

BMJ Open Efficacy and safety of Wuling San for treatment of breast-cancer-related upper extremity lymphoedema: study protocol for a pilot trial

Huiru Zhu,¹ Zheng Peng,² Meiyu Dai,² Yan Zou,² Fengxian Qin,² Jifei Chen,² Liuying Song,² Baoyu He,² Xiaolan Lv,³ Shengming Dai²

To cite: Zhu H, Peng Z, Dai M, *et al.* Efficacy and safety of Wuling San for treatment of breast-cancer-related upper extremity lymphoedema: study protocol for a pilot trial. *BMJ Open* 2016;**6**:e012515. doi:10.1136/bmjopen-2016-012515

► Prepublication history and additional material is available. To view please visit the journal (<http://dx.doi.org/10.1136/bmjopen-2016-012515>).

HZ and ZP are the co-first authors

Received 4 May 2016
Revised 24 October 2016
Accepted 25 October 2016



CrossMark

For numbered affiliations see end of article.

Correspondence to
Dr Shengming Dai;
daishm@sina.com

ABSTRACT

Introduction: Breast-cancer-related upper extremity lymphoedema (BCUL), a common complication of mastectomy, can cause physical discomfort, psychological distress, cosmetic defects, functional disability and chronic recurrent erysipelas in the affected arm(s). It is a challenge to physicians involved in the management of these patients. Wuling San, a classic prescription in Traditional Chinese Medicine used in treating oedema for thousands of years, is reported by many Chinese journals to perform well in BCUL. Therefore, the aim of this study is to verify its efficacy and evaluate its safety using rigorous methodological designs in patients with BCUL.

Methods and analysis: To verify the efficacy and assess the safety of Wuling San over a placebo, this double-blind, randomised, placebo-controlled, multicentre trial will be carried out in three hospitals. A total of 200 eligible patients with BCUL will be randomly allocated, in a ratio of 1:1, to either the experimental medicine group or the placebo group. The primary outcome measure will be the proportion of absolute reduced limb volume, as measured by perometry. The second outcome measure will be the number of participants with adverse events. The assessment will be carried out at the following time points: before enrolment (baseline) and 2, 4, 6 and 8 weeks after treatment.

Ethics and dissemination: This trial will be conducted in accordance with the Declaration of Helsinki and supervised by the institutional review board of the Fourth Affiliated Hospital of Guangxi Medical University (approval number PJK2016088). All patients will receive information about the trial in verbal and written forms and will give informed consent before enrolment. This trial will help to demonstrate whether Wuling San is effective in the treatment of patients with BCUL. The results will be published in peer-reviewed journals or disseminated through conference presentations.

Trial registration number: NCT02726477; Pre-results.

BACKGROUND

As a common symptom caused by insufficient lymph drainage following radical

Strengths and limitations of this study

- This is the first clinical study focusing on the efficacy and safety of the use of Wuling San for breast-cancer-related upper extremity lymphoedema (BCUL).
- This study should provide a reference for future large-scale studies if applicable.
- Subsequent studies will be considered for comparisons between treatment with Wuling San and other therapies in patients with BCUL, if it is proved efficacious.

mastectomy or modified radical mastectomy, breast-cancer-related upper extremity lymphoedema (BCUL) afflicts over 30% of post-operative patients who undergo axillary lymph node dissection (ALND).¹ Based on the severity, which depends on the extent of the axillary operation, the frequency of radiotherapy, lymph node status, tumour burden, age of the patients and obesity,²⁻³ BCUL can be classified into three stages. Stage I is characterised by a 'reversible' protein-rich fluid accumulation. Stage II, known as 'spontaneously irreversible', is characterised by an increased number of keratinocytes and connective tissue cells. Stage III, also called 'elephantiasis', is characterised by a conspicuous increase in the size of the limb, with thickened rough skin due to massive hyperkeratosis.⁴ This can result in physical discomfort, psychological distress, functional disability, cosmetic defect and chronic recurrent erysipelas.⁵ Affected arms are often stiff and prone to infections, which often require hospitalisation for antibiotics,⁶ or even surgery,⁷ a significant source of expenditure and hardship for many patients. To prevent deterioration from the swelling, patients are repeatedly obliged to wear uncomfortable elastic compression stockings,

which serve as a continuous reminder of their cancerous status, increasing their anxiety and reducing their quality of life.⁸ However, as a poorly understood symptom with few effective therapies, the management of BCUL is still a challenge for physicians.⁹

A basic concept in the theory of Traditional Chinese Medicine (TCM) is that related symptoms of certain diseases are often summarised as a syndrome ('zheng' in Chinese).¹⁰ In TCM, lymphoedema is put into the same category as oedema and is considered to be caused by a qi (chi) deficiency and blood stasis. Several prescriptions are available to manage this symptom, and Wuling San is one of the most popular. Wuling San is composed of extracts from *Poria*, *Rhizoma Alismatis*, *Polyporus*, *Cortex Cinnamomi* and *Rhizoma Atractylodis Macrocephalae*. With the ability to promote qi transformation, warm yang and drain dampness, this formula is from the *Treatise on febrile diseases caused by cold* (Shang Han Lun) written by Zhongjing Zhang during the Chinese Eastern Han Dynasty (about 200 AD), and has been used for thousands of years since then in East Asia.^{11–13}

Both the early clinical reports in Chinese journals^{14–17} and the clinical data gathered by the physicians in our team have shown that Wuling San somehow decreases swelling and relieves the symptoms of lymphoedema in the upper extremities after ALND, probably by promoting kidney function, diuresis, and other pathways. But these are only experience-based medical accounts with little scientific experimental evidence. Therefore, the aim of this trial is to check its efficacy and assess its safety in the treatment of women with modest lymphoedema (stage I or II) after mastectomy for breast cancer.

Method and analysis

The present protocol was designed according to Standard Protocol Items: Recommendations for Interventional Trials 2013 (SPIRIT 2013; see online supplementary file S1).

Study design

This double-blind trial will be carried out in three medical centres: the Fourth Affiliated Hospital of Guangxi Medical University, Liuzhou Maternity and Child Healthcare Hospital and the Third Affiliated Hospital of Guangxi University of Chinese Medicine. The trial will be conducted from September 2016 to June 2018. A total of 200 patients will be recruited, and for each participant a standard treatment will be performed with the same dosage and duration. The flow chart of this trial is outlined in figure 1.

Recruitment of participants

The coordinators with the assistance of physicians in each centre, will identify eligible participants preliminarily based on the inclusion and exclusion criteria. Their eligibility will then be confirmed by the physicians in charge after a baseline evaluation. Written informed

consent will be obtained from every patient before enrolment.

Inclusion and exclusion criteria

The following inclusion criteria will be adopted in this study: women aged 20–40 with unilateral BCUL, stage I or II (mild to moderate lymphoedema with a minimum 10% and maximum 40% increase in volume compared with the unaffected arm based on perometry evaluation); body mass index 18–25; who have completed all primary and adjuvant treatments (surgery, chemotherapy, radiotherapy) without any evidence of breast cancer recurrence. Patients who meet the following criteria will be excluded: bilateral or stage III lymphoedema; history of bilateral ALND; recent history of cellulitis in the affected extremity (within the last 3 months); recurrent breast cancer or other malignancies; current use of chemotherapy for breast or other malignancies (within the last 30 days); current use of radiation for breast or other malignancies (within the last 3 months); pregnant or lactating women; patients who are taking diuretic drugs such as diosmin or other investigational drugs at the time of enrolment (within the last 30 days); serious renal or cardiac failure; unable to comply with the protocol or the measurement schedule.

Loss to follow-up and data management

Patients may drop out of the trial at any time for any reason. If a patient intends to drop out, the physician in charge should ask for the exact reason and give proper advice and assistance. Once a patient decides to withdraw, data on lymphoedema will immediately be collected and the duration of administration will be recorded. Patients will be able to withdraw from the study on the basis of disease progression or serious complications. Incidences of loss to follow-up will be reported to the chief designer of this trial every month. Data from the trial will be collected in case report forms using the double entry method. The coordinator in each centre will check each completed report once a month to ensure the quality of the case report form.

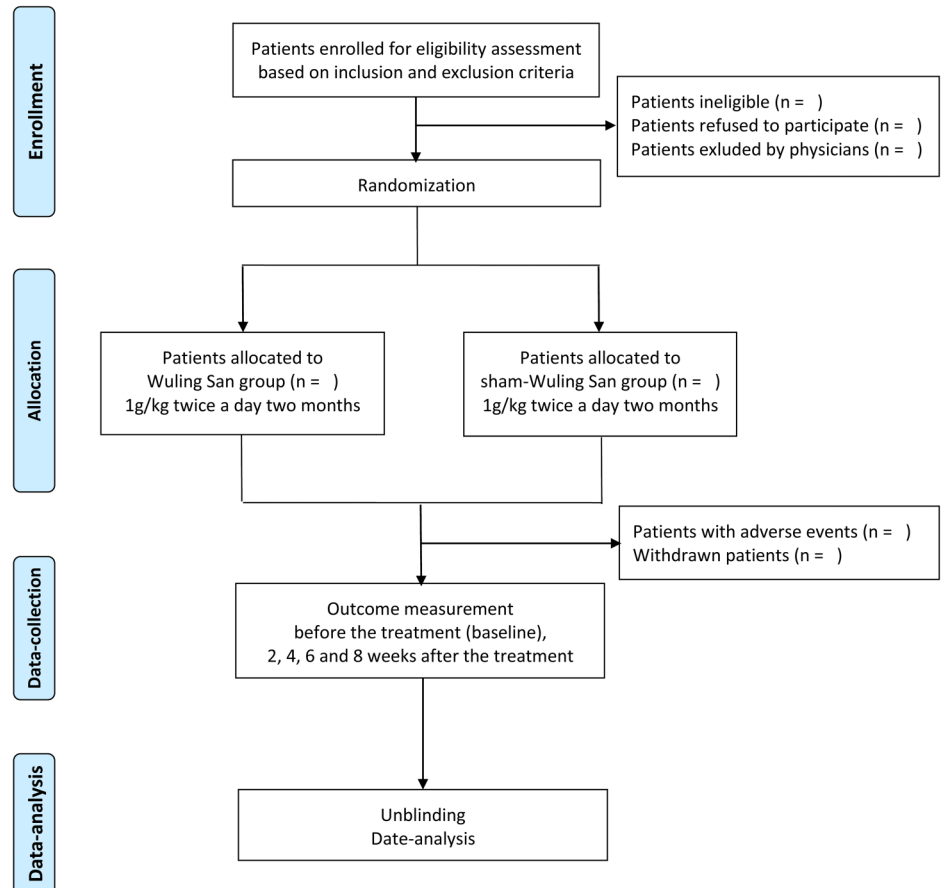
Forbidden drugs and concomitant treatments

This trial is not compatible with any of the following interventions: diuretics, diosmin and hesperidin. Other concomitant treatments should be discussed with the physician in charge and carefully recorded.

Randomisation and blinding

According to the inclusion and exclusion criteria, eligible patients will receive a standard interview and receive more information about the trial. After informed consent has been obtained and a baseline evaluation performed, patients will be randomised to the experimental or placebo group in a ratio of 1:1. As it is a double-blind trial, randomisation is performed by the chief designer. The randomisation sequence (blocked,

Figure 1 Flow chart.



stratified for centres) will be generated using the RAND function in Microsoft Excel (see online supplementary file S2). Each centre will receive a set amount of drug/ placebo in envelopes with consecutively coded labels. All of the drugs (including the placebo) will be provided by the pharmacy department of the Fourth Affiliated Hospital of Guangxi Medical University, and will be labelled by the chief designer according to the randomisation sequence and given to the coordinators. Emergency letters on each coded drug will be sent to each centre and properly safeguarded in case of any possible serious adverse event. Treatment assignments will be kept from both patients and investigators (including statisticians) until the study is completed.

Intervention

Experimental group

Patients in the experimental group will be given Wuling San dissolved in warm water at a dosage of 1 g/kg twice a day for 8 weeks. The ingredients (purchased from the China National Pharmaceutical Group Corporation) are listed in table 1. These medical herbs will be made into powder at the pharmacy department of the Fourth Affiliated Hospital of Guangxi Medical University, using a herbal pulveriser by experienced and licensed TCM doctors qualified for at least 3 years. The powder will be sifted through a sieve of 150 µm.

Table 1 Prescription of Wuling San

Medical herbal name	Name in Chinese	Origin	Amount (g)
Polyporus	Zhu Ling	Gansu	10
Poria	Fu Ling	Anhui	10
Alismatis rhizome	Ze Xie	Sichuan	15
Cortex Cinnamomi	Rou Gui	Guangdong	7
Rhizoma	Bai Zhu	Zhejiang	10
Atractylodis Macrocephalae			

Control group

Patients in the control group will be given placebo powder with the same dosage, frequency and duration. The placebo powder, similar to Wuling San in colour, smell, taste and packaging, is composed of 5% Wuling San, 93% starch and 2% food colouring. All the test drug packages will be tagged with the name of the patients by coordinators in each centre and dispensed by nurses in our team, who will be responsible for recording any incidents such as reactions to the drug, symptoms related to the drug and concomitant treatments during the trial.

In addition to the Wuling San treatment, both groups will receive standard decongestive therapy, consisting of daily manual lymph drainage, gentle exercise and elastic

compression garments. All these steps will be implemented for a fixed duration of 2 hours a day and 5 days a week. Otherwise, detailed records will be made.

Outcome measurements

For every patient, measurement of both limbs by perometry will be carried out at the following time points: before treatment (baseline), 2, 4, 6 and 8 weeks after treatment (table 2). After the limb volumes have been collected for each patient, the proportion of absolute reduced limb volume after the therapy will be calculated using the following formula adapted from Andersen *et al*¹⁸

$$\begin{aligned} & \text{proportion of absolute reduced limb volume (\%)} \\ &= \frac{(V_{LB} - V_{CB}) - (V_{LA} - V_{CA})}{(V_{LB} - V_{CB})} \times 100\% \end{aligned}$$

V_L is the volume of the affected arm with lymphoedema; V_C is the volume of the contralateral arm; V_{LB} is the volume of the affected arm with lymphoedema measured before treatment; V_{CB} is the volume of the contralateral arm measured before treatment; V_{LA} is the volume of the affected arm with lymphoedema measured after treatment; V_{CA} is the volume of the contralateral arm measured after treatment.

Data such as measurements collected at weeks 2, 4 and 6 after treatment will also be recorded for monitoring and interim analyses. In the case of withdrawn patients, the assessment will be performed before the withdrawal. The number of participants with serious and non-serious adverse events will serve as the secondary outcome measure.

Safety outcomes

Routine tests, such as urine test, stool test, blood test, liver function test, renal function test and ECG, will be carried out for each patient every week during the treatment.

Adverse events

Every adverse event will be recorded in detail and closely monitored before stabilisation or resolution. The chief designer of this trial and the corresponding coordinator will be informed immediately unless it has been confirmed that it was not caused by the treatment. They will cooperate with the physician in charge to evaluate

the severity and determine the causality of the events. All relevant adverse events will be reported to the institutional review board of the Fourth Affiliated Hospital of Guangxi Medical University within the relevant time frames. The chief designer of the trial will be responsible for reporting all adverse events. The coordinators will be responsible for establishing the standard procedures and the training of relevant staff before trial initiation. Regular monitoring will be used to ensure that all adverse events are identified and addressed appropriately.

Sample size calculation

To the best of our knowledge, no multicentred, randomised, placebo-controlled trial investigating the efficacy of Wuling San for BCUL has been conducted. Therefore, there is no reference for the sample size needed in this trial. However, to perform this pilot trial and collect adequate data, we hypothesise the effect size, risk of type 1 error (α) and risk of type 2 error (β) to be 0.25 (medium), 0.05 and 0.2, respectively, based on the recommendation from the manual of G-Power (V.3.1). Using the F test and choosing 'ANOVA fixed effects omnibus one way' and 'A Priori compute required sample size given α , power and effect size', then 159 is the minimum required sample size. If the estimated dropout rate is set at 15%, at least 183 patients should be recruited for this trial (see online supplementary file S3). We intend to include 200 patients, 100 for each arm.

Data analysis

An independent statistician will be invited to perform the data analysis, made up of a per-protocol (PP) analysis and an intent-to-treat (ITT) analysis. The PP analysis will be restricted to participants who strictly follow the protocol and complete the study. In contrast, the ITT analysis will include all the patients who have ever received any treatment in this trial, where missing data will be supplemented using the LOCF (last observation carried forward) method. Mean and SD will be used for continuous variables, and percentages for categorical variables. One-way analysis of variance will be used to compare the treatment groups with the placebo group and to analyse the possible blocking factor due to the multicentre design. Covariance adjusted for clinical centre and baseline will also be used in the analysis if significant differences are found between centres. Interim analyses, using the data collected during the

Table 2 Summary of measurements conducted in this trial at all time points

Measurement	Data collection instrument	Baseline	Treatment				
			First treatment	Week 2	Week 4	Week 6	Week 8
Volume of both arms	Perometer	√*	√	√	√	√	√†
Adverse events	Adverse events report card	√	√	√	√	√	√
Credibility of blinding	Questionnaire on blinding		√				√

*Limb volume at baseline.

†Limb volume after treatment; All measurements are conducted after the completion of treatment at each time point.

trial, will be performed by the Data and Safety Monitoring Board (DSMB) so as to have active monitoring on the ongoing status of the trial and to make sure the trial is not continued simply because it has begun. Statistical analyses will be performed using SPSS (V.16.0). For all comparisons, $p < 0.05$ will be considered significant.

Trial oversight

Three groups will be responsible for the supervision of this trial.

1. The Clinical Trial Steering Committee (CTSC)

The CTSC is composed of the chief trial designer and coordinators at each centre, who will have a meeting every month to review and address key technical and operational problems.

2. The Coordinating Committee

The Coordinating Committee, composed of local research members in each centre, will work closely with the CTSC to coordinate trial activities and will be responsible for the management of trial sites, preservation and distribution of trial materials, dissemination of information from the trial, collection, organisation and preservation of data and documents, safety reports, electronic case report forms, and training of trial staff.

3. DSMB

The DSMB, serving as an independent third party, is composed of experienced and knowledgeable experts. It will be responsible for periodical review and data evaluation for participants' safety and trial progress, and make recommendations to the CTSC regarding the modification or termination of the trial. The board members will meet every month.

DISCUSSION

In recent years, instead of ALND, sentinel lymph node biopsy (SLNB) has become a more common procedure in breast cancer surgery, which has reduced the incidence of BCUL.¹⁹ However, a certain proportion of patients still develop arm lymphoedema, especially when SLNB is combined with axillary radiotherapy.²⁰ Various conservative therapies, such as physical therapy, lymphatic drainage, massage, acupuncture, pneumatic pumps, oral pharmaceuticals, laser therapy, compression garments, limb exercises and psychological support, have been applied in clinical practice for patients with BCUL. However, investigations and comparisons of these therapies performed in two systematic reviews^{21 22} found it difficult to make definitive therapy recommendations. Moreover, most therapies were shown to be merely more beneficial than doing nothing at all for the lymphoedematous limb. Therefore, there is still an urgent need to find an effective and convenient therapy for those patients who go on to develop BCUL after breast cancer treatment.²⁰ If this therapy is economically feasible, it will be more beneficial to patients, because of the chronic process of BCUL.²³

In TCM, lymphoedema including BCUL is classified as a kind of oedema, which is considered to be a syndrome of internal stagnation of fluid dampness due to stasis of the blood and a deficiency of the qi, and the treatment indication is Wuling San. Identified as a prescription for strengthening the yang qi and promoting water metabolism in organs such as the kidneys and bladder, Wuling San manages qi stagnation and blood stasis. Of the five ingredients of the Wuling San prescription, Polyporus Poria and Alismatis rhizome are the main ones with the ability to induce diuresis and eliminate dampness; Rhizoma Atractylodis Macrocephalae is considered to enhance the efficacy of Poria, and Cortex Cinnamomi is considered to strengthen the yang qi to promote water metabolism in organs such as the kidneys and bladder. Together, these five herbs endow Wuling San with the ability to restore the balance between yin and yang, promote water metabolism, and reduce stasis.

Some scientific reports have demonstrated that Wuling San can promote kidney function and induce diuresis.^{24 25} A clinical study reported that the use of Wuling San could lead to a significant increase in urine volume and a reduction in body weight in patients with nephritic syndrome.²⁶ In addition, there are reports that Wuling San can inhibit the activity of the renal renin-angiotensin system in normal rats²⁷ and in rats with adriamycin-induced nephrotic syndrome,²⁸ thereby protecting the podocytes from injury. The efficacy of Wuling San in renal oedema has been observed in patients with diabetic nephropathy.²⁹

Similar efficacies of the five ingredients of Wuling San have also been reported. Poria has been found to attenuate hypertonicity-induced cell death in the collecting tubule³⁰ and ameliorate chronic kidney diseases by intervening in certain metabolic pathways in rats.³¹ A similar effect was found in patients with chronic kidney disease.³² Polyporus aqueous extract has been reported to have significant diuretic activity in rats, with a reduced level of aquaporin and an increased output of urinary Na^+ , K^+ and Cl^- .³³ In addition, aqueous extract of Alismatis rhizome has been found to promote diuresis in rats³⁴ and to have the ability to remove urinary calculi in patients with ureter calculi.³⁵ Cortex Cinnamomi has been found to improve renal function effectively in mice.³⁶ Furthermore, the bioactive components or extracts of the Atractylodis macrocephalae rhizome have been reported to enhance immunity in aged rats.³⁷ In summary, these reports indicate that Wuling San might have diuretic efficacy and renal protective effects by enhancing kidney function and inhibiting stress response.

As it was greatly valued by their predecessors, the Chinese have used Wuling San in the treatment of oedema for thousands of years.^{11–13} In recent years, there have been several case reports in Chinese journals on the good clinical performance of Wuling San in the treatment of lymphoedema.^{14–17} Based on our clinical observation in practice, women with SCUL in stage I or II

show a significant reduction in the size of the affected limb after Wuling San treatment in combination with standard routine management composed of daily use of compression stockings, exercise and skin care. Increased vitality and quality of life and fewer adverse events were reported by women receiving Wuling San, compared with those receiving other therapies. Moreover, the ingredients are inexpensive and natural, with few side effects.

However, no scientific clinical trial has confirmed the efficacy of Wuling San in the treatment of BCUL. Therefore, to maximally exclude the placebo effects and to demonstrate whether Wuling San is effective for treating BCUL, we designed this methodologically rigorous, randomised, double-blind trial. Sham-Wuling San can be used for blinding purposes because of the rare experience of Wuling San among patients with BCUL. In previous studies, no examples have used Sham-Wuling San. For practical purposes, we plan to use starch mixed with 5% Wuling San and 2% food colouring as a sham powder. A detailed description of our methods for recruitment, randomisation, allocation, intervention and data analysis is provided above.

However, there are also some limitations to this protocol. First, owing to limited studies in this field, the primary focus of this trial is mainly on the verification of its efficacy and the investigation of its safety; no further research is involved. Second, subsequent studies will be needed for other assessments, including comparisons between Wuling San and other therapies in patients with BCUL, if it is proved efficacious.

In conclusion, this pilot trial will verify the efficacy and investigate the safety of Wuling San in the treatment of BCUL, assess the feasibility of the study design, and provide a clinical foundation for future large-scale studies (if applicable).

Author affiliations

¹Department of Galactophore, The Third Affiliated Hospital of Guangxi University of Chinese Medicine, Liuzhou, Guangxi, China

²Department of Clinical Laboratory, The Fourth Affiliated Hospital of Guangxi Medical University, Liuzhou, Guangxi, China

³Department of Clinical Laboratory, Liuzhou Maternal and Child Health Care Hospital, Liuzhou, Guangxi, China

Acknowledgements We are grateful to Xuexiang Liu for help with statistical analysis.

Contributors SD is the chief designer of this trial. HZ and ZP drafted the manuscript. ZP, HZ and XL are the coordinators and responsible for the screening and enrolment of patients. MD, YZ, LS, JC, BH, and FQ are involved in the recruitment of patients. SD is responsible for supervision of the study and revision of the manuscript. All authors read and approved the final version of the manuscript.

Funding This study was supported by Key Laboratory Construction of Tumor Diseases Prevention in Liu Zhou, Guang Xi (No (2014G020403)).

Competing interests None declared.

Patient consent Obtained.

Ethics approval Institutional review board of the Fourth Affiliated Hospital of Guangxi Medical University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The results of this pilot study will be disseminated via peer-reviewed publications and conference presentations. All of the data are available.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

REFERENCES

1. Maclellan RA, Greene AK. Lymphedema. *Semin Pediatr Surg* 2014;23:191–7.
2. Coriddi M, Khansa I, Stephens J, *et al*. Analysis of factors contributing to severity of breast cancer-related lymphedema. *Ann Plast Surg* 2015;74:22–5.
3. Paskett ED, Dean JA, Oliveri JM, *et al*. Cancer-related lymphedema risk factors, diagnosis, treatment, and impact: a review. *J Clin Oncol* 2012;30:3726–33.
4. Ridner SH. Pathophysiology of lymphedema. *Semin Oncol Nurs* 2013;29:4–11.
5. Chachaj A, Malyszczak K, Pyszel K, *et al*. Physical and psychological impairments of women with upper limb lymphedema following breast cancer treatment. *Psychooncology* 2010;19:299–305.
6. Deng J, Fu MR, Armer JM, *et al*. Factors associated with reported infection and lymphedema symptoms among individuals with extremity lymphedema. *Rehabil Nurs* 2015;40:310–19.
7. Granzow JW, Soderberg JM, Dauphine C. A novel two-stage surgical approach to treat chronic lymphedema. *Breast J* 2014;20:420–2.
8. Taghian NR, Miller CL, Jammallo LS, *et al*. Lymphedema following breast cancer treatment and impact on quality of life: a review. *Crit Rev Oncol Hematol* 2014;92:227–34.
9. Maclellan RA, Couto RA, Sullivan JE, *et al*. Management of primary and secondary lymphedema: analysis of 225 referrals to a center. *Ann Plast Surg* 2015;75:197–200.
10. Jiang M, Lu C, Zhang C, *et al*. Syndrome differentiation in modern research of traditional Chinese medicine. *J Ethnopharmacol* 2012;140:634–42.
11. Yu F, Takahashi T, Moriya J, *et al*. Traditional Chinese medicine and Kampo: a review from the distant past for the future. *J Int Med Res* 2006;34:231–9.
12. Ehling D. Oriental medicine: an introduction. *Altern Ther Health Med* 2001;7:71.
13. Chen FP, Chen FJ, Jong MS, *et al*. Modern use of Chinese herbal formulae from Shang-Han Lun. *Chin Med J* 2009;122:1889.
14. Luo C, Huang L. Clinical observation on treatment of upper limb lymphedema after breast cancer operation using modified Wulingsan formula. *Liaoning J Tradit Chin Med* 2006;33:1132–2.
15. Dong J, Yi J. Recent development of breast cancer treatment by traditional Chinese medicine and neoadjuvant chemotherapy. *Guangming J Chin Med* 2008;23:689–91.
16. Li X. Treatment of 100 cases special edema using adjusted Wuling powder. *Hebei J Tradit Chin Med* 1999;21:24–24.
17. Liu S, Yin D. Clinical observation on 92 cases of breast cancer treated by traditional Chinese medicine. *Jilin J Tradit Chin Med* 2008;28:333–4.
18. Andersen L, Hojris I, Erlandsen M, *et al*. Treatment of breast-cancer-related lymphedema with or without manual lymphatic drainage—a randomized study. *Acta Oncol* 2000;39:399–405.
19. Lyman GH, Temin S, Edge SB, *et al*. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2014;32:1365–83.
20. Penha TR, van Roozendaal LM, Smidt ML, *et al*. The changing role of axillary treatment in breast cancer: who will remain at risk for developing arm morbidity in the future? *Breast* 2015;24:543–7.
21. Badger C, Preston N, Seers K, *et al*. Physical therapies for reducing and controlling lymphoedema of the limbs. *Cochrane Database Syst Rev* 2004;(4):Cd003141.
22. Stuijver MM, ten Tusscher MR, Agasi-Idenburg CS, *et al*. Conservative interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing lymphoedema after breast cancer therapy. *Cochrane Database Syst Rev* 2015;(2):Cd009765.
23. Moseley AL, Carati CJ, Piller NB. A systematic review of common conservative therapies for arm lymphoedema secondary to breast cancer treatment. *Ann Oncol* 2007;18:639–46.

24. Yang Y, Zhang DM, Liu JH, *et al.* Wuling San protects kidney dysfunction by inhibiting renal TLR4/MyD88 signaling and NLRP3 inflammasome activation in high fructose-induced hyperuricemic mice. *J Ethnopharmacol* 2015;169:49–59.
25. Ding XQ, Pan Y, Wang X, *et al.* Wuling san ameliorates urate under-excretion and renal dysfunction in hyperuricemic mice. *Chin J Nat Med* 2013;11:214–21.
26. Jin R, Yu R, Gao H, *et al.* Comparative study of Wuling powder and Wuling decoction for nephrotic syndrome patients of water-damp collecting internally syndrome. *J Tradit Chin Med* 2012;53:572–577.
27. Ahn YM, Cho KW, Kang DG, *et al.* Oryeongsan (Wulingsan), a traditional Chinese herbal medicine, induces natriuresis and diuresis along with an inhibition of the renin–angiotensin–aldosterone system in rats. *J Ethnopharmacol* 2012;141:780–5.
28. He L, Rong X, Jiang JM, *et al.* Amelioration of anti-cancer agent adriamycin-induced nephrotic syndrome in rats by Wulingsan (Gorei-San), a blended traditional Chinese herbal medicine. *Food Chem Toxicol* 2008;46:1452–60.
29. Xiong KW, Lin SG, Zhong L, *et al.* Clinical observation of Wuling San in the treatment of early diabetic nephropathy edema. *J. Clin. Exp.Med* 2011;10:1023–4.
30. Lee SM, Lee YJ, Yoon JJ, *et al.* Effect of Poria cocos on hypertonic stress-induced water channel expression and apoptosis in renal collecting duct cells. *J Ethnopharmacol* 2012;141:368–76.
31. Zhao YY, Lei P, Chen DQ, *et al.* Renal metabolic profiling of early renal injury and renoprotective effects of Poria cocos epidermis using UPLC Q-TOF/HSMS/MS E. *J Pharm Biomed Anal* 2013;81-82:202–9.
32. Hsu PC, Tsai YT, Lai JN, *et al.* Integrating traditional Chinese medicine healthcare into diabetes care by reducing the risk of developing kidney failure among type 2 diabetic patients: a population-based case control study. *J Ethnopharmacol* 2014;156:358–64.
33. Zhang G, Zeng X, Han L, *et al.* Diuretic activity and kidney medulla AQP1, AQP2, AQP3, V 2 R expression of the aqueous extract of sclerotia of Polyporus umbellatus fries in normal rats. *J Ethnopharmacol* 2010;128:433–7.
34. Feng YL, Chen H, Tian T, *et al.* Diuretic and anti-diuretic activities of the ethanol and aqueous extracts of Alismatis Rhizoma. *J Ethnopharmacol* 2014;154:386–90.
35. Fan LC, Yin CP, Liu JH, *et al.* Study on effect of aqueous extract from Alisma Orientatis on urinary oxalate calcium stone formation. *China Pharm* 2010;13:1701–4.
36. Ozbayer C, Kurt H, Ozdemir Z, *et al.* Gastroprotective, cytoprotective and antioxidant effects of Oleum cinnamomi on ethanol induced damage. *Cytotechnology* 2014;66:431–41.
37. Guo L, Sun YL, Wang AH, *et al.* Effect of polysaccharides extract of rhizoma atractylodis macrocephalae on thymus, spleen and cardiac indexes, caspase-3 activity ratio, Smac/DIABLO and HtrA2/Omi protein and mRNA expression levels in aged rats. *Mol Biol Rep* 2012;39:9285–90.