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Effect of Chinese herbal medicine as an adjunctive technique to standard treatment for people with diabetic foot ulcers: A meta-analysis

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ABSTRACT The meta-analysis aimed to assess and compare the effect of Chinese herbal medicine as an adjunctive technique to standard treatment for people with diabetic foot ulcers. This meta-analysis investigated the results through either dichotomous or contentious random or fixed effect models, calculating the odds ratio (OR) and mean difference (MD) along with 95% confidence intervals (CIs). The analysis included 17 studies conducted between 2006 and 2021, comprising a total of 1140 individuals with diabetic foot ulcers. Chinese herbal medicine had a significantly higher total effective rate (OR, 2.77; 95% CI, 1.89-4.07, $p < 0.001$), lower wound size after treatment (MD, -2.44; 95% CI, -3.46- -1.43, $p < 0.001$), lower number of patients without any improvement (OR, 0.26; 95% CI, 0.15-0.45, $p < 0.001$), and lower time of diabetic wound ulcer healing (MD, -10.46; 95% CI, -14.91- -6.37, $p < 0.001$) compared to standard treatment in personal with diabetic foot ulcers. However, no significant differences were found between Chinese herbal medicine and standard treatment in the number of patients with 30% or more reductions in the ulcer area of the diabetic foot ulcer (OR, 2.69; 95% CI, 0.70-10.30, $p = 0.15$). The examined data revealed that Chinese herbal medicine had a significantly higher total effective rate, lower wound size after treatment, lower number of patients without any improvement, and lower time of diabetic wound ulcer healing, however, no significant differences were found in the number of patients with 30% or more reductions in the ulcer area compared to standard treatment in personal with diabetic foot ulcers. However, caution should be exercised when interpreting its findings, as many of the chosen studies had a small sample size, and certain comparisons were based on a limited number of selected studies.

INDEX TERMS Cis, OR, MD and meta analysis.

I. INTRODUCTION

One of the worst effects of diabetes is diabetic foot ulcers, which appear in 15-25% of people with the disease [1]. Diabetic foot ulcers not only result in physical discomfort and mental stress but also a lower quality of life [2]. Additionally, diabetes is linked to 28% to 89% of nontraumatic lesion amputations, with wide regional variations. These discrepancies may be influenced by changes in diabetes occurrence and the accessibility of medical care [3]. Additionally, diabetic foot ulcers place a significant financial strain on society as well as patients and their families. According to the same technique, the yearly cost of treating diabetic foot ulcers and amputations was assessed to be billions of dollars [4]. Due to the rising

prevalence of diabetes, there will likely be an increase in the global burden of diabetic foot ulcers [5]. Finding some affordable therapies for diabetic foot ulcers is so essential and urgent. Because diabetic foot ulcers are such a difficult problem, multidisciplinary treatment has been suggested. For the treatment of diabetic foot ulcers, it was advised to identify and maximize systematic, local, and extrinsic variables, such as debridement, infection management, a moist wound environment, or pressure redistribution, as well as supplementary therapy [6]. Chinese herbal medicine has been used for wound healing in China for thousands of years. Chinese herbal medicine has been employed as an additional treatment for diabetic foot ulcers in more recent years. Numerous experimental research supported its virtues, citing

things like Chinese herbal medicine's antidiabetic characteristics and improving fibroblast viability [7-9]. A few clinical trials also looked at the efficiency of Chinese herbal medicine in treating diabetic foot ulcers [10-12]. According to their findings, Chinese herbal medicine may help individuals with diabetic foot ulcers. However, as case-series studies, case reports, or randomized controlled trials (RCTs), these research findings were insufficient to support the use of Chinese herbal medicine in the treatment of diabetic foot ulcers. According to reports, 25% of patients receiving care in internal wards consumed herbal or dietary additions [13]. Therefore, it is necessary and crucial to answer the following two questions about whether or not patients with diabetic foot ulcers benefit from Chinese herbal medicine as a form of therapy and the safety to utilize Chinese herbal medicine to treat diabetic foot ulcers. Given that RCTs are regarded as the "gold standard" for evaluating the efficacy of treatments, a meta-analysis of RCTs may be a viable option for answering these concerns. For patients with diabetic foot ulcers, a systematic evaluation of RCTs utilizing Chinese herbal medicine was therefore required. To answer the concerns of whether Chinese herbal medicine is beneficial as an additional therapy for controlling diabetic foot ulcers, this meta-analysis conducted a systematic evaluation of RCTs for persons with diabetic foot ulcers.

II. METHODOLOGY

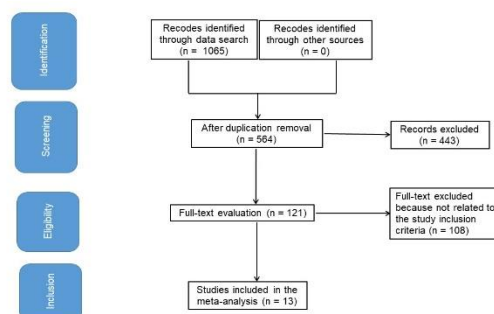
A. DESIGN OF THE EXAMINATION

The meta-analyses adhered to a predetermined evaluation procedure and were incorporated into the epidemiological report. Multiple databases, such as OVID, PubMed, the Cochrane Library, Cochrane Central Register of Controlled Trials, the Chinese Biomedical database, Cumulative Index to Nursing, Allied & Complementary Medicine Resources, Allied Health Literature, Embase, and Google Scholar, were accessed for data collection and analysis. These datasets were employed to gather studies that assessed the impact of Chinese herbal medicine as an adjunctive approach to standard treatment for individuals with diabetic foot ulcers.

B. DATA POOLING

The assessment of Chinese herbal medicine in contrast to standard treatment for diabetic foot ulcers yielded various clinical outcomes. The principal inclusion criterion for these results was the presence of diabetic foot ulcers. Language restrictions were not a factor in candidate screening and examination selection. There were no limitations on the number of candidates recruited for the studies. Exclusions in this synthesis encompassed reviews, editorials, or letters as they lacked an intervention component. The detailed process of examination identification is illustrated in Figure 1.

FIGURE 1. Schematic diagram of the examination procedure.



III. IDENTIFICATIONS OF STUDIES

A search strategy protocol was formulated and specified based on the PICOS principle, which outlines the following criteria: P (population) individuals with diabetic foot ulcers; I (intervention) or E (exposure): Chinese herbal medicine; C (comparison): comparative effectiveness of Chinese herbal medicine versus standard treatment; O (outcome): diabetic foot ulcers; S (study design): the planned examination had no limitations. Using the keywords and related phrases outlined in Table I, we conducted an extensive search of selected databases up to July 2023. All papers' titles and abstracts were included in a reference management program, and examinations that did not correlate treatment types with clinical outcomes were thoroughly reviewed. Additionally, two authors served as reviewers to identify relevant tests.

TABLE I
Database Search Technique for Examining Content

Database	Search strategy
Google Scholar	#1 "burn wound ulcer" OR "wound healing time" #2 "traditional herbal medicine" OR "Basic Fibroblast Growth Factor" #3 #1 AND #2
Embase	#1 'burn wound ulcer' /exp OR 'wound healing time' #2 'traditional herbal medicine'/exp OR 'Basic Fibroblast Growth Factor'/ #3 #1 AND #2
Cochrane library	#1 (burn wound ulcer):ti,ab,kw (wound healing time):ti,ab,kw (Word variations have been searched) #2 (traditional herbal medicine):ti,ab,kw OR (Basic Fibroblast Growth Factor):ti,ab,kw (Word variations have been searched) #3 #1 AND #2
Pubmed	#1 "burn wound ulcer"[MeSH] OR "wound healing time"[All Fields] #2 "traditional herbal medicine"[MeSH Terms] OR "Basic Fibroblast Growth Factor"[All Fields] #3 #1 AND #2
OVID	#1 "burn wound ulcer"[All Fields] OR "wound healing time" [All Fields] #2 "traditional herbal medicine"[All fields] OR "Basic Fibroblast Growth Factor"[All Fields] #3 #1 AND #2

IV. SCREENING OF STUDIES

Data reduction was implemented based on specific criteria, including the presentation of examination and personal features in a standardized format, the first author's last name, examination time and year, the nation where the examination was conducted, gender, recruited population type, total number of individuals, qualitative and quantitative evaluation methods, demographic information, and clinical and treatment characteristics. Two anonymous reviewers assessed both the likelihood of bias in each test and the quality of methodologies used in the selected examinations for further investigation. Each examination's technique underwent independent assessment by the two reviewers.

V. STATISTICAL ANALYSIS

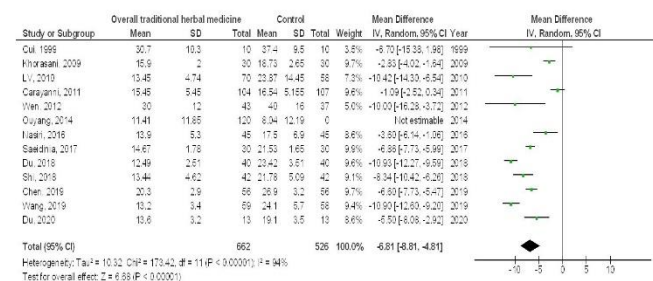
In the present meta-analysis, dichotomous or continuous random- or fixed-effect models were employed to calculate the odds ratio (OR) and the mean difference (MD) along with a 95% confidence interval (CI). The I² index, ranging from 0 to 100 (in percent), was computed. An I² value of 0 indicates no heterogeneity, while higher values indicate greater heterogeneity. When I² was 50% or above, the random effect was chosen; if I² was less than 50%, the preference for employing the fixed effect increased [14]. As mentioned earlier, subcategory analysis was conducted by categorizing the results of the initial examination. Begg's and Egger's tests were employed for quantitative analysis to evaluate publication bias, with the determination of its presence if $p > 0.05$. Two-tailed analysis was used to calculate p-values. Graphs and statistical analyses were generated using Jamovi 2.3.

VI. RESULTS

After reviewing 1065 relevant examinations, 17 tests conducted from 2006 to 2021 were incorporated into the meta-analysis as they met the inclusion criteria [15-31]. Table 2 summarizes the findings of these investigations. 1140 personals with diabetic foot ulcers were in the used studies' starting point, 575 of them were using Chinese herbal medicine, and 565 were using standard treatments. The sample size was 21 to 120 personals. Chinese herbal medicine had significantly higher total effective rate (OR, 2.77; 95% CI, 1.89-4.07, $p < 0.001$) with no heterogeneity (I² = 0%), lower wound size after treatment (MD, -2.44; 95% CI, -3.46- -1.43, $p < 0.001$) with high heterogeneity (I² = 90%), lower number of patients without any improvement (OR, 0.26; 95% CI, 0.15-0.45, $p < 0.001$) with no heterogeneity (I² = 0%), and lower time of diabetic wound ulcer healing (MD, -10.46; 95% CI, -14.91- -6.37, $p < 0.001$) with high heterogeneity (I² = 75%)

compared to standard treatment in personal with diabetic foot ulcers, as revealed in Figures 2-5. However, no significant differences were found between Chinese herbal medicine and standard treatment in the number of patients with 30% or more reductions in the ulcer area of the diabetic foot ulcer (OR, 2.69; 95% CI, 0.70-10.30, $p = 0.15$) with moderate heterogeneity (I² = 73%), as revealed in Figure 6. The quantitative Egger regression test and visual interpretation of the funnel plot ($p = 0.89$) did not reveal any signs of examination bias. Nevertheless, it was observed that a significant portion of the pertinent examinations exhibited suboptimal methodological quality and lacked evidence of bias in selective reporting.

FIGURE 2. The overall effect's forest plot of the traditional herbal medicine compared to standard treatment on wound healing time in personals with burn



wound ulcers.

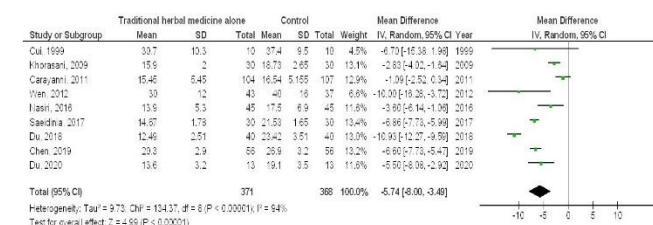


FIGURE 3. The effect's forest plot of the traditional herbal medicine alone compared to standard treatment on wound healing time in personals with burn wound ulcers.

TABLE II

Characteristics of Studies

Study	Country	Total	Traditional Chinese medicine	Control
Cui, 1999 ⁷	China	20	10	10
Khorasani, 2009 ⁸	Iran	60	30	30
LV, 2010 ⁹	China	128	70	58
Carayanni, 2011 ¹⁰	Greece	211	104	107
Wen, 2012 ¹¹	China	80	43	37
Ouyang, 2014 ¹²	China	240	120	120
Nasiri, 2016 ¹³	Iran	90	45	45
Saeidinia, 2017 ¹⁴	Iran	60	30	30
Du, 2018 ¹⁵	China	80	40	40
Shi, 2018 ¹⁶	China	84	42	42
Chen, 2019 ¹⁷	Korea	112	56	56
Wang, 2019 ¹⁸	Korea	117	59	58
Du, 2020 ¹⁹	China	26	13	13
	Total	1282	649	633

VII. CONCLUSION

17 examinations from 2006 to 2021 were enrolled for the present meta-analysis comprising 1140 personals with diabetic foot ulcers in the used studies' starting point, 575 of them were using Chinese herbal medicine, and 565 were using standard treatments [15-31]. The examined data revealed that in Chinese herbal medicine had a significantly higher total effective rate, lower wound size after treatment, lower number of patients without any improvement, and lower time of diabetic wound ulcer healing compared to standard treatment in personal with diabetic foot ulcers. However, no significant differences were found between Chinese herbal medicine and standard treatment in the number of patients with 30% or more reductions in the ulcer area of the diabetic foot ulcer. Yet, attention should be implemented while relating to its values since most of the selected examinations had low sample size (16 out of 17 examinations were > 100) and some comparisons had a low number of selected examinations e.g. number of patients with 30% or more reductions in the ulcer area. According to these meta-analysis results, Chinese herbal medicine may be a useful supplemental therapy for people who have diabetic foot ulcers. It was not able to come to a solid conclusion, nevertheless, because the included research had tiny sample sizes and generally poor quality. Chinese herbal medicine may be secure for treating diabetic foot ulcers, according to this meta-analysis. However, as herbal medicines varied throughout trials and some examinations did not document side effects, it is challenging to reach a firm

conclusion. Blinding is also a crucial step in ensuring that the placebo effect or observer bias does not have an impact on research findings. The best blinding should conceal participants, healthcare professionals, outcome judges, and statisticians. Only 1 examination employed a placebo to successfully establish participant and healthcare provider blinding, even though placebo plays a crucial role in this process[20]. The 16 examinations used open examinations with a significant risk of bias since patients in the experimental groups received Chinese herbal medicine in addition to conventional treatment whereas those in the standard treatment groups received only conventional care. Examples of successful preparations of Chinese herbal medicine are Yunnan Baiyao capsules and Danqi Piantang Jiaonang [32,33]. In examinations testing Chinese herbal medicine, researchers should focus on the caliber of the placebo, to put it simply. Furthermore, the effectiveness of blinding should be evaluated, for example, by requesting patients to identify their group by guessing. Although the meta-analysis did not reveal any statistical heterogeneity between the examinations, clinical heterogeneity was observed during the examination. The variety of available treatments was one of the primary causes of this. The outcome of Chinese herbal medicine was difficult to determine because every experiment utilized a different treatment. Therefore, future research on herbal treatments must be standardized. Before a medicine can be referred to as a fixed herbal remedy, it must go through the following steps: To ensure that the remedy complies with Chinese herbal medicine guidelines, national Chinese herbal medicines specialists must agree on the therapeutic tenets and ingredients of the remedy. The best available evidence should be used to logically recommend the herbs to be included in the cure. Before using the treatment in an RCT, a small-sample examination must be conducted to evaluate it. Because these herbs were utilized in multiple RCTs and had favorable results, the outcomes of the present research suggested that Flos Carthami Tinctorii, Radix Angelicae Sinensis, Radix astragali, and Semen Persicae may be components of a fixed remedy for patients with diabetic foot ulcers. In addition to the aforementioned details, the meaning of conventional treatment in the examinations that were included lacked sufficient clarity. For instance, the management of some severe consequences, such as osteomyelitis, was not described. Since osteomyelitis often occurs in 15% of patients with diabetic foot ulcers, it was unclear how often the patients' were X-rayed or whether both groups had equivalent access to X-ray inspection[34]. Additionally, only 1 examination utilized limb salvage as an outcome, and other examinations failed to report how many personals in each group underwent amputations. Amputation should be taken into consideration as a significant endpoint for evaluating an intervention

because, as was already indicated, it imposed a significant load on both the personals' families and society [35-37]. Limitations of the meta-analysis were as next; there could be an assortment bias because some of the examinations that were chosen for the meta-analysis were excluded. Despite this, the omitted examination did not meet the requirements for inclusion in the meta-analysis. We also required the information to control if factors like age, gender, and ethnicity affected the outcomes. The examination's objective was to review how Chinese herbal medicine is an adjunctive technique to standard treatment for personal with diabetic foot ulcers. Utilizing inaccurate or incomplete data from a prior analysis may have introduced bias. The individual's nutritional status, as well as factors such as race, gender, and age, likely served as the underlying causes for potential discrimination. The presence of incomplete data and the omission of certain unpublished studies might unintentionally impact the accuracy of the values. The examined data revealed that in Chinese herbal medicine had a significantly higher total effective rate, lower wound size after treatment, lower number of patients without any improvement, and lower time of diabetic wound ulcer healing compared to standard treatment in personal with diabetic foot ulcers. However, no significant differences were found between Chinese herbal medicine and standard treatment in the number of patients with 30% or more reductions in the ulcer area of the diabetic foot ulcer. Yet, attention should be implemented while relating to its values since most of the selected examinations had a low sample size (16 out of 17 examinations were > 100) and some comparisons had a low number of selected examinations e.g. number of patients with 30% or more reductions in the ulcer area.

REFERENCES

1. Peck, M.D. *Epidemiology of burns throughout the world. Part I: Distribution and risk factors*. Burns **37**(7): p. 1087-1100 (2011).
2. Peck, M.D. *Epidemiology of burns throughout the World. Part II: intentional burns in adults*. Burns **38**(5): p. 630-637 (2012).
3. Sadeghi-Bazargani, H. and R. Mohammadi *Epidemiology of burns in Iran during the last decade (2000–2010): review of literature and methodological considerations*. Burns **38**(3): p. 319-329 (2012).
4. Weinstein, R.A. and C.G. Mayhall *The epidemiology of burn wound infections: then and now*. Clinical infectious diseases **37**(4): p. 543-550 (2003).
5. Kayton, M.L., V. Staab, B. Stahl, et al. *Health inequities in pediatric trauma*. Children **10**(2): p. 343 (2023).
6. Sheikhbahaei, S., T.J. Trahan, J. Xiao, et al. *FDG-PET/CT and MRI for evaluation of pathologic response to neoadjuvant chemotherapy in patients with breast cancer: a meta-analysis of diagnostic accuracy studies*. The oncologist **21**(8): p. 931-939 (2016).
7. Cui, Y., Z. Luo, and Y. Xue *Enhancing effect of traditional herbal medicine mixture on peripheral blood lymphocyte proliferation and interleukin in-2 production in patients of burn*. Chinese. Journal of Integrated Traditional and Western Medicine **19**(7): p. 407-9 (1999).
8. Khorasani, G., S.J. Hosseinimehr, M. Azadbakht, et al. *Aloe versus silver sulfadiazine creams for second-degree burns: a randomized controlled study*. Surgery today **39**: p. 587-591 (2009).
9. LV, G., L. Cai, and J. Yu *Effectiveness of traditional Chinese medicine and western medicine in treating residual deep burn wound*. Chinese. Journal of Reparative and Reconstructive Surgery **24**(8): p. 937-9 (2010).
10. Carayanni, V.J., E.G. Tsati, G.C. Spyropoulou, et al. *Comparing oil based ointment versus standard practice for the treatment of moderate burns in Greece: a trial based cost effectiveness evaluation*. BMC complementary and alternative medicine **11**(1): p. 1-16 (2011).
11. Wen, Y., Q. Li, and G. LEI *Effect of Wuhuang traditional Chinese medicine preparation on the treatment of residual burn wounds of extremities*. China Medicine and Pharmacy **24**: p. 105-108 (2012).
12. Ouyang, J., Y.-c. Chen, G.-x. Luo, et al. *A randomized and controlled multicenter prospective study of the chinese medicinal compound fufang xuelian burn ointment for the treatment of superficial and deep second-degree burn wounds*. Cell biochemistry and biophysics **69**: p. 467-474 (2014).
13. Nasiri, E., S.J. Hosseinimehr, A.Z. Hosseinzadeh, et al. *The effects of Arnebia euchroma ointment on second-degree burn wounds: a randomized clinical trial*. Journal of ethnopharmacology **189**: p. 107-116 (2016).
14. Saeidinia, A., F. Keihanian, A.P. Lashkari, et al. *Partial-thickness burn wounds healing by topical treatment: a randomized controlled comparison between silver sulfadiazine and centiderm*. Medicine **96**(9) (2017).
15. Du, W. *Observation on the clinical Effect of Treatment of Residual Wounds after Mass Depth Burn with Chinese Medicine Bathing Combined with Dressing Change*. World Chinese Medicine **1704**(7): p. 1697-9 (2018).
16. Shi, Y. *Clinical investigation of integrated traditional Chinese medicine and western medicine therapy for large area residual*

- burn wounds. Chinese Journal of Modern Drug Application **12**(20): p. 86-8 (2018).
17. Chen, B., Q. Jia, and S. Xu *Evaluation of the efficacy of self-made Chinese medicine Zhangpiointment in treating small deep second degree burn wounds*. Journal of Modern Medicine & Health **35**(21): p. 3272-4 (2019).
18. Wang, Q. *Effect of Traditional Chinese and Western Medicine Combination Dressing Change on Inflammatory Indexes in Patients with Severe Burn after Immersion in Traditional Chinese Medicine*. Journal of Sichuan of Traditional Chinese Medicine **37**(6): p. 133-6 (2019).
19. Du, Y., G.-Z. Lv, S. Yu, et al. *Long-term medical treatment of patients with severe burns at exposed sites*. World Journal of Clinical Cases **8**(16): p. 3515 (2020).
20. Lee, S.Y., S.Y. Joo, Y.S. Cho, et al. *Effect of extracorporeal shock wave therapy for burn scar regeneration: A prospective, randomized, double-blinded study*. Burns **47**(4): p. 821-827 (2021).
21. Forbes-Duchart, L., J. Cooper, B. Nedelec, et al. *Burn Therapists' Opinion on the Application and Essential Characteristics of a Burn Scar Outcome Measure*. Journal of Burn Care & Research **30**(5): p. 792-800 (2009).
22. Chakrabarti, S., B. Mazumder, J. Rajkonwar, et al. *Basic Fibroblast Growth Factor and collagen matrix hydrogel attenuates burn wound inflammation through activation of ERK and TRK pathway*. Scientific reports **11**(1): p. 3357 (2021).
23. Boehm, D. and H. Menke *A history of fluid management—from “one size fits all” to an individualized fluid therapy in burn resuscitation*. Medicina **57**(2): p. 187 (2021).
24. Mashiko, T., T. Minabe, T. Yamakawa, et al. *Platelet-derived Factor Concentrates with Hyaluronic Acid Scaffolds for Treatment of Deep Burn Wounds*. Plastic and Reconstructive Surgery – Global Open **4**(10): p. e1089 (2016).
25. Aziz, Z., S.F. Abu, and N.J. Chong *A systematic review of silver-containing dressings and topical silver agents (used with dressings) for burn wounds*. Burns **38**(3): p. 307-318 (2012).
26. Vishali, S., E. Kavitha, and S. Selvalakshmi *Therapeutic Role of Essential Oils*. Essential Oils: Extraction Methods and Applications: p. 953-976 (2023).