion of all studies. Of note, many of the studies labelled as RCTs and conducted in China did not utilize rigorous randomization procedures.¹⁹ There were also reviews by Fanghua et al., Rui Chen et al. and Qi F et al. but these reviews were not done systematically and prone to biases. In their reviews, several Chinese herbal medicines may have beneficial effects on cancer related fatigue and quality of life for cancer patients. Some of the Chinese herbal medicine mentioned were Radix Astragali (*Astragalus propinquus*, Huangqi), Bojungikki-tang, Bu-Zhong-Yi-Qi-Tang in combination with Xiao-Chai-Hu-Tang, Shi-Quan-Da-Bu-Tang (Juzen-taiho-to in Kampo), TJ-41, Liu-jun-zi-tang, PHY906, Coumarin, Aescine, BanZhiLian, Huachansu injection, Shenqi fuzheng injection, and Kanglaite injection.³⁰⁻⁴⁰

In our current systematic review, it was found that Yi-fei-bai-du decoction, Fei-liu-ping extract, Hai-shen-su, Fu-zheng-jie-du decoction Kang-la-te injection, Shen-qi-fu-zheng injection, Compound ku-shen injection, Kang-ai injection, Zi-jin-long tablet, Xiao-ai-ping injection, Shen-fu injection, 2000 mg of American ginseng, Ren Shen Yangrong Tang (RSYRT), Bojungikki-tang and Panax Ginseng may have beneficial effects on cancer related fatigue and quality of life for cancer patients.²⁴⁻²⁹ However, these studies were also found to have biases in terms of small number of subjects, no allocation concealment and no blinding. We found two Chinese papers with abstracts in English and full text in Chinese. However due to lack of funds it was not translated by a professional translator (expensive payment fee required). In the abstract the results were similar to our systematic review whereby the Chinese herbal medicine may have may have beneficial effects on cancer related fatigue and quality of life for cancer patients.

CONCLUSION

a) Management of fatigue

There was limited low to fair level of evidence to suggest that Chinese herbal medicines was effective in improving the QoL such as fatigue symptoms severity when used as an adjunct management for fatigue in cancer patients receiving chemotherapy. Most of the side effects of the Chinese herbal medicine in these studies were mild such as agitation, anxiety, insomnia, nausea, and vomiting. There were no morbidity and severe adverse events reported. There was no retrievable evidence on cost-effectiveness. However, the retail price of certain Chinese herbal medicine in Malaysia ranges from RM 26 to RM 151 per 100 gm. However, small number of subjects limited most of the studies and most studies did not report on allocation concealment as well as blinding. The studies included involved the use of many different types of Chinese herbal medicines and many different types of assessment tools were used to measure the efficacy / effectiveness of the

Chinese herbal medicines for the management of fatigue in cancer patients receiving chemotherapy. Articles of other languages including Chinese, which may have quality evidence, were not able to be included in this review.

b) Management of muscle weakness

There was no retrievable evidence on effectiveness, safety and cost effective of Chinese herbal medicine as an adjunct management for muscle weakness in cancer patients receiving chemotherapy

Recommendation

Based on the above review, most of the studies suggested that Chinese herbal medicines such as Yi-fei-bai-du decoction, Fei-liu-ping extract, Hai-shen-su, Fu-zheng-jie-du decoction Kang-la-te injection, Shen-qi-fu-zheng injection, compound ku-shen injection, Kang-ai injection, Zi-jin-long tablet, Xiao-ai-ping injection, Shen-fu injection, American ginseng, Ren Shen Yangrong Tang (RSYRT), Bojungikki-tang and Panax Ginseng may have potential benefit for the management of fatigue in cancer patients receiving chemotherapy. However, the evidence retrieved was limited and had biases. More rigorous and well-designed clinical trials investigating the effects of Chinese herbs on relieving the fatigue and muscle weakness effect in cancer patients receiving chemotherapy is warranted. Hence, Chinese herbal medicines may be used for the management of fatigue in cancer patients receiving chemotherapy in a research environment by a certified and registered practitioner.

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Appendix 1

PTK-FM-02 Pin.1/2016

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL THE EFFECT OF CHINESE HERBAL MEDICINES AS AN ADJUNCT MANAGEMENT OF FATIGUE AND MUSCLE WEAKNESS IN CANCER PATIENTS RECEIVING CHEMOTHERAPY

1. BACKGROUND INFORMATION

A National Health & Morbidity Survey was conducted in year 2015 to study the prevalence usage of traditional & complementary medicine (T&CM) in Malaysia. From the survey, the overall prevalence of ever used T&CM with consultation was 29.25% (95% CI: 27.66 – 30.89). The prevalence of T&CM use within the last twelve months was 21.51% (95% CI: 20.11 – 22.98). T&CM practices are mainly used to maintain wellness.¹

Chinese herbal medicines originated in ancient China and have evolved over thousands of years. The basic concept of traditional Chinese medicines is to help patients achieve balance with the application of essence-*qi*-spirit theory, *yin-yang* theory and five elements theory.

Throughout the years, large number of Chinese herbal medicines was used to treat different health conditions. Studies have been done on the effectiveness of single herbs entity, multiple herbs entity that use individually, concurrently with mainstream medicines to treat selected diseases.

Currently in Malaysia, Chinese herbal medicines treatments are available at four Ministry of Health hospitals namely National Cancer Institute, Hospital Kepala Batas (Pulau Pinang), Hospital Sultan Ismail (Johor Bahru) and Hospital Likas (Sabah). A guideline was developed to document the practice of using traditional and complementary medicine on herbal therapy as an adjunct treatment for cancer.² In the guideline, it was mentioned that an adjunct is define as a supporting treatment for chemotherapy and radiotherapy. The aim of herbal treatment is usually to produce persisting improvements in well being. There are four categories of patients that will be referred for the herbal therapy. i.) Newly diagnosed cancer patients on radiotherapy or chemotherapy or surgery. ii.) Patients completed chemotherapy with recurrence. iii.) Advanced stage cancer on palliative treatment. iv.) Cancer patients who refused medical treatment. As a standard of practice, it was mentioned in the guideline that all cancer patients seeking for adjunct treatment at T&CM unit should be referred by medical oncologist, properly investigated and a precise diagnosis has been made. The herbs given to the patients are prepared in concentrated extract granule, packed in the form of sachet which will be prescribed by qualified herbal practitioner.

With the development of herbal therapy as an adjunct for the cancer patients during or after chemotherapy, there are always issues that need to be discussed and considered by the practitioners for the effectiveness of the treatments.³

This Health Technology Assessment (HTA) focuses on the study of Chinese herbal medicines concept in management of the side effects of fatigue and muscle weakness in cancer patients receiving chemotherapy. According to the syndrome of Qi, the herbs that are claimed to be suitable for fatigue and muscle weakness includes ren shen, dang shen, huang qi, bai zu, fu ling, gan cao, huang jing and hong zao.

This HTA was requested Senior Principal Assistant Director from Traditional and Complementary Division, Ministry of Health to look into the available evidences on the use of Chinese herbal medicines in the management of side effects of fatigue and muscle weakness in cancer patients receiving chemotherapy.

2. POLICY QUESTION

Should Chinese herbal medicine be used as an adjunct in the management of fatigue and muscle weakness in cancer patients receiving chemotherapy?

3. OBJECTIVES

- 3.1 To assess the efficacy/effectiveness of using certain Chinese herbal medicines as an adjunct management of fatigue and muscle weakness in cancer patients receiving chemotherapy.
- 3.2 To assess the safety of using certain Chinese herbal medicines as an adjunct management of fatigue and muscle weakness in cancer patients receiving chemotherapy.

- 3.3 To assess the economic implications of using certain Chinese herbal medicines as an adjunct management of fatigue and muscle weakness in cancer patients receiving chemotherapy.
- 3.4 To assess the organizational issues to the use of certain Chinese herbal medicines as an adjunct management of fatigue and muscle weakness in cancer patients receiving chemotherapy.

Research questions

- i. How safe is Chinese herbal medicines as an adjunct in the management of fatigue and muscle weakness in cancer patients receiving chemotherapy?
- ii. What are the benefits of using Chinese herbal medicines as an adjunct in the management of fatigue and muscle weakness in cancer patients receiving chemotherapy?
- iii. What is the economic implication of using Chinese herbal medicines as an adjunct in the management of fatigue and muscle weakness in cancer patients receiving chemotherapy?
- iv. What are the organisational issues related to the use of Chinese herbal medicines as an adjunct in the management of fatigue and muscle weakness in cancer patients receiving chemotherapy?

4. METHODS

4.1 Search strategy

Electronic databases will be searched through the Ovid interface (examples);

- v. MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present
- vi. EBM Reviews - Cochrane Central Register of Controlled Trials
- vii. EBM Reviews – Database of Abstracts of Review of Effects
- viii. EBM Reviews - Cochrane database of systematic reviews
- ix. EBM Reviews - Health Technology Assessment
- x. NHS economic evaluation database

Other databases (example);

- xi. PubMed
- xii. Horizon Scanning database (National Horizon Scanning Centre, Australia and New Zealand Horizon Scanning Network, National Horizon Scanning Birmingham)
- xiii. FDA website
- xiv. INAHTA
- xv. MHRA
- xvi. Chinese Journal Database if available.

Google will also be used to search for additional web-based materials and information

Additional articles such as from reviewing the bibliographies of retrieved articles or contacting the authors

4.2. Inclusion and exclusion criteria

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection.

4.2.1 Inclusion criteria

Population	Cancer patients suffering from fatigue and muscle weakness receiving chemotherapy
Interventions	Chinese herbal medicine
Comparators	<ul style="list-style-type: none"> • Placebo
Outcomes	<ul style="list-style-type: none"> • effectiveness/efficacy • fatigue <ul style="list-style-type: none"> - daily living - sound - speech • muscle weakness <ul style="list-style-type: none"> - muscle power - muscle tone - muscle atony - muscle spasticity - muscle wastage - muscle loss - muscle bulk/mass - muscle fatigability • performance status <ul style="list-style-type: none"> - ECOG - Karnofsky • safety/adverse events • quality of life • improvement in fatigue, asthenia • improvement in fatigue tiredness, exhaustion, lack of energy, lethargy • weakness of four limbs • economic evaluation <ul style="list-style-type: none"> - cost - cost analysis - cost-effectiveness • Organizational issues <ul style="list-style-type: none"> - training - accreditation - length of hospital stay - administrative, resource, man power - legal implications
Study design	Health Technology Assessments (HTA), Systematic Reviews, Randomised controlled trials (RCT), non-randomised controlled trials with surrogate end points, cohort studies, case control, cross sectional, case series.
	English full text articles

4.2.2 Exclusion criteria

Study design	Case reports, surveys, anecdotal, claims, narrative review, laboratory study/animal study.
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4.3 Critical Appraisal of Literature

The methodological quality of all relevant articles will be assessed by using Critical Appraisal Skills Programme (CASP) depending on the type of study design. Quality assessment will be conducted by a reviewer and checked by a second reviewer.

4.4 Analysis and synthesis of evidence

4.4.1 Data extraction strategy

The following data will be extracted:

- Details of methods and study population characteristics
- Details of intervention and comparator.
- Details of individual outcomes for effectiveness, safety, cost-effectiveness.
- Details of organizational and legal implications related to the use of Chinese herbal medicines.

Data from included studies is suggested to be extracted by a reviewer and checked by a second reviewer using a pre-tested data extraction form. Disagreements are to be resolved through discussion. A third person, whose decision is final, will be consulted if disagreements persist after discussion.

4.4.2 Methods of data synthesis

Data on clinical effectiveness, safety, and cost-effectiveness will be presented in tabulated format with narrative summaries. A decision on whether to pool efficacy, safety and accuracy outcomes will be taken following the updated search and based on clinical and statistical heterogeneity and the range of outcomes measures reported.

5. REPORT WRITING

References

1. Institute for Public Health, Ministry of Health Malaysia. National Health & Morbidity Survey 2015 Traditional & Complementary Medicine Volume IV. 2015.
2. Traditional and Complementary Medicine Division. Traditional and complementary medicine practice guidelines on herbal therapy as adjunct treatment for cancer. First Edition, July 2009
3. American Cancer Society assessed on 14/3/2016.

Appendix 2

SEARCH STRATEGIES USED IN THE MAJOR ELECTRONIC BIBLIOGRAPHIC DATABASES

Medline (Pubmed)

1. neoplasm[MeSH Terms] – (2643748)
2. (neoplasm[MeSH Terms]) OR neoplasm[Title/Abstract] - (2651194)
3. (cancer[MeSH Terms]) OR cancer[Title/Abstract] - (2901023)
4. (tumor[MeSH Terms]) OR tumor[Title/Abstract]- (2865857)
5. chinese herbal medicine[MeSH Terms]- (0)
6. chinese herbal medicine[MeSH Terms] Schema: all – (0)
7. (chinese herbal medicine[MeSH Terms]) OR chinese herbal medicine[Text Word] – (2185)
8. (((neoplasm[MeSH Terms]) OR neoplasm[Title/Abstract])) OR ((cancer[MeSH Terms]) OR cancer[Title/Abstract])) AND ((tumor[MeSH Terms]) OR tumor[Title/Abstract]) – (269492)
9. (chinese medicine[MeSH Terms]) OR chinese medicine[Text Word]- (12618)
10. (chinese traditional medicine[MeSH Terms]) OR chinese traditional medicine[Text Word] – (13270)
11. (((chinese herbal medicine[MeSH Terms]) OR chinese herbal medicine[Text Word])) OR ((chinese medicine[MeSH Terms]) OR chinese medicine[Text Word])) AND ((chinese traditional medicine[MeSH Terms]) OR chinese traditional medicine[Text Word]) - (4775)
12. ((((((neoplasm[MeSH Terms]) OR neoplasm[Title/Abstract])) OR ((cancer[MeSH Terms]) OR cancer[Title/Abstract])) AND ((tumor[MeSH Terms]) OR tumor[Title/Abstract])) AND (((chinese herbal medicine[MeSH Terms]) OR chinese herbal medicine[Text Word])) OR ((chinese medicine[MeSH Terms]) OR chinese medicine[Text Word])) AND ((chinese traditional medicine[MeSH Terms]) OR chinese traditional medicine[Text Word])) – (381)

Ovid Medline (R) in-Process & other Non-Indexed citations and Ovid Medline (R) 1948 to present.

- 1 cancer sufferer*.tw. (159)
- 2 cancer patient/ (162479)
- 3 adjuvant chemotherapy/ (30972)
- 4 chemotherapy, adjuvant.tw. (296)
- 5 chemotherapy,adjuvant.tw. (296)
- 6 cancer chemotherapy/ (141577)
- 7 ((anticancer or antineoplastic or tumo?r) adj chemotherapy).tw. (1709)
- 8 Carcinochemotherapy.tw. (0)
- 9 chemotherapy, cancer.tw. (132)
- 10 Chemotherapy/ (101288)
- 11 Chemotherapeutics.tw. (6036)
- 12 chemotherapy induced anemia/ (930)
- 13 chemotherapy induced anaemia.tw. (143)
- 14 1 or 2 (162576)
- 15 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (269362)
- 16 14 and 15 (31907)
- 17 fatigue/ (130118)
- 18 fatigue.tw. (94018)
- 19 cancer fatigue/ (1859)

- 20 cancer fatigue.tw. (208)
- 21 Tiredness.tw. (4356)
- 22 Fatigue Impact Scale/ (341)
- 23 fatigue impact scale.tw. (651)
- 24 Fatigue Severity Scale/ (894)
- 25 Fatigue Severity Scale.tw. (1424)
- 26 muscle fatigue/ (9488)
- 27 musc* fatigue.tw. (4270)
- 28 fatigue,muscle.tw. (245)
- 29 or/17-28 (169518)
- 30 muscle weakness/ (33057)
- 31 muscle weakness.tw. (14245)
- 32 (musc* adj (strength loss or insufficiency or weak*)).tw. (16266)
- 33 neuromuscular fatigue.tw. (308)
- 34 weakness, muscle.tw. (262)
- 35 or/30-34 (38831)
- 36 Chinese medicine/ (26323)
- 37 ch'i.tw. (94743)
- 38 medicine, chinese traditional.tw. (3)
- 39 qi.tw. (6593)
- 40 traditional chinese medicine.tw. (14992)
- 41 yin-yang.tw. (920)
- 42 Chinese drug/ (10743)
- 43 Chinese drug.tw. (406)
- 44 Chinese herb/ (3864)
- 45 Chinese herb.tw. (2226)
- 46 or/36-45 (141076)
- 47 29 or 35 (203184)
- 48 16 and 46 and 47 (40)
- 49 14 or 15 (400031)
- 50 46 and 47 and 49 (209)

Others Database

EBM Reviews - Cochrane Central Register of Controlled Trials	}	
EBM Reviews - Database of Abstracts of Review of Effects		Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Cochrane database of systematic reviews		
EBM Reviews - Health Technology Assessment		
PubMed		
NHS economic evaluation database		
National Horizon Scanning unit		
Australia and New Zealand Horizon Scanning Network		
INAHTA		
FDA		

Appendix 3

DESIGNATION OF LEVELS OF EVIDENCE

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

Appendix 4

EVIDENCE TABLES

This appendix contains the evidence tables with data extracted from the 37 studies included in this HTA report.

The evidence tables are arranged according to the effectiveness and safety of Chinese herbal medicine as an adjunct for management of fatigue and muscle weakness in cancer patients receiving chemotherapy

THE EFFECT OF CHINESE HERBAL MEDICINES AS AN ADJUNCT MANAGEMENT FOR FATIGUE AND MUSCLE WEAKNESS IN CANCER PATIENTS RECEIVING CHEMOTHERAPY

Evidence Table: Effectiveness

Question: Is Chinese herbal Medicine effective as an adjunct for fatigue in cancer patients receiving chemotherapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
1. Wu X, Chung VCH, Lu P et al. Chinese Herbal Medicine for Improving Quality of Life Among Nonsmall Cell Lung Cancer Patients. <i>Medicine</i> 2016 Vol 95 (1) DOI: 10.1097/MD.0000000000002410	Systematic review. SRs focus on randomized controlled trials (RCTs) with comparison of CHM plus chemotherapy against chemotherapy alone on QoL among NSCLC patients	1	Patients diagnosed with NSCLC using pathology, cytology, or biopsy methods were considered. From 14 SRs, 61 RCTs (n=4247) assessing 11 different CHM were included.	CHM plus chemotherapy. A total of 11 CHM were used: Shen-qi-fu-zheng injection,, Kang-ai injection, Compound ku-shen injection , Kang-lai-te injection, Xiao-ai-ping injection, Zi-jin-long tablet, Shen-fu injection, Yi-fei-bai-du decoction, Fei-liu-ping extract , Hai-shen-su (a protein extract from <i>Tegillarca granosa</i> L.) and Fu-zheng-jiedu decoction.	Chemotherapy alone or placebo or another CHM plus chemotherapy		From 14 SRs, 61 RCTs (n=4247) assessing 11 different CHM were included. Result from pairwise meta-analyses showed: <ul style="list-style-type: none"> 6 CHM (Kang-lai-te injection, Shei-qi-fu-zheng injection, Compound kushen, injection, Kang-ai injection, Zi-jin-long tablet, and Shen-fu injection) has significant beneficial effect on QoL (including fatigue) among NSCLC patients when used with chemotherapy, even after adjustment for publication bias. Pooled RR varied from 1.38 (95% CI: 1.11–1.72, Kang-lai-te injection) to 3.36 (95% CI: 1.30–8.66, Zi-jin-long tablet). One trial comparing Hai-shen-su (a protein extract from <i>Tegillarca granosa</i> L.) plus chemotherapy with chemotherapy also demonstrated beneficial effect of combined treatment (RR 3.13, 95% CI: 1.41–6.98). Results from NMA showed no differences on the comparative effectiveness among CHM, but Hai-shen-su plus chemotherapy has the highest probability (62.3%) of being the best option for improving QoL (including fatigue) . Use of CHM on top of chemotherapy can significantly improve QoL in NSCLC patients.

*THE EFFECT OF CHINESE HERBAL MEDICINES AS AN ADJUNCT MANAGEMENT FOR
FATIGUE AND MUSCLE WEAKNESS IN CANCER PATIENTS RECEIVING CHEMOTHERAPY*

Evidence Table: Effectiveness

Question: Is Chinese herbal Medicine effective as an adjunct for fatigue in cancer patients receiving chemotherapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
2. Barton DL, Liu H, Dakhil SR et al. Wisconsin Ginseng (<i>Panax quinquefolius</i>) to Improve Cancer-Related Fatigue: A Randomized, Double-Blind Trial, N07C2. <i>J Natl Cancer Inst</i> ;2013;105:1230–1238. DOI:10.1093/jnci/djt181	double-blind randomized trial on fatigued cancer survivors. Eligible participants included adult men and women with cancer-related fatigue (CRF) defined as a score of 4 or more on an 11-point scale where 0 is “no fatigue” and 10 is “as bad as it can be.” Participants with all cancers, other than brain or CNS lymphoma, undergoing or having undergone curative intent treatment, were eligible, but participants had to have been diagnosed within the past 2 years. Participants could be getting cancer treatment or have completed treatment, but they could not be scheduled to change treatment status during the 8-week trial	II-I	364 patients were enrolled from 40 different sites, mostly community cancer centres. .	The treatment group was given 2000 mg of American ginseng in a capsule (n=183)	Placebo consisting of capsule with rice powder (n=181)	8 weeks	Changes from baseline at 4 and 8 weeks were evaluated between arms by a two-sided, two-sample <i>t</i> test. Toxicities were evaluated by self-report and the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) provider grading. The results were as below: <ul style="list-style-type: none"> • Changes from baseline in the general subscale of the MFSI-SF were 14.4 (standard deviation [SD] = 27.1) in the ginseng arm versus 8.2 (SD = 24.8) in the placebo arm at 4 weeks (<i>P</i> = .07). • A statistically significant difference was seen at 8 weeks with a change score of 20 (SD = 27) for the ginseng group and 10.3 (SD = 26.1) for the placebo group (<i>P</i> = .003). • Greater benefit was reported in patients receiving active cancer treatment vs those who had completed treatment. • More participants had a positive response to the ginseng and more had a strong clinical benefit (≥30% improvement) from ginseng compared with placebo. • Toxicities per self-report and CTCAE grading did not differ statistically significantly between arms.

*THE EFFECT OF CHINESE HERBAL MEDICINES AS AN ADJUNCT MANAGEMENT FOR
FATIGUE AND MUSCLE WEAKNESS IN CANCER PATIENTS RECEIVING CHEMOTHERAPY*

Evidence Table: Effectiveness

Question: Is Chinese herbal Medicine effective as an adjunct for fatigue in cancer patients receiving chemotherapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
3. Xu Y, Chen Y, Li P et al. Ren Shen Yangrong Tang for Fatigue in Cancer Survivors: A Phase I/II Open-Label Study. <i>The Journal of Alternative and Complementary Medicine</i> 2015. 21; 5:281–287. DOI: 10.1089/acm.2014.0211.	open-label, prospective, phase I/II trial to establish the safety and efficacy of Traditional Chinese Medicine (TCM) herbal products for treating non-anemia-related fatigue in patients with cancer.	II-2	Thirty-three patients, who visited a TCM clinic in a tertiary cancer hospital in Beijing between June 2006 and October 2008, who had completed cancer treatment (surgery, radiotherapy, or chemotherapy), had stable disease and no anemia, and reported moderate to severe fatigue (rated ≥ 4 on a 0–10 scale) were enrolled in a TCM outpatient clinic.	Patients took Ren Shen Yangrong Tang (RSYRT) decoction, a soup containing 12 TCM herbs of which ginseng (often replaced by dangshen in current TCM practice) and Huangqi are the backbone components, twice a day for 6 weeks. RSYRT aimed to correct qi deficiency	-	6 weeks	<p>Fatigue was assessed before and after RSYRT therapy, which all patients completed. No discomfort or toxicity was observed. Before the study, all patients had fatigue for at least 4 months. The result showed that:</p> <ul style="list-style-type: none"> Fatigue severity decreased significantly from before therapy to 6 weeks after therapy: from 7.06 to 3.30 on a 0–10 scale ($p < 0.001$). Fatigue category (mild, moderate, severe) shifted significantly ($p = 0.024$): Of 22 patients with severe fatigue (rated ≥ 7) before therapy, 11 had mild fatigue and 11 had moderate fatigue after TCM treatment. The time-to-fatigue-alleviation was 2–3 weeks. <p>The author concluded that RSYRT therapy was safe and was associated with fatigue improvement in nonanemic cancer survivors. However, decoction RSYRT warrants further study in randomized clinical trials to confirm its effectiveness for managing moderate to severe fatigue.</p>

*THE EFFECT OF CHINESE HERBAL MEDICINES AS AN ADJUNCT MANAGEMENT FOR
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Evidence Table: Effectiveness

Question: Is Chinese herbal Medicine effective as an adjunct for fatigue in cancer patients receiving chemotherapy?

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4. Xue D, Han S and Jiang S et al. Comprehensive geriatric assessment and traditional Chinese medicine intervention benefit symptom control in elderly patients with advanced non-small cell lung cancer. <i>Med Oncol</i> 2015; 32:114 DOI 10.1007/s12032-015-0563-5	RCT to observe symptom improvement and clinical benefit in elderly patients with advanced non-small cell lung cancer (NSCLC). Patients hospitalized in the Department of Integrative Medicine and Geriatric Oncology, Peking University Cancer Hospital, from August 2012 to March 2013 were selected for this study.	II-I	On the basis of Comprehensive geriatric assessment (CGA) results, the patients were categorized into: a) function independent: without instrumental activities of daily life (IADL) dependence and activities of daily life (ADL) dependence, and with good nutritional status [n=10]; b) mildly function impaired: with at least one item of IADL dependence, without ADL dependence, and at risk of malnutrition; [6] and c) function dependent: ≥85 years old, with at least one item of ADL dependence, and with malnutrition [8]. EORTC QLQ-C30 core scale, LC13 scale, and MDASI–TCM scale were used to assess relevant symptoms before and after treatment.	traditional Chinese medicine	No traditional Chinese medicine		<p>After treatment for 3 weeks, function-dependent patients:</p> <ul style="list-style-type: none"> it was shown by QLQ-C30, LC13 scales, that the physical and role performances and the global health status were improved and the symptoms of fatigue and cough were alleviated; by MDASI–TCM scale, the symptoms of fatigue, cough, and expectoration were improved. <p>In function-independent and mildly function-impaired elderly patients,</p> <ul style="list-style-type: none"> there were no significant changes in functional status and symptoms. <p>But in non-elderly patients,</p> <ul style="list-style-type: none"> the physical and social performances were lowered, and the symptoms of fatigue, constipation, and poor appetite were aggravated. <p>The elderly patients with advanced NSCLC were categorized on the basis of CGA findings, and traditional Chinese medicine may be beneficial to symptom control of function-dependent patients</p>

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5. Jeong JS, Ryu BH, Kim JS et al. Bojungikki-Tang for Cancer-Related Fatigue: A Pilot Randomized Clinical Trial Integrative Cancer Therapies 2010, 9(4) 331– 338 DOI: 10.1177/1534735410383170. http://ict.sagepub.com	pilot randomized clinical trial. The inclusion criteria were as follows: (a) 18 years of age or older diagnosed with a malignancy; (b) had fatigue after cancer diagnosis due to cancer therapy or cancer itself with baseline global fatigue level 40 mm or above as measured by 100-mm Visual Analogue Scale (VAS); (c) Eastern Cooperative Oncology Group (ECOG) scale 2 or below; (d) at least 2 months must have elapsed since the last chemotherapy or radiotherapy	II-1	total of 40 patients with cancer-related fatigue were randomized into an experimental or a waiting list control group	Bojungikki-tang for cancer-related fatigue (n=20)	waiting list control group = no intervention (n=20)	2 weeks	<p>The results were:</p> <ul style="list-style-type: none"> • The experimental group showed statistically significant improvements in fatigue level assessed by the Visual Analogue Scale of Global Fatigue (VAS-F) measuring the severity of fatigue (experimental vs control: -1.1 ± 2.1 in the experimental group versus 0.1 ± 0.9 in the control group, $P < .05$) • Results of Functional Assessment of Cancer Therapy–General (FACT-G), Functional Assessment of Cancer Therapy–Fatigue (FACT-F), and Trial Outcome Index–Fatigue (TOI-F) also showed significant improvements <ul style="list-style-type: none"> ○ (FACT-G, 3.7 ± 9.9 in the experimental group versus -2.4 ± 9.5 in the control group, $P < .05$; ○ FACT-F, 8.0 ± 13.6 in the experimental group versus -2.2 ± 14.1 in the control group, $P < .05$; ○ TOI-F, 6.5 ± 9.2 in the experimental group versus -0.5 ± 10.9 in the control group, $P < .05$). <p>The authors suggested that the results of this study indicated that Bojungikki-tang may have beneficial effects on cancer-related fatigue and quality of lives in cancer patients. More rigorous trials are needed to confirm the efficacy of Bojungikki-tang.</p>

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Bibliographic citation	Study Type / Methodology	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
6.Yennurajalingam S, Reddy A, Tannir NM et al. High-Dose Asian Ginseng (Panax Ginseng) for Cancer-Related Fatigue: A Preliminary Report. Integrative Cancer Therapies 2015, Vol. 14(5) 419 –427. DOI: 10.1177/1534735415580676	Pre and post intervention study at the MD Anderson Cancer Center in Houston, Texas.	II-3	30 patients that have been diagnosed with cancer and were undergoing outpatient chemotherapy and experiencing cancer-related fatigue (CRF) with an average intensity of ≥ 4 on the Edmonton Symptom Assessment Scale (ESAS; a 0-10 scale) during the 24 hours prior to enrolling in the study.	Patients received high-dose Panax Ginseng (PG) at 800 mg orally daily for 29 days.	Pre and post	29 days	<p>Patients received high-dose PG at 800 mg orally daily for 29 days. Scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale, Edmonton Symptom Assessment System (ESAS), and Hospital Anxiety and Depression Scale (HADS) were assessed at baseline, day 15, and day 29. Global Symptom Evaluation (GSE) was assessed at day 29. The results showed that:</p> <ul style="list-style-type: none"> • Of the 30 patients enrolled, 24 (80%) were evaluable. The median age was 58 years; 50% were females, and 84% were white • No severe (\geqgrade 3) adverse events related to the study drug were reported. • Of the 24 evaluable patients, 21 (87%) had an improved (by ≥ 3 points) FACIT-F score by day 15 • The mean ESAS score (standard deviation) for well-being improved from 4.67 (2.04) to 3.50 (2.34) ($P = 0.01374$) • GSE score of Panax Ginseng (PG) for fatigue was ≥ 3 in 15/24 patients (63%) with median improvement of 5. <p>The authors suggested that PG was safe and improved CRF fatigue in these cancer patients.</p>

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Question: Is Chinese herbal Medicine safe as an adjunct for fatigue in cancer patients receiving chemotherapy?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
1. Barton DL, Liu H, Dakhil SR et al. Ginseng (<i>Panax quinquefolius</i>) to Improve Cancer-Related Fatigue: A Randomized, Double-Blind Trial, N07C2. <i>J Natl Cancer Inst</i> ;2013;105:1230–1238. DOI:10.1093/jnci/djt181	double-blind randomized trial on fatigued cancer survivors. Eligible participants included adult men and women with cancer-related fatigue (CRF) defined as a score of 4 or more on an 11-point scale where 0 is “no fatigue” and 10 is “as bad as it can be.” Participants with all cancers, other than brain or CNS lymphoma, undergoing or having undergone curative intent treatment, were eligible, but participants had to have been diagnosed within the past 2 years. Participants could be getting cancer treatment or have completed treatment, but they could not be scheduled to change treatment status during the 8-week trial	II-I	364 patients were enrolled from 40 different sites, mostly community cancer centres. .	The treatment group was given 2000 mg of American ginseng in a capsule (n=183)	Placebo consisting of capsule with rice powder (n=181)	8 weeks	Results on toxicities and side effects were as follows: <ul style="list-style-type: none"> • Only five toxicities greater than 1% incidence were attributed to study treatment, and these were not statistically significantly different between arms per CTCAE grading by study personnel. These toxicities were agitation, anxiety, insomnia, nausea, and vomiting p>0.05. • Patient-reported toxicities, controlling for baseline, were also not statistically significantly different between the arms, over the 8 weeks of treatment. • Scores changed little over the course of the study (no more than 5 points out of 100) for nausea, vomiting, nervousness, anxiety, trouble sleeping, and loose stools. • Only loose stools at 4 weeks (–0.8) and pain at 8 weeks (–0.3) were worse than baseline, and these occurred only in the placebo group. • All other symptoms improved over the course of the study

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Appendix 5

LIST OF EXCLUDED STUDIES FOR EVIDENCE TABLE

1. Miller J. Combining Traditional Chinese Medicine and Modern Medicine in the Treatment of Cancer: Clinical Pearls. Cancer Strategies Journal - Winter 2013 -- www.cancerstrategiesjournal.com
2. Liao GS, Apaya MK, and Shyur LF. Herbal Medicine and Acupuncture for Breast Cancer Palliative Care and Adjuvant Therapy. Evidence-Based Complementary and Alternative Medicine. 2013; Article ID 437948. <http://dx.doi.org/10.1155/2013/437948>
3. Zhao H, Zhang Q, Zhao L et al. Spore Powder of Ganoderma lucidum Improves Cancer-Related Fatigue in Breast Cancer Patients Undergoing Endocrine Therapy: A Pilot Clinical Trial. Evidence-Based Complementary and Alternative Medicine 2012. Article ID 809614. doi:10.1155/2012/809614
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13. Sun DZ, Jiao JP, Zhang X et al. Therapeutic Effect of Jinlongshe Granule on Quality of Life of Stage IV Gastric Cancer Patients Using EORTC QLQ-C30: A Double-Blind Placebo-Controlled Clinical Trial. Chin J Integr Med. 2015; 21(8):579-586

14. Yang L, Li TT, Chu YT et al. Traditional Chinese Medical Comprehensive Therapy for Cancer-Related Fatigue. *Chin J Integr Med.* 2016;22(1):67-72
15. Wanga YY, Lib XX, Liua JP et al. Traditional Chinese medicine for chronic fatigue syndrome: A systematic review of randomized clinical trials. *Complementary Therapies in Medicine.* 2014; 22: 826—833
16. Smith ME and Bauer-wu S. Traditional Chinese Medicine for Cancer-related symptoms. *Seminars in oncology nursing.* 2012; 28: 64-74