academicJournals

Vol. 9(12), pp. 174-194, December 2017
DOI: 10.5897/IJMMS2017.1309
Article Number: 0F1EAC366764
ISSN 2006-9723

http://www.academicjournals.org/IJMMS

International Journal of Medicine and Medical Sciences

Full Length Research Paper

Is moist exposed burn ointment effective for diabetic foot ulcers? A meta-analysis of randomized controlled trials

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Received 26 April, 2017: Accepted 13 September, 2017

This meta-analysis aimed to assess the effectiveness of moist exposed burn ointment (MEBO) for diabetic foot ulcers (DFU). Two researchers independently assessed the quality and validity of included randomized controlled trials (RCTs) in 7 electronic databases. Risk of bias was assessed using Cochrane handbook guidelines. Twenty seven trials which include 1,979 patients were involved for analysis. Comparison of the same intervention strategies revealed significant differences in total effectiveness rates between BEBO and conventional therapy group (Risk Ratio [RR], 6.36, [95% confidence interval (CI), 3.20, 12.64], P < 0.00001); MEBO combined with standard therapy (Risk Ratio [RR], 1.19, [95% confidence interval (CI), 1.08, 1.31], P = 0.0007); and healing time of DFU (Mean Difference [MD], 14.15, [95% confidence interval (CI), -18.14, -10.17], P < 0.00001). MEBO may be effective for treating DFU. However, a firm conclusion could not be reached because of the poor quality of the included trials. Further trials with higher quality are justified.

Key words: Exposed wound ointment (MEBO), diabetic foot ulcers (DFU), recombinant bovine, basic fibroblast growth factor (rb-bFGF), vacuum sealing drainage (VSD).

INTRODUCTION

Diabetic foot ulcers (DFU) are one of the major causes of mortality in diabetic patients, which is developed in about 15 to 25% of patients with diabetes (Mazze et al., 1985). DFU is a serious diabetic chronic complication caused by peripheral vascular disease, neuropathy, foot deformity and trauma and can result in amputation, disability, reduced quality of life, and increased economic burden. About 28 to 89% of amputations performed for non-traumatic lesions are associated with diabetes (Lavery et al., 1996). Statistics show that there was an increase of about 4 million patients with diabetic foot in 2012 and in every 30 sec there is an amputation of diabetic foot.

As early as in 2009, President Barack Obama proposed to eliminate the amputation caused by diabetic

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foot and this is becoming the world focus as a serious health problem (Søndergaard et al., 2015). Impaired wound healing is a prominent characteristic of DFU. Principles of treatment for diabetic foot ulcers involve the relief of pressure and protection of the ulcer, restoration of skin perfusion, treatment of infection, metabolic control and treatment of co-morbidities, local wound care, education of patient and relatives, determining the cause and preventing recurrence (Wolcott, 2015);(Yotsu et al., 2014). The annual cost of managing DFU and amputations was estimated to be $10.9 billion in the United States, whereas the cost was estimated to be $385 million in the United Kingdom, based on the same methodology (Søndergaard et al., 2015); (Wolcott, 2015). The various drugs and therapies for the management of diabetic foot ulcers comprise diabetes education, diet, exercise, standard anti-diabetic treatment, neuropathic drugs, blood vessel dilation medicine, cleaning and desloughing ulcers daily, wound dressings change, debridement and drainage or compression bandaging, skin substitutes, growth factors and inflammatory modulators (Scott, 2013); (Albert, 2002). Standard of care debridement, off-loading, antimicrobial exudate transfer dressing and moist wound care are the fundamental standard of care for DFU (Karri et al., 2015); (Wang et al., 2015). The majority of these therapies target the treatment of diabetic foot ulcers to address the altered biochemical composition of the diabetic wound. However, no single treatment can be definitively recommended for the treatment of diabetic foot ulcers. Surgical revision like angiosome-targeted revascularization in DFU is often the final stage in treatment and has important implications for both patients and society (Yao et al., 2014); (Smith-Strøm et al., 2016). Patients referred for surgical revision of DFU are often severely ill and have a high one-year mortality rate (36%) and a high frequency of co-morbidity (Dhatariya et al., 2016). The global burden of DFU is expected to be raised because of the increasing incidence of diabetes. Therefore, it is necessary and urgent to find some cost-effective treatments for DFU (Dhatariya et al., 2016); (Serra et al., 2015).

As a comprehensive ancient theory and method originated from oriental philosophy and culture, TCM is widely used for treatment of diabetes and its complications, including DFU (Chen et al., 2010; Li et al., 2011). There is recent evidence that good hydration is the single most important external factor responsible for optimal wound healing, moist exposed wound ointment (MEBO) (Julphar Gulf Pharmaceutical Industries, UAE, and SanTou MEBO Pharmaceutical CO,LTD ,China) reduces evaporation from the wound surface, thereby offering a moist environment for wound healing without compromising the immune defense mechanisms (Sakr et al., 2012). It has a similar property to silver sulfadia zinc in controlling burn wound sepsis *in vivo*, which has been shown experimentally to exhibit a significantly superior wound healing potential on rabbit corneal epithelium as compared to saline, homologus serum, vitamin A and dexamethasone as well as on rabbit skin burns treated with VaseliBe (Sakr et al., 2012; Tsati et al., 2004).

In modern times, MEBO has been used as an adjunctive method for managing DFU. Several experimental studies justified its merits, such as enhancing fibroblast viability and anti-diabetic properties of MEBO (Al-Numairy, 2000). However, to our knowledge the potential benefits of MEBO for patients with DFU have justify their recommendation or clinical role which have not been evaluated. So, it is urgent and important to find answers to these two questions: (1) Is MEBO effective as a kind of therapy for patients with DFU? (2) Is MEBO safe for managing DFU?

Thus, the aim of this research was to conduct a systematic review of RCTs for patients with DFU, and to address the questions regarding whether MEBO is effective and safe as an adjunctive therapy for managing DFU.

MATERIALS AND METHODS

Data sources and search strategy

To identify relevant randomized clinical trials (RCTs), two reviewers (Lian Liu and Song Wei Su) systematically searched the Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Data Base (EMBASE), Cochrane Central Register, China National Knowledge Infrastructure database, Chinese Scientific Journals Full Text Database, Wanfang Data Knowledge Service Platform, and the Chinese Biomedical Literature Service System, using the search terms “Diabetic Foot ulcers,” “DFU,” “MoistExposed Wound Ointment,” “MEBO” and “randomized controlled trial,” or “RCRs.”

In this study, we included papers dating from the earliest citation in the databases until September 2016. This search strategy was used with a method filter for clinical controlled trials and includes articles published in all languages which were considered. The references of all selected publications and reviews were manually searched for further relevant articles. Publication languages and types were not limited, including the conference proceedings, abstract only on articles and theses as long as they met the inclusion criteria.

Study selection

Types of studies

Only randomized controlled trials (RCTs) were included. Quasi-RCTs, nonrandomized controlled trials or randomized trials with false randomization methods, observational studies, cohort studies, or studies with incorrect intervention, not recognized control, inappropriate clinical outcome assessment, and no data for extraction, were ruled out.

Types of participants

Trials were included, in which participants met the following criteria: first, patients were diagnosed as having diabetes according to the diagnostic criteria recommended by World Health Organization (WHO) and the American Diabetes Association (ADA) (Watkins,

2003); second, patients were also diagnosed as having DFU, which included neuropathic, ischemic, and neuro-ischemic ulcers. Studies including other types of foot ulcers (ulcers caused by vasculitis, venous disease or any conditions other than diabetes) were excluded.

There were no set limitations on participant age, gender, or nationality. Studies were performed as a RCT describing a correct randomization procedure. Trials were excluded if any of the following factors were identified:

(1) Inappropriate methods of randomization (for example, open alternation).
(2) Insufficient information concerning evaluation rates.
(3) Lack of MEBO treatment.
(4) Mixed interventions in the experimental group (for example, MEBO combined with internal TCM).
(5) Researches of pharmacological mechanism of MEBO.
(6) Animal trials.

Types of interventions

The focused experimental groups received either MEBO or MEBO combined with conventional therapy. No limitations were set on dosages, times, intervals, duration of MEBO administration, or types of conventional therapy used. The conventional therapy was defined as standard anti-diabetic treatment with or without the use of antibiotics and debridement. These treatment options referred to pressure-relieving interventions, wound dressings, de-compressive surgery, etc.

Control group treatments

Control groups were defined as patients who received any type of conventional therapy for DFU, without MEBO treatments, including;

(1) Diabetes education, diet, exercise.
(2) Standard anti-diabetic treatment (acarbose taken orally, regular measurement of blood glucose concentration).
(3) Basic routine hypoglycemic, anticoagulant, thrombolytic and anti-inflammatory treatment.
4) Wound dressings or cleaning and desloughing ulcers daily (Iodophor, normal saline, 3% hydrogen peroxide, gentamicin etc).
(5) Decompressive surgery or percutaneous transluminal angioplasty.
(6) Other treatment options (spray with recombinant bovine basic fibroblast growth factor (rb-bFGF), pressure-relieving interventions, vacuum sealing drainage, infrared physiotherapy, frequency spectrograph irradiation, etc).

Types of outcome measures

Considering that the outcome measures of most studies of MEBO were focusing on the number of patients whose ulcers healed, reduced or did not reduce; the primary efficacy endpoints considered in this study were the total effectiveness rates of DFU. Complete ulcer closure was defined as skin closure (100% Re-epithelization), without drainage or dressing requirements. Ulcer improvement is defined as decrease in Wagner's grade ≥ 1 and/or decrease in ulcer area of ≥ 50%. A decrease in Wagner's grade ≤1 and ulcer area of ≤ 50% was assigned to the invalid group.

Wagner's ulcer grade and wound assessment were determined on the basis of medical examination and/or X-ray photograph of the sick foot by two experienced physicians (Yotsu et al., 2014). Controversy was resolved through discussion. The secondary efficacy endpoints include date of change in ulcer size, absolute change in wound size, number of wounds completely healed, healing time of ulcers, quality of life, pain, and any adverse effects from the interventions.

In this meta-analysis, healing time was defined as the only secondary efficacy endpoints, because no valid information of the other secondary efficacy endpoints from the included studies was extracted.

Data extraction and quality assessment

Two independent reviewers (Lian Liu and Song Wei Su) reviewed the selected trials from which was extracted the details of data on participants, generation of random allocation sequence, allocation concealment, blinding, interventions, comparisons, outcome measures, while follow-up of two reviewers (Ping Zhou and Ru Song) independently assessed the methodological quality of the included studies using the 7-point Jadad scale (Jadad et al., 1996). The use of modified JADAD scale evaluation mainly includes 4 aspects:

(1) The generation of random sequence.
(2) Random hidden.
(3) The use of blind method.
(4) Loss of access and withdrawal from the report.

The highest score is 7 points while the lowest is divided into 0 points. At present, 1 to 3 is considered as a low quality, and 4 to 7 is considered as a high quality (Table 1). In addition, these two reviewers also evaluated the internal validity of the studies with an 11-item scale developed by Cochrane back review group (van Tulder et al., 2003). Discrepancies between the two reviewers' assessments were resolved by discussion. The data extracted from the first author included study characteristics (that is, year, duration, setting, and design); participant characteristics (that is, mean age, sample size, and systemic therapy); external application of the experimental and control group treatments; measured outcomes.

For patients with multiple ulcers, only the larger/largest (ulcers at the same Wagner's grade) or the higher/highest grade (ulcers at different Wagner's grades) ulcer was enrolled [28]. For studies with insufficient information, the reviewers contacted the primary authors, when possible, to acquire and verify the data.

Data synthesis and analysis

The data were analyzed with Review Manager, version 5.3.1 (Cochrane Community, London, United Kingdom) using Mentel-Haenszel method (Higgins et al., 2011). Comparisons of treatment effects were made between standard therapy combined with MEBO and standard therapy used alone. Heterogeneity among trials was tested using a chi-squared test with a p-value < 0.10 to define a significant degree of heterogeneity. I^2 statistics were used with a cutoff point of 25%. If heterogeneity among trials existed, the data were pooled from the included trials with a random-effect model; otherwise, the fixed model would be selected.

The dichotomous data were reported as relative risk (RR) with a corresponding 95% confidence interval (95% CI). For continuous data, a standardized mean difference was calculated. A sensitivity analysis was planned according to study quality ratings on the Jadad scale. In addition, subgroup analyses were planned according to external application of BEBO alone compared to conventional therapy based on the same intervention strategies or MEBO combined with standard therapy.

For each study, we abstracted the following descriptive data: detailed description of baseline characteristics (for example, main demographic characteristics, type and duration of diabetes, size

Table 1. Characteristics of Included trials.

Study ID	Participants (experimental/control)	Treatment of experimental group; External application of MEBO alone or combined with the conventional treatment	Conventional treatment of control group	Outcome measures	Jadad score
Cui et al. (2008)	Sample size 60(30/30); Sex (male/female) (36/24); Age (Mean ± SD (60-80, M=70years); Experiment Duration (2004.11-2007.6); Diabetes duration (not mentioned); Ulcer size (2*1-2.2*5.0 cm2); Duration of DFU (1-26 months); Diabetes control (>7.8 mmol/L); Baseline equivalence (p>0.05)	MEBO alone; External application of MEBO onto the wounds at 1.5 mm-2.0 mm thickness. Treatments given once a day, for 28 day	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment (acarbose taken orally, regular measurement of blood glucose concentration); 3. Antibiotics; 4. Cleaning and desloughing ulcers daily (Iodophor, normal saline, 3% hydrogen peroxide, gentamicin), covered with dry sterile dressings. Treatments given once a day, for 28 day	TER, MHT	3
Li et al. (2016)	Sample size 81(16/16); Sex (male/female)(38/43); Age (Mean ± SD (32-79 M=58.29±11.97years); Experiment Duration (2010.1-2011.6); Diabetes duration (6.23 ± 5.25 years); Ulcer size (not mentioned); Duration of DFU (not mentioned); Diabetes control (not mentioned L); Baseline equivalence (p>0.05)	MEBO alone; External application of MEBO at 3 g/cm2 thickness, twice a day. Treatments given for 28 days	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers daily; 5. Blood vessel dilation medicine; 6. External application of rb-bFGF gel. Treatments given once a day for 28 day	TER,	3
Sun (2012)	Sample size 60(30/30); Sex (male/female)(13/17,14/16); Age (Mean ± SD (41-80, M=58.0±3.45/42-81M=60.5±3.52years); Experiment Duration (2010.1-2011.1); Diabetes duration (10.8±4.5/11.2±5.3years); Ulcer size (not mentioned); Duration of DFU (not mentioned); Diabetes control (not mentioned); Baseline equivalence (p>0.05)	MEBO alone; External application of MEBO 10 g combined with 2-4 U insulin onto the wounds at 2.0 mm thickness 10 g, covered with dry sterile dressings once or twice a day. Treatments given for 14 day	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers daily (normal saline, 3% hydrogen peroxide, gentamicin 80000 U diluted with 10 ml normal saline). Treatments given once or twice a dayfor14 day	TER	3
Li et al. (2012)	Sample size; 63 ;(33/30); Sex (male/female) (15/18, 14/16); Age (Mean ± SD (62.4±11.2/64.6±9.5 years); Experiment Duration (2008.5-2011.7); Diabetes duration (not mentioned); Ulcer size (15.3±7.1) / 19.18±5.38 cm^2);	MEBO alone; External application of MEBO onto the wounds twice a day, last for 21 days	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers daily ;(iodophor, 1‰Ethacridine Lactate); 5. Blood vessel dilation medicine.	TER	3

Table 1. Cont`d.

	Duration of DFU (12.9 ±5.2d) / 11.7±6.8d); Diabetes control (10.55±3.76 / 10.84±5.48mmol/L); Baseline equivalence (p>0.05)		Treatments given twice a day		
Sakr et al. (2012)	Sample size 128(66/62); Sex (male/female)(51/15,48/14); Age (Mean ± SD (58.4±8.2/55.6±12.3 years); Experiment Duration (2005.1-2010.1); Diabetes duration (27.1±7.2.24.5±8.2mouths); Ulcer size (0.5-8.1 / 1-15.6cm2); Duration of DFU (2.0-4.1mouths/1-15.6years); Diabetes control (10.55±3.76 / 10.84±5.48mmol/L); Baseline equivalence (p>0.05)	MEBO alone; External application of MEBO at 1 mm-2 mm thickness, at 6 hourly intervals, covered with dry gauze and dressing, pressure relieving with a Scotshcast. Treatments given for 28 day	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers daily (normal saline); 5. Blood vessel dilation medicine. Treatments given once a day for 28 day.	TER	4
Qi (2013)	Sample size 60(40/20); Sex (male/female)(23/17,12/8); Age (Mean ± SD (55±11.8/53±12.6years); glycosylated hemoglobin(%) (8.2±4.6 / 7.9±5.4); body mass index(28.9±9.6/30.5±7.8); Experiment Duration (2009.1-2012.10); Diabetes duration (not mentioned); Ulcer size (4.2±2.36 / 3.9±2.49cm2); Duration of DFU (not mentioned); Diabetes control (not mentioned); Baseline equivalence (p>0.05).	MEBO alone; External application of MEBO at 1 mm-2 mm thickness. Treatments given twice a day for 28 day	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers daily(0.5%iodophor,normalsaline100mL, a-chymotrypsin hydrogen peroxide ,6-542injection20mg,VitB1200mg,VitB121mg, insulin20u,); 5. Blood vessel dilation medicine. Treatments given twice a dayfor 28 day.	TER, MHT	3
Ren (2016)	Sample size 32(16/16); Sex (male/female) (12/24, 13/23); Age (Mean ± SD (40-64,M=53.9±7.5/39-65,M=54.4±7.6 years); Experiment duration (2005.1-2015.10); Diabetes duration (not mentioned); Ulcer size (17.86±6.26 / 19.18±5.38 cm^2); Duration of DFU(3-12, M=5.5±1.4 mouths/3-12, M=5.4±1.3 mouths); Diabetes control (not mentioned); Baseline equivalence (p>0.05).	MEBO alone; External application of MEBO at 1mm-2mm thicknes, covered with dry sterile. dressings, once a day for 1 mouths	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers; daily (normalsaline, hydrogen peroxide, Vitamin C, vitamin E); 5. Blood vessel dilation; medicine (Anisodamine, Dansen, mecobalamine). Treatments given once a day, last for 1 months	TER, MHT	3
Liang et al. (2007)	Sample size 66(33/33);		1. Diabetes education, diet, exercise;	TER, MHT	3

Table 1. Cont`d.

	Sex (male/female)(45/21); Age (Mean ± SD (43-86 years); Experiment Duration (2003.1-2006.12); Diabetes duration (not mentioned); Ulcer size (3 cm*4 cm - 18 cm*28 cm^2); Duration of DFU (not mentioned); Diabetes control (not mentioned); Baseline equivalence (p>0.05).	MEBO alone; External application of MEBO, 2-3times a day	2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers; daily (iodophor) 5. Blood vessel dilation medicine; 6. Frequency spectrograph irradiation for 10 min-20 min. Treatments given 5 times a day.		
Gong (2011)	Sample size 78(42/36); Sex (male/female) (26 /16, 20/16); Age (Mean ± SD (45-68,M=62/45-70M=64 years); Experiment Duration (2003.1-2008.11); Diabetes duration (not mentioned); Ulcer size (not mentioned); Duration of DFU (not mentioned); Diabetes control (not mentioned); Baseline equivalence (p>0.05).	MEBO alone; External application of MEBO at 1 mm-2 mm thickness, covered with dry sterile dressings, once a day for 1 mouths.	1. Diabetes education, diet, exercise; 2. Standard antidiabetictreatment(Insulin, oral hypoglycemic drugs); 3. Antibiotics; 4. Cleaning and desloughing ulcers; daily (iodophor, normal saline20ml, Insulin40u, anisodamine10 mg); 5. Blood vessel dilation medicine; 6.Infrared physiotherapy for 20 minutes.	TER,	3
Lou and Sun (2006)	Sample size 40(20/20); Sex (male/female)(21/19); Age (Mean ± SD (50-80 years); Experiment Duration (2004.5-2005.5); Diabetes duration (5-20,M=10.2 years); Ulcer size (1cm*2cm-4cm*3cm, M=2. 5 cm*2 cm); Duration of DFU (3-20 M=14 days); Diabetes control (4.3-6.3 M=5. 3±0. 7 mmol/L); glycosylated hemoglobin (%)4. 3%-6. 0%,M=5. 1± 0. 6% Baseline equivalence (p>0.05).	MEBO alone; External application of MEBO, wound dressing change once a day. Treatments given for 28 day.	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers daily (iodophor,normalsaline, hydrogen peroxide) covered withdry sterile dressings; 5. Blood vessel dilation medicine. Treatments given once a day for 28 day.	TER,	3
Qing and Wei (2015)	Sample size 40(20/20); Sex (male/female) (27/13); Age (Mean ± SD (58-83 M=68 years); Experiment Duration (2013.8-2014.6); Diabetes duration (4-12years); Ulcer size (<15*15 cm^2); Duration of DFU (1-7 mouths); Diabetes control (10.55±3.76/10.84±5.48 mmol/L); Baseline equivalence (p>0.05).	MEBO alone; External application of MEBO 2-4times a day. Treatments given for 28 day.	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughingulcers daily (0. 9% sodium chloride); 5. Blood vessel dilation medicine; 6. Vacuum Sealing Drainage (vacuum pressure 40-60 kPa) for 7-8days. Treatments given once a day for 28 day.	TER,	3

Table 1. Cont`d.

Zhang and Zhang (2005)	Sample size 60(30/30); Sex (male/female)(33/27); Age (Mean ± SD (40-69,M=54.5years); Experiment Duration (2003.5-2004.6); Diabetes duration (2-6 , M=4years); Ulcer size (1.2cm *1.9 cm-10cm*20cm); Duration of DFU (not mentioned); Diabetes control (not mentioned); Baseline equivalence (p>0.05).	CT+ MEBO; External application of MEBO at 1 mm thickness, covered with dry sterile dressings, 4 times a day, for 1 mouths	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4.Cleaning and desloughing ulcers; daily(Entoiodine, 3%Hydrogen peroxide,0. 9% sodium chloride, 0.1% chlorhexidine); 5. Blood vessel dilation; medicine (VitB1,VitB6,Aspirin,Dansen); 6. Infrared radiation0.5 h, twice a day Treatments given once a day.	TER	3
Yang et al. (2011)	Sample size 82(42/40); Sex (male/female)(52/30); Age (Mean ± SD (30-86 M=59.8±17.3 years); Experiment Duration (2006.2-2010.2); Diabetes duration (5-32 M=18.60±10.40years); Ulcer size (not mentioned); Duration of DFU (1-17 days); Diabetes control (1.60±4.65mmol/L); Baseline equivalence (p>0.05).	CT+MEBO; External application of MEBO at 1mm-1.5mm thickness, at 4-6 hourly intervals, exposed therapy， electromagnetic wave irradiation for 15-20 min.	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers daily; 5. Blood vessel dilation medicine; Treatments given once or twice a day for 28 day.	TER,	Yang et al. (2011)
Deng and Li (2007)	Sample size 58(29/29); Sex (male/female) (23/35); Age (Mean ± SD (35-85,M=63 years); Experiment Duration (2002.6-2006.10); Diabetes duration (20 days-23 years); Ulcer size (0.5 cm*0.5cm-7.3cm*9.0cm); Duration of DFU (not mentioned); Diabetes control (not mentioned);Baseline equivalence (p>0.05).	CT+ MEBO; External application of MEBO at 1 mm thickness, covered with dry sterile dressings, 4 times a day	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers; daily (3% Hydrogen peroxide,0.9% sodium chloride, 0.25%iodophor); 5. Blood vessel dilation medicine. (ligustrazine120-160 mg+anisodamine20-30 mg); 6. Frequency spectrum therapy apparatus irradiation for 30 min (Irradiation distance 15-20 cm twice a day. Treatments given once a day.	TER	3
Wang (2015)	Sample size 50(25/25); Sex (male/female)(16/9, 15/10); Age (Mean ± SD (61.08±6.97/61.42±6.49 years); Experiment Duration (2009.6-2014.6); Diabetes duration (not mentioned); Ulcer size (11.92±2.35 / 12.20±2.39cm2); Duration of DFU (not mentioned); Diabetes control (5.87 ±0.93/6.12 ±0.73mmol/L);	CT+ MEBO; External application of MEBO at 1mm thickness, covered with dry sterile dressings , 4 times a day,10 day as a course	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers aily(3%Hydrogen peroxide,0.9% sodium chloride); 5. Blood vessel dilation medicine.; 6 Hyperbaric oxygen therapy for 60 minutes, at 1-2 intervals,10 day as a courser.	MHT	3

Table 1. Cont`d.

Renliang et al. (2010)	Sample size 138(75/63); Sex (male/female) (40/35,33/30); Age (Mean±SD 27-78M=52.7±3.25)/28-76 M=50.5 ±3.87years); Experiment Duration (2010.1-2011.6); Diabetes duration (4.2mouths-5.6years/8mouths-5.5years); Ulcer size (2.0cm*1.8 cm-15cm*12 cm,M=4.0 cm*2.3 cm /2.4 cm*1.8 cm-13.5cm*11.2cm,M=3.9cm*2.4cm); Duration of DFU (10.6 ±1.21mouths /9.8±1.78mouths); Diabetes control (10.55 ±3.76 / 10.84 ±5.48 mmol/L); Baseline equivalence (p>0.05).	CT+ MEBO; External application of MEB, covered with dry sterile dressings, once a day. Treatments given for 56 day.	1. Diabetes education, diet,exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughingulcers daily; 5.Bloodvessel dilation medicine(compound danshen injection);. 6.Spray withrb-bFGF 150 AU/cm2 covered withdry sterile dressings.; Treatments given once a day, for 56 days.	TER	4
Li et al. (2010)	Sample size 94(59/33); Sex (male/female) (44/33); Age (Mean ± SD M=75.2years); Experiment Duration (2006.6-2009.6); Diabetes duration (not mentioned); Ulcer size (not mentioned); Duration of DFU (not mentioned); Diabetes control (not mentioned); Baseline equivalence (p>0.05).	CT+ MEBO; External application of MEBO. Treatments given for 28 day	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Basic routine hypoglycemic， anticoagulant，thrombolytic and anti-inflammatory treatment; 4. Cleaning and desloughing ulcers daily (Hydrogen peroxide solution, iodine, oil gauze strip); 5. Blood vessel dilation medicine; 6. PTA surgery; Treatments given once a day for 28 day.	TER, MHT	3
Zhang et al. (2015)	Sample size 60(31/29); Sex (male/female)(17/14, 16/13); Age (Mean ± SD (18-75,55.03±13.03)/19-73,53.76 ±12.15years); Experiment Duration (2013.6-2015.5); Diabetes duration (not mentioned); Ulcer size (6.1-16.8 M=11.61±4.84/5.7-15.9M=11.40±4.13cm2); Duration of DFU (5-17 M=11.55±4.37days/7-15 M=11.31±3.40days); Diabetes control (not mentioned); Baseline equivalence (p>0.05);	CT+ MEBO; External application of MEBO combined with TCM syndrome differentiation, covered with dry sterile dressings twice a day. Treatments given for 28 day	1. Diabetes education, diet, exercise; 2. Standard anti-diabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers daily; 5. Blood vessel dilation medicine; 6. External use of rb-Bfgf; Treatments given once a day for 28 day.	TER	3
	Sample size 60(33/27); Sex (male/female)(19/14, 15/12);		1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment, Blood pressure	TER, MHT	3

Table 1. Cont`d.

Wang (2013)	Age (Mean ± SD (42-73,M=57.5 M=5.3 /40-75,M=58.8 M=5.1 years); Experiment Duration (2007.1-2012.1); Diabetes duration (3 -32 / 2 -30years); Ulcer size (not mentioned); Duration of DFU (2 mouths-6 years/ 1 mouth-5years); Diabetes control (7.65 ±3.44 / (7.54±3.31 mmol/L); Baseline equivalence (p>0.05),	CT+ MEBO; External application of MEBO onto the wounds at 1.5 mm-2.0 mm thickness combined with epidermal growth factor sprayed on the wound, once a day	control; 3. Cleaning and desloughingulcers daily (normal saline, 3%hydrogen peroxide potassium permanganate solution, Antibiotics, insulin), covered withdry sterile dressings; 4. Bloodvessel dilation medicine. Treatments given once a day for 28 day.		
Wu et al. (2015)	Sample size 67(34/33); Sex (male/female)(18/16/19/14); Age (Mean ± SD (48-79,M=64.3years); Experiment Duration (2010.9-2014.9); Diabetes duration (5-23 years); Ulcer size (1.5 cm* 1.7 cm-2.5 cm*4cm); Duration of DFU (3weeks-2 mouths); Diabetes control (6.0-8.0mmol/L); Baseline equivalence (p>0.05).	CT+ MEBO; External application of MEBO onto the wounds at 2.0 mm thickness.	1. Diabetes education, diet,exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4.Cleaning and desloughingulcers daily(iodophor, hydrogen peroxide,rh-a FGF); 5.Bloodv essel dilation medicine (TCM:FuFangDanCanDiWan,Danhong,Honghuahuangsesu); Treatments given once a day,5 weeks as a course.	TER, MHT	3
Cao et al. (2015)	Sample size 48(24/24); Sex (male/female)(14/10,13/11); Age (Mean ± SD (52-79M=63.46years); Experiment Duration (2013.1-2014.12); Diabetes duration (12-30years); Ulcer size (not mentioned); Duration of DFU (not mentioned); Diabetes control (not mentioned); Baseline equivalence (p>0.05).	CT+ MEBO; External application of MEBO onto the wounds. Treatments given once a day for 30 day	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics, lipid and blood pressure control; 4. Cleaning and desloughing ulcers daily; 5. Blood vessel dilation medicine; 6. Laser radiation for 20 minutes, twice a day. Treatments given once a day for 30 day	TER	3
Yang and Liu (2010)	Sample size 52(26/26); Sex (male/female)(35/17); Age (Mean ± SD (47-78(57.8±12.4) years); BMI (22.9± 3.2); Experiment Duration (2004.1-2010.1); Diabetes duration (12.6± 2.1years); Ulcer size (17.86±6.26 / 19.18±5.38cm2); Duration of DFU (7.06±3.59/ 6.5±3.4years); Diabetes control (10.55±3.76 / 10.84±5.48 mmol/L); Baseline equivalence (p>0.05).	CT+ MEBO; External application of MEBO at 1-2 mm thickness, twice a day. Treatments given for 28 day	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4.Cleaning and desloughing ulcers; daily(3%Hydrogen peroxide,0.9% sodium chloride, Gentamicin 80000U, insulin12U); 5. Blood vessel dilation medicine. Treatments given once a day for 28 day.	TER, MHT	4

Table 1. Cont`d.

Jiang (2012)	Sample size 32(16/16); Sex (male/female)(42/33); Age (Mean ± SD (47-78M=55.6±12.4years); Experiment Duration (2004.5-2011.7); Diabetes duration (13.4±2.3years); Ulcer size (not mentioned); Duration of DFU (not mentioned); Diabetes control (not mentioned); Baseline equivalence (p>0.05).	CT+ MEBO; External application of MEBO at 1-2mm thickness; Treatments given once a day for 28 day	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers daily (insulin12U, ethacridine lactate); 5. Blood vessel dilation medicine; 6.Tongmai Decoction taken orally(ingredients: Angelica sinensis20g，radix scrophulariae20g,honeysuckle30 g ， peach kernel10g,Carthamustinctorius 10 g, Radix Paeoniae Rubra 12 g ， bombyx batryticatus10g,Astragalus membranaceus30 g, Salvia miltiorrhiza20 g, Caulis Spatholobi20 g，radix cyathulae 20 g Ligusticum wallichii15g Treatments given once a day for 28 day.	TER, MHT	4
Du et al. (2012)	Sample size 32(16/16); Sex (male/female)(7/9,9/7); Age (Mean ±SD)(58.5±5.5/59.0±6.1 years); Experiment Duration (2010.1-2011.6); Diabetes duration (not mentioned); Ulcer size (17.86±6.26 / 19.18±5.38 cm^2); Duration of DFU (7.06±3.59/6.5±3.4 years); Diabetes control (10.55±3.76 / 10.84±5.48 mmol/L); Baseline equivalence (p>0.05).	CT+ MEBO; External application of MEBO onto the wounds at 1-2 mm thickness, twice a day; treatments given last for 20 days	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Route dressing change (Iodophor, normal saline, 3%hydrogen peroxide); 5. Debridement and drainage; 6. Vacuum sealing drainage (200-400 mmHg) for 5-7 days; Treatments given once a day for 20 day.	TER,	4
Liu (2016)	Sample size 100(50/50); Sex (male/female)(27/23, 26/24); Age (Mean ± SD (50-75 M=64.7±7.4/64.1±7.4 years) Experiment Duration (2013.7-2015.6 years); Diabetes duration (11.8±4.2/ 12.1±3.8 years); Ulcer size (not mentioned); Duration of DFU (2.1±1.1/2.4±1.2 years); Diabetes control (7.5±3.1/7.6±3.1 mmol/L); Baseline equivalence (p>0.05).	CT+ MEBO; External application of MEBO onto the wounds at 1-2 mm thickness once a day, last for 2 mouths	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers daily (normal saline, 3%hydrogen peroxide potassium permanganate solution, insulin, epidermal growth factor); 5. Blood vessel dilation medicine; Treatments given once a day for 2 mouths.	TER, MHT	3
	Sample size 60(30/30); Sex (male/female)(12/18,15/15); Age (Mean ± SD (45-68 / 43-69 years); Experiment Duration (2009.5-2010.12);		1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers daily (chlorhexidine	TER, MHT	3

Table 1. Cont`d.

Wu et al. (2012)	Diabetes duration (not mentioned); Ulcer size (17.86±6.26/19.18±5.38 cm^2); Duration of DFU (2 weeks-3 years / 3 weeks-3 years); Diabetes control (7. 53 ± 1. 84 mmol/L); Baseline equivalence (p>0.05).	CT+ MEBO; External application of MEBO at 2 mm-3 mm thickness, once or twice a day, lasts for 20 days	solution,3%Hydrogen peroxide,0. 9% sodium chloride); 5. Blood vessel dilation medicine; 6. Micro balloon expansion treatment; Treatments given once a day.		
Wang et al. (2011)	Sample size 73(24/49); Sex (male/female)(13/11,27/22); Age (Mean ± SD (54.12±12.56/57.32±13.68 years); Experiment Duration (2009.1-2010.1); Diabetes duration (not mentioned); Ulcer size (5.24±3.45/ 6.32±4.36cm2); Duration of DFU (not mentioned); Diabetes control (7.62±3.21/7.81±4.65mmol/L); Baseline equivalence (p>0.05).	CT+ MEBO; External application of MEBO onto the wounds at 1-2 mm thickness, wounds were covered withdry sterile dressing, once a day. Treatments given for 28 day	1. Diabetes education, diet, exercise; 2. Standard antidiabetic treatment; 3. Antibiotics; 4. Cleaning and desloughing ulcers daily (normal saline, 3%hydrogen peroxide potassium permanganate solution); 5. Route dressing change (Metronidazole 0.5 g, gentamicin 80000Udiluted with 50 ml normal saline，With insulin 8u diluted with normal saline1ml, sprayingrb‐bFGF(150AU/cm2), covered with dry sterile dressings; 6. Blood vessel dilation medicine. Treatments given once a day for 28 day;	TER, MHT	3

a In trials in which baseline data were reported per group, we used slashes to separate them. As suggested in the table (experimental/control), on the left side of the data belong to the experimental group, whereas data on the right side belong to the control group. In trials that did not report baseline data separately, we used the data of the whole sample as reported. Data were listed asmean±standard deviation or mean only, the units were attached behind the numbers.
b In the intervention groups, both standard therapy and MEBO were used. The unit g refers to gram. Some trials did not specify the dose used, so the doses were not listed in thistable.
c In the control groups, only standard therapy was used. The only difference between groups was the administration of MEBO in the intervention group.
d DFU, diabetic foot ulcers; ST, standard therapy; TER,Total effective rate; MHT, Mean Healing Time;rb-bFGF, recombinant bovine basic fibroblast growth factor; PTA, percutaneous transluminal angioplasty.

and duration of the ulcer) and interventions received (active or control) for all participants enrolled. We also extracted data for outcomes and assessment of methodological quality. Extracted data were collated by a third independent reviewer, and inconsistencies were resolved by referring to the full-text article.

Methodological quality and risk of bias assessment

The risk of bias in each study was assessed by two independent authors (Ping Zhou and Ru Song) Using the Cochrane Risk of Bias tool (Ezzo et al., 1998); disagreements were resolved either by consensus or by a third reviewer (Hong Yan Sun). Two reviewers independently assessed the quality of studies included. The outcome ascertainment, adjustment for confounders, proportion of patients lost to follow-up, and sample selection were assessed in each study.

Randomized trials were evaluated using the Cochrane risk of bias assessment tool (Ezzo et al., 1998); domains assessed included randomization, blinding, allocation concealment, baseline imbalances, loss to follow-up data, and bias due to funding. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods (Higgins et al., 2011) the evidence grading can be increased (if a large effect is observed) or decreased if other factors are noted, such as studies being at increased risk of bias or imprecise (small with wide confidence intervals [CIs]).

Assessment of publication bias

In this study, the funnel plots for incidence rate of phlebitis and total effectiveness rate of MEBO combined with conventional therapy 14 RCTs and 26 RCTs, respectively (Figures 3 to 5). Regarding these studies of MEBO for phlebitis, the publication bias was small because the spots were substantially symmetric, and none of the studies lies outside the limits of the 95% CI. However, the probability of publication bias may also exist in our study because of most of the included trials are published in Chinese.

Sensitivity analysis

Sensitivity analysis using the leave-one-out approach indicated that, the finding was reliable and are not dependent on anyone study, the with the removal of each study in turn, indicating that the meta-analysis was robust and the data was not overly influenced by any direction of

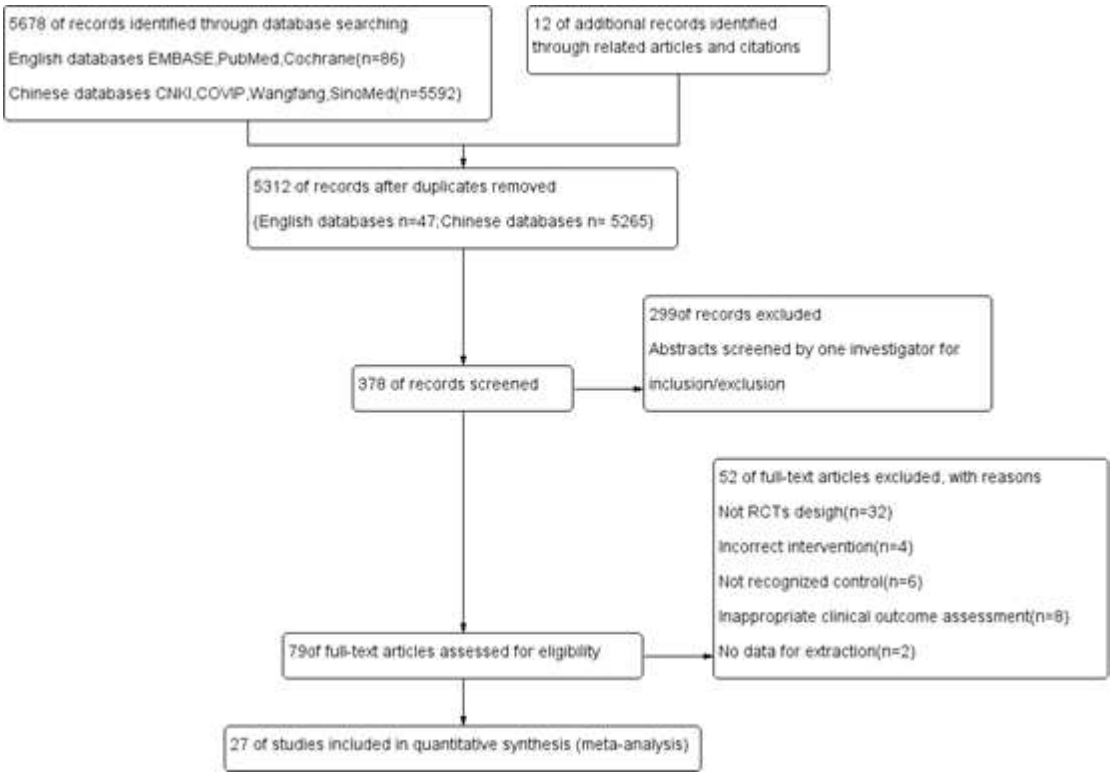

Figure 1. Summary of the literature identification and selection process, CNKI indicates the Chinese National Knowledge Infrastructure database; CQVIP, the Chinese Scientific Journals Full Text database; Sino Med, the Chinese Biomedical Literature Service System; TCM, traditional Chinese medicine; RCT, randomized clinical trials.

the combined estimates did not vary markedly study.

RESULTS

Study identification and characteristics

This review systematically assessed mainly Chinese-sourced RCT studies related to the effects of MEBO, as a complementary therapy. In the initial screening, 5,690 articles were identified in which the title, the abstract, or both mentioned the use of MEBO for managing DFU. Of the 5,690 articles 5,312 were excluded for duplicates. In addition, 299 articles were excluded by one investigator for inclusion/exclusion after screening abstracts.

Fifty-two records were excluded because they were quasi-RCTs, reported trials of non-diabetic foot ulcers, and other unacceptable factors. Finally, 27 RCTs were included for analysis including 26 pure-Chinese trials (Cui et al., 2008); (Li et al., 2012); (Qi, 2013); (Wang et al., 2011), and one English-Chinese trials (Sakr et al., 2012). A total of 1,039 patients were allocated in experimental groups (standard therapy combined with topical use of MEBO or topical administration of MEBO alone), while 930 participants were allocated to control groups (standard therapy used alone). All these RCTs were conducted in mainland China.

Figure 1 shows more details of the screening process, including how many articles were found in the databases. The 27 included trials were small-sample-size trials; the largest one included a total of 138 patients (Renliang et al., 2010). Important data on the characteristics of the 27 studies are summarized in Table 1. Despite the fact that most of the trials had small sample sizes and poor methodological quality, analysis of the pooled data showed a consistently superior effect of MEBO or MEBO combined with conventional therapy in terms of total effectiveness rates, when compared to the control groups. There were fewer severe adverse effects; only one trial mentioned the adverse effect of MEBO, which was not related with external application of MEBO directly. No patients dropped out of their trials due to MEBO-related adverse effects, suggesting that MEBO is safe for clinical use.

Methodological quality and risk of bias assessment of the included trials

The methodological quality of all included trials was poor (Figure 2), with the scores of the 11-item scale ranging from 3 to 4 and the scores of the Jadad scale as 3 to 4

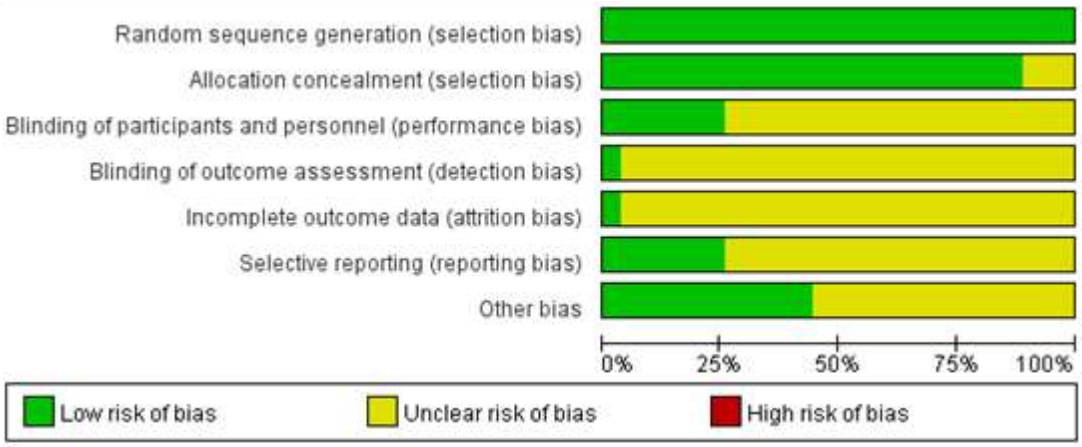

Figure 2. Risk of bias graph.

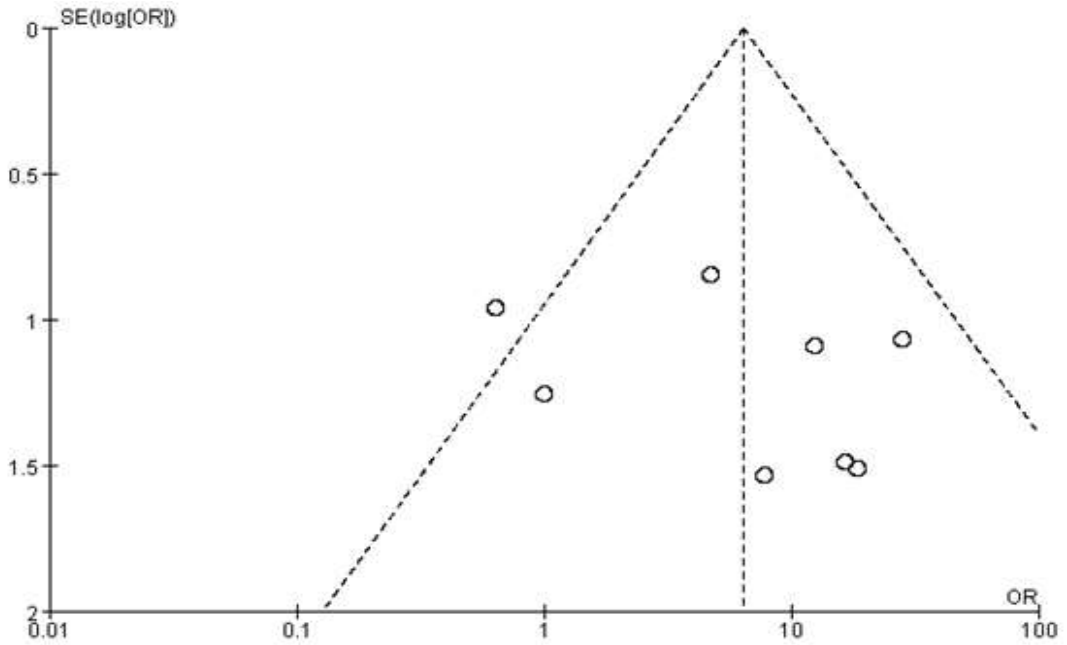

Figure 3. Funnel plot of total effectiveness rate of BEBO versus conventional therapy based on the same intervention strategies

(Table 1). Although all these trials reported randomization, only three adequately described the randomization method: three with a random number table (Renliang et al., 2010); (Yang and Liu, 2010); (Jiang, 2012), and one using clinic record numbers (Du et al., 2012).

Moreover, none of the studies reported information such as allocation conceal mentor blinding of participants and study personnel; only one reported the details of the blinding of outcome assessment (Sakr et al., 2012). All of the relevant trials adequately addressed incomplete outcome data and selective reporting. There were no other biases in these trials; however, considering their poor methodological quality, it was determined that an unclear risk of bias should be given to all the included trials.

Primary efficacy endpoint

Total effectiveness rates of mebo versus conventional therapy

The 11 RCTs contained 853 patients; the experimental

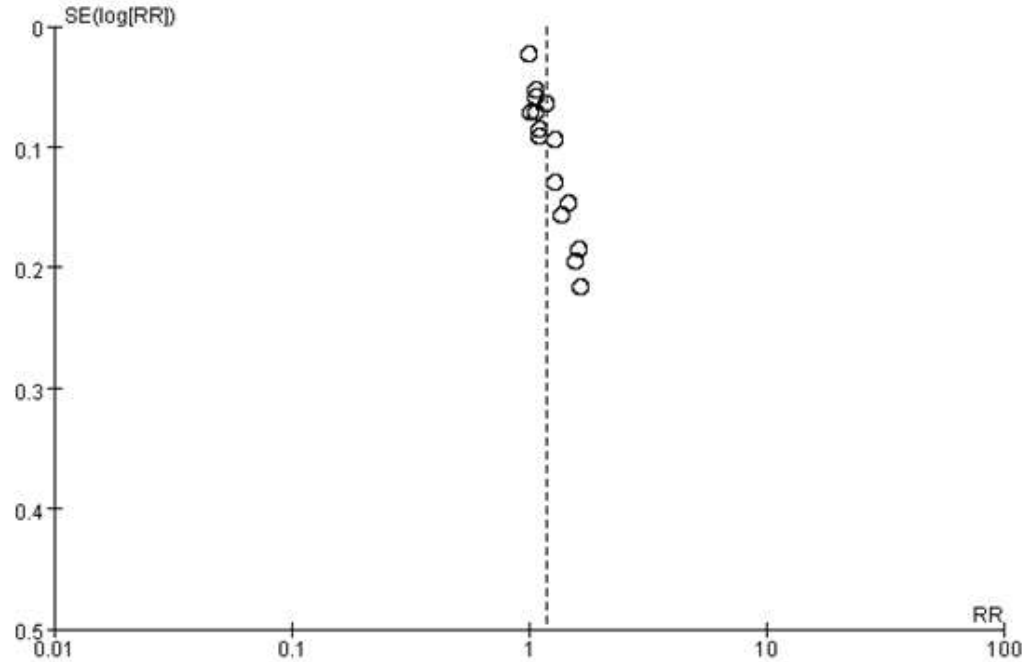

Figure 4. Funnel plot of total effectiveness rates of mebo combined with conventional therapy versus conventional therapy alone.

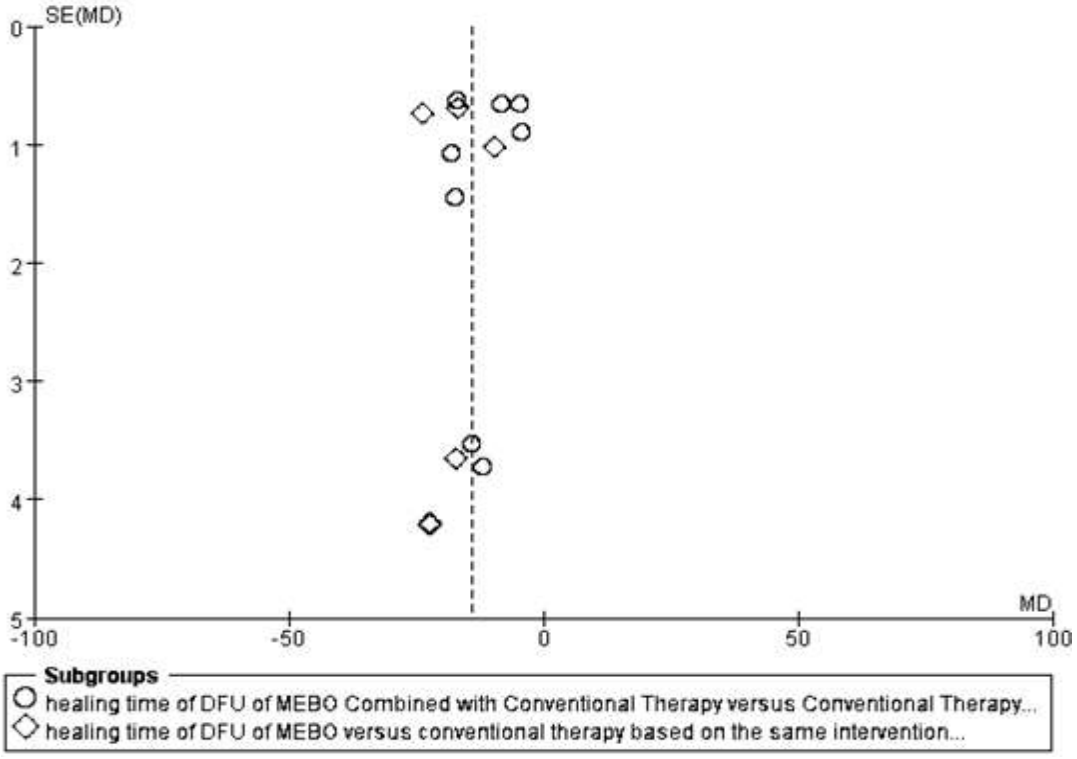

Figure 5. Funnel plot of healing time of DFU of MEBO combined with conventional therapy.

and control groups received MEBO and conventional therapy based on the same intervention strategies, respectively (Cui et al., 2008); (Qing and Wei, 2015). All subjects from the two groups received basic intervention

strategies, including diabetes education, diet, exercise, standard anti-diabetic treatment, neuropathic drugs, blood vessel dilation medicine, cleaning and desloughing ulcers daily, wound dressings change, debridement and drainage or compression bandaging, and conventional therapy included skin substitutes, growth factors and inflammatory modulators.

Pooling of the results from these trials showed a significant difference in the total effectiveness rate between the MEBO and conventional therapy groups (Risk Ratio [RR], 6.36, [95% confidence interval (CI), 3.20, 12.64], <0.00001) using the fixed-effects model (Table 2).

Total effectiveness rates of EA-TCM combined with conventional therapy versus conventional therapy alone

Considering that the outcome measurements of some trials were different from the others so, the data of studies that had used the same outcome measurements were combined,15 studies with 1,016 subjects reported that the experimental groups received EA-TCM combined with conventional therapy and the control groups received conventional therapy only (Zhang and Zhang, 2005);(Deng and Li, 2007); (Renliang et al., 2010); (Wang et al., 2011).

Results of meta-analysis using the random-effects model indicated a significantly higher total effectiveness rate for EA-TCM combined with conventional therapy compared to that of the control groups (Risk Ratio [RR], 1.19, [95% confidence interval (CI), 1.08, 1.31], P = 0.0007) (Table 3).

Secondary efficacy endpoint

To evaluate the healing time of DFU of MEBO topical application alone or combined with conventional therapy versus conventional therapy, data were extracted from 13 trials including 937 patients. There were significant differences of healing time of DFU of MEBO healing time (Mean difference [MD], 14.15, [95% confidence interval (CI), -18.14, -10.17], P < 0.00001) with random-effects model, with respect to blood flow volume in the dorsal artery of the foot (This was measured using color Doppler ultrasound).

Significant differences were found between subgroups of healing time of DFU of MEBO versus conventional therapy based on the same intervention strategies (Mean difference [MD], -17.90, [95% confidence interval (CI), -23.76, -12.03], P < 0.00001) and healing time of DFU of MEBO combined with conventional therapy versus conventional therapy alone (Mean difference [MD], -11.87, [95% confidence interval (CI), -16.42, -7.31], P < 0.00001) (Table 4).

Adverse events

Only one trials reported that four patients died in each group after 13 to 22 months of their enrollment in the study, in which the dead were older at presentation as compared with the rest of the group, and the deaths were due to myocardial infarction, stroke, pneumonia, and septicemia as a result of an infected foot ulcer, which had no statistically significant difference between treatment and control groups in terms of adverse events (Sakr et al., 2012).

Some trials reported that nausea was reduced after the patients were told to take MEBO after meals (Al-Meshaan et al., 2008). The other trial reported that, although epigastric pain, drymouth, and diarrhea were experienced, the patients' liver and renal functions were not affected and these symptoms were not related to topical application of MEBO (Qi, 2013).

DISCUSSION

Limitations of this research

In these studies, several limitations are acknowledged. Specifically, the distorting effects of publication and location bias on systematic reviews and meta-analyses have been well documented (van Tulderet al., 2003). Although, we are confident that our search strategy is located in all the relevant studies which remains certain to the degree of uncertainty. The quality scores of the included RCTs were generally poor (Table 1). Although, all of the included studies had a randomization design, only three described the details of the randomization (Renliang et al., 2010; Yang and Liu, 2010; Jiang, 2012).

Furthermore, information on allocation concealment or participant and personnel blinding was missing, and only one study reported any details of the blinding of outcome assessments (Sakr et al., 2012). Cochrane's χ^2 and I^2 tests revealed no statistical heterogeneity in the total effectiveness rate among these studies; an unpredictable clinical heterogeneity was present nonetheless. For example, basic intervention strategies and conventional standard therapies, dosages and intervals of MEBO, wound-cleaning methods, and care approaches were different in each RCT.

Possible pharmacological mechanisms for MEBO for DFU

The etiology of diabetic foot ulcer is multifactorial, peripheral neuropathy, foot deformity, and trauma which is considered as the most common factors that contribute to it (Alavi et al., 2014). TCM theory categorizes DFU into "Xiao Ke" or "TuoJu", a condition which is due to ill-nourishment of the distal end of extremities in case where

Table 2. Total effectiveness rate of BEBO versus conventional therapy based on the same intervention strategies.

Study or subgroup	Experimental		Control			Risk radio
	Events	Total	Events	Total	Weight (%)	M-H, Random, 95% CI
Cao et al. (2015)	22	24	16	24	5.0	1.38[1.01,1.87]
Deng and Li (2007)	28	29	26	29	8.0	1.08[0.93,1.24]
Du et al.(2012)	16	16	10	16	3.9	1.57[1.07,2.30]
Gong (2011)	39	42	30	36	7.5	1.11[0.94,1.32]
Jiang (2012)	33	38	25	37	5.8	1.29[1.00,1.66]
Li et al. (2010)	59	59	35	35	9.3	1.00[0.96,1.05]
Liang et al., (2007)	33	33	31	33	8.6	1.06[0.96,1.18]
Liu (2016)	50	50	42	50	8.2	1.19[1.05,1.35]
Qing and Wei (2015)	18	20	11	20	3.5	1.64[1.07,2.50]
Wang et al.(2011)	46	49	22	24	8.0	1.02[0.89,1.18]
Wang (2013)	31	33	23	27	7.2	1.10[0.92,1.32]
Wu et al. (2012)	26	30	16	30	4.2	1.63[1.13,2.34]
Yang et al. (2011)	51	56	40	56	7.1	1.27[1.06,1.53]
Zhang et al. (2015)	31	31	27	29	8.4	1.07[0.96,1.21]
Zhang and Zhang (2015)	28	30	19	30	5.3	1.47[1.10,1.97]
Total (95% CI)	-	540	-	476	100	1.19[1.08,1.31]
Total events	511	-	373	-	-	-

Heterogeneity: Tau^2=0.03; Chi^2=86.08, df =14(P<0.00001); I^2=84%; Test for overall effect: Z=3.40(P=0.0007).

Table 3. Total effectiveness rates of MEBO combined with conventional therapy versus conventional therapy alone.

Study or subgroup	Experimental		Control			Odd radio
	Events	Total	Events	Total	Weight (%)	M-H,FIXED,95% CI
Cui et al. (2008)	30	30	27	30	5.6	7.76 [0.38,157.14]
He et al. (2010)	75	75	63	63	-	Not estimable
Li et al. (2012)	31	33	23	30	18.4	4.72 [0.90,24.85]
Li et al. (2016)	43	43	38	38	-	Not estimable
Lou and Sun (2006)	20	20	14	20	4.3	18.38 [0.96,352.57]
Sakr et al. (2012)	82	82	78	78	-	Not estimable
Qi (2013)	38	40	19	20	16	1.00[0.09,11.74]
Ren (2016)	35	36	20	36	7.0	28.00[3.45,227.21]
Sun (2012)	29	30	21	30	8.8	12.43[1.46,105.74]
Wu et al. (2015)	34	34	27	23	5.0	16.31[0.88,302.32]
Yang and Liu (2010)	23	26	24	26	34.9	0.62[0.10,4.18]
Total(95%CI)	-	440	-	404	100	6.36[3.20,12.64]
Total events	440	-	354	-	-	

Heterogeneity: Chi^2=11.25, df=7(P=0.13);I^2=38%; Test for overall effect: Z=5.27(P<0.00001).

there is deficiency of qi and yin, stasis and obstruction of blood vessels in essence and attacks of damp-heat superficially. It is a morbid condition of depletion and deficiency in origin (deficiency of both qi and yin) and excess in superficiality (stagnant blood and heat pathogen).

In addition, by exposure to heat pathogens, insufficiency of the liver and kidney, deficiency of qi and yin, the obstructed channels will prevent the yang-qi from going downward to the distal end of extremities. Consequently, DFU will take place (Liu and Feng, 2005; Lee et al., 2016). Modern pharmacology has demonstrated that the impaired wound healing is probably caused by deficiencies in local growth factors, changes in the extracellular matrix, diminished fibroblast function, diminished antimicrobial activity of leukocytes and disturbances in the macro and micro circulation. Besides, levels of matrix metalloproteinase-2(MMP-2)

Table 4. (a) Healing time of DFU of MEBO Combined with Conventional Therapy versus Conventional Therapy Alone and b) healing time of DFU of MEBO versus Conventional therapy based on the same intervention strategies.

Study or subgroup	Experimental			Control				Mean difference
(a)	Mean	SD	Total	Mean	SD	Total	Weight (%)	M-H,Random,95%CI
Jiang (2012)	24	2.9	38	41	2.6	37	8.3	-17.00[-18.25,-15.75]
LI et al. (2010)	26.14	4.01	59	30.31	4.23	33	8.2	-4.17[-5.94,-2.40]
Liang et al., (2007)	21	13.2	33	33	16.8	33	6.5	-12.00[-19.29,-4.71]
Liu (2016)	43.1	7.1	50	60.4	7.4	50	8.0	-17.30[-20.14,-14.46]
Wang et al. (2011)	31.21	11.56	49	45.34	15.27	24	6.7	-14.13[-21.04,-7.22]
Wang (2013)	21.3	3.6	27	39.5	4.7	33	8.2	-18.20[-20.30,-16.10]
Wang (2015)	29.42	3.06	50	37.75	3.52	50	8.3	-8.33[-9.62,-7.04]
Wu et al. (2012)	14.3	2.5	30	18.9	2.6	30	8.3	-4.60[-5.89,-3.31]
Subtotal (95%CI)	-	-	336	-	-	290	62.5	-11.87[-16.42，-7.31
(b)								
Cui et al. (2008)	25	10.5	30	47.3	20.4	30	6.2	-22.30[-30.51,-14.09]
Qi (2003)	28.3	12.3	40	45.8	13.8	20	6.6	-17.50[-24.65,-10.35]
Ren (2016)	25	3.2	36	34.8	5.2	36	8.2	-9.80[-11.79,-7.81]
Wu et al. (2015)	43.1	3.2	34	60.1	2.4	33	8.3	-17.00[-18.35,-15.65]
Yang and Liu (2010)	23	2.4	26	47	2.9	26	8.3	-24.00[-25.45,-22.55]
Subtotal (95%CI)	-	-	166	-	-	145	37.5	-17.90[-23.76,-12.03]
Total (95%CI)	-	-	502	-	-	435	100	-14.15[-18.14,-10.17]

a) Heterogeneity: Tau^2=39.86; Chi^2=319.63, df=7(P<0.00001); I^2=98%; Test for overall effect: Z=5.10(P<0.00001).
b) Heterogeneity: Tau^2=39.34; Chi^2=133.88, df=4(P<0.00001); I^2=97%; Test for overall effect: Z=5.98(P<0.00001).
Total; Heterogeneity: Tau^2=49.43; Chi^2=652.36,df=12(P<0.00001); I^2=98%; Test for overall effect: Z=6.98(P<0.00001); Test for subgroup differences: Chi^2=2.53,df=1(P=0.11);I^2=60.5%

and matrix metalloproteinase-9 (MMP-9) are elevated in the plasma of diabetic patients, and disruption of balance between MMPs and tissue inhibitors of metal proteinase (TIMPs), indicating abnormalities in extracellular matrix metabolism (Sun, 2012); (Li et al.,2012). Moreover, the correlation between MMP-9 and vascular endothelial growth factor (VEGF) suggests that, the tissue repair and turnover in connective tissue metabolism are significantly associated with angiogenesis and tissue healing of DFU (Tang et al., 2014).

Management of DFU is largely determined by its severity (grade) and vascularity, and the presence of infection (Wagner, 1981; Elraiyah et al., 2016). For ulcer healing and limb salvage, a multidisciplinary approach should be employed which does not only include wound control but also microbiological, mechanical, vascular, metabolic, and educational control (Sakr et al., 2012). Wound healing in diabetic patients is generally known to be slow, which is accomplished by an orderly sequence of three phases: inflammation, proliferation and remodeling, thus, the principles of care for DFU involves treatment of infection, revascularization, and off-loading of the ulcer site (Perez-Zabala., 2016; Maydick et al., 2016). Pharmaceutical preparations used in wound management include wound cleansing solutions, antimicrobial and wound debriding agents as well as dressing materials and products. The rapid development of topical wound dressings during the last 3 decades has left the physician with a confusing number of choices ranging from exotic products such as egg membranes and banana leaves to hi-tech engineered biomaterials. Collectively, sterilization, promoting blood circulation and eliminating stasis to activate blood circulation, removing necrosis and promoting granulation may be their main effects. Biologically active products, systemic hyperbaric oxygen treatment, silver or other anti-microbial agent containing dressings and bio-engineered skin substitutes have also been widely used, but they have not been established in routine management. Endogenous growth factors, such as recombinant bovine basic fibroblast growth factor (rb-bFGF), platelet-derived growth factor (PDGF) and vascular endothelial-derived growth factor (VEGF), and dressings containing ionic silver have become the focus of interest in topical treatment (Zhang et al., 2015). However, their effectiveness remains to be confirmed (Tang et al., 2014). Even if effective, they are expensive in terms of both product costs and professional time.

MEBO is the basis of moist exposed burn therapy (MEBT) which was popularized 3 decades ago by Xu Rongxiang of Beijing Rongxiang Institution of Regenerative Medicine in China, and supposedly represents a revolution in the management of burns by encouraging the bum wound to heal and regenerate

spontaneously without surgical intervention. MEBO was made according to a traditional Chinese medicine formula, the application no. 201010261094X, which is light yellow-brown in color, consists of natural ingredients including beeswax, sesame oil, seventeen amino acids, *Radix scutellaria*, *Cortex phellodendri*, *Rhizoma coptidis*, earthworms, fourteen fatty acids and four polysaccharides. The development of this formula is completely in accordance with the nutritional spectrum for cells regeneration. The inventors use sesame oil because it has a complete spectrum of regenerative nutrition and beeswax instead of vaseline. Beeswax has a form of beeswax of frame, while the metabolism of vaseline cannot help to play a role of wound breath and support; *R. scutellariae, R. coptidis, C. phellodendri* in Compendium of Materia Medica has detailed introduction where practice shows that it is safe and reliable in hundreds and thousands of years; earthworms have the strongest regenerative ability in animals and its nutrition spectrum are taken advantage of. The general theory behind MEBT was rather vague and broad that comprised the following:

(1) Protection of the injured nerve endings and alleviation of the spasm of arrector pilorum of fine hair to relieve pain.
(2) Absorption of the residual heat in burn wound using a frame-structured ointment to avoid secondary thermal injury.
(3) Removal of necrotic skin through a non-damaging liquefaction process, to promote the regeneration of surviving tissue.
(4) Provision of an optimal physiological moist environment for the damaged burn tissues and reduction of wound water evaporation to promote necrotic tissue discharge and epithelial regeneration.
(5) Triggering skin regeneration with a mode of compliance with tissue regeneration (Vincy, 2004; EL-Hadidy et al., 2014). It has been shown also to effectively prevent the formation of pathologic scars following primary healing (Sakr et al., 2012).

Modern pharmacology research suggests that MEBO shows antibacterial, anti-inflammatory and analgesic effects. Antibacterial acts mainly as a hyperosmolar medium, which prevents bacterial growth, at the same time changes the biological behavior of bacteria, decreases the bacterial toxicity and invasive capacity, increases the bacterial sensitivity to antibiotics and enhances both the local and systemic immunity (Jewo et al.,2009; Hindy 2009; See et al., 2001; Atiyeh et al., 2002).

Furthermore, it is thought that this oil-based ointment provides a moist environment for epithelial regeneration to occur with the added anti-inflammatory effects of beta-sitosterol and anti-microbial effects of berberine (Zhang et al., 2005); (Tsati et al., 2004). More researches has shown that local administration of MEBO for eight days markedly increased the levels of VEGF and basic fibroblast growth factor (bFGF) by 77.5 and 90.8%, respectively (all $P<0.01$), when compared with the model group. Furthermore, qPCR (quantitative polymerase chain reaction) analysis indicated that MEBO treatment for eight days led to an increase in the mRNA expression of VEGF and bFGF by 40.9 and 97.1%, respectively, when compared with the rb-bFGF group (all $P<0.05$) (Tsati et al., 2004). The results indicate that MEBO increases the protein expression levels of VEGF and bFGF to promote angiogenesis/vasculogenesis and vascular permeability, and enhances endothelial cell proliferation and migration as well as the adhesion of leukocytes, implicating the potential mechanism of MEBO for delayed cutaneous wound healing.

In addition, VEGF promotes epithelialization and collagen deposition in the wound. Recent data indicated that bFGF-mediated angiogenesis refers to endothelial cell proliferation, migration, and tube formation by activating c-Jun N-terminalkinase/stress-activated protein kinase signaling. Moreover, CK19 is considered as a bio-marker specifically expressed in epidermal stem cells. A study had investigated the effect of MEBO topical application on activation and proliferation of epidermal stem cells through the immunohistochemical localization of cytokeratin 19 (CK19). During the first 2 weeks post-randomization, the cumulative MRSA infection rates at 14 days for control group and MEBO group were 38.5 and 37.4%, respectively(Xu,2015). In addition, MEBO also can significantly increase the mRNA expression of VEGF, bFGF, epidermal growth factor in granulation tissue, while increasing the content of mRNA in beta catenin, inhibit the expression level of Smad3mRNA, increase the expression level of mitogen-activated protein kinase (MAPKK) mRNA and c-myc mRNA of the water level, thereby promoting wound fibroblasts and new capillaries proliferation, increasing the formation of extracellular matrix and granulation tissue formation. The moist burn ointment can also increase the content of Bcl-2 protein in the wound tissue while reducing the content of (Bcl-2-Associated × Protein) Bax protein, thus inhibit the apoptosis of diabetic wound cell (Tang et al., 2014). Moreover, studies have shown that MEBO appeared to bring greater pain relief for the post-dressing assessment during the first week after burns, which is attributable to the presence of the layer of oily ointment that shields the burn wound from the external environment (Allam et al., 2007).

Implication of this meta-analysis

To the best knowledge of the authors, this is the first meta-analysis of MEBO used as an adjunct treatment for patients with DFU, suggesting that MEBO may work effectively and safely for patients with DFU. At present,

there are many methods of diabetic foot treatment at home and abroad, but Xu Rong Xiang, the inventors of standardized process of MEBO-DFU regenerative therapy in the treatment of DFU, thinks the key factor to evaluate its meritis is efficacy.

No matter the articles published in foreign magazines, the academic theory put forward, the new treatment methods introduced in the international academic conference; they do not have the right to speak as there is no realization of wound healing of diabetic foot. The biggest advantage of MEBO-DFU regenerative therapy is that it reaches the end point of diabetic foot treatment, namely the healing of the wound (Xu, 2015). In addition, the above lecture is focused on the local treatment of diabetic foot since stressed diabetic foot is a systemic disease. The local treatment of MEBO should be combined with the systemic treatment of blood sugar control, anti-infection and nutritional support (Sakr et al., 2012).

Moreover, it is very difficult to ascertain whether the ulcer improvement was induced by a single herb or by the synergistic action brought about by the interaction among several ingredients, as treatment protocols were different across studies (Atiyeh et al., 2002). Some studies did not report adverse events; it is difficult to draw a definite conclusion. Furthermore, to compare with Western medicine, the toxicity and adverse effects of Chinese medicine are few and relatively more common in a single herb. For example, intravenous injection of large doses of Coptis chinensis and Huanglian (Chinese name), with an essential component in MEBO extract can cause respiratory depression, oral administration of *Rheum officinale* Baill and Dahuang (Chinese name) can cause nausea, vomiting, dizziness, abdominal pain and liver damage (Chen et al., 2010; Ang et al., 2000).

Although all these effects mentioned above were found in acute toxicity tests by intravenous or oral administration and are rarely seen in the long-term toxicity tests and special toxicological tests, the interactions among the herbs may produce synergistic effects and neutralize potential toxicity or side effects of the individual constituents. It seems that side effects of topical application of these Chinese compounds are relatively rare; more pharmacological and toxicological research is needed to clarify the safety of MEBO (Ang et al., 2003; Ezzo et al., 1998).

Conclusion

This meta-analysis showed that MEBO may be beneficial as an adjunctive for patients with DFU. Everyone should clearly recognize that the effect of MEBO-DFU regenerative therapy for treating diabetic foot is true and reliable; it is worth to be popularized in order to benefit humans. However, it is difficult to draw a firm conclusion because of the insufficient high-quality evidence. This meta-analysis does suggest that large-sample-size and well-designed RCTs are needed to justify the use of MEBO in further clinical practice.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

ACKNOWLEDGMENTS

This study was supported by a grant from the Department of science and technology of Sichuan Province--Luzhou Municipal People's Government-joint special foundation, of Luzhou Medical College (Grant No.14JC0070); Department of science and technology of Sichuan Province--Luzhou Municipal People's Government--(Grant No.2013LZLY-J35).

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