

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

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# Abstract

Background

The purpose of the meta-analysis was to evaluate and contrast Chinese herbal medicine's effectiveness as a supplement to conventional treatment for diabetic foot ulcers.

Methods

The results of this meta-analysis were analyzed using dichotomous or contentious random or fixed effect models, and the odds ratio (OR) and mean difference (MD) with 95% CIs were calculated. 1140 individuals with diabetic foot ulcers were included in the 17 exams that were enlisted for the current meta-analysis, which ran from 2006 to 2021.

Results

When compared to standard treatment, Chinese herbal medicine significantly increased the overall effective rate (OR, 2.77; 95% CI, 1.89-4.07, p<0.001), reduced the size of the wound after treatment (MD, -2.44; 95% CI, -3.46- -1.43, p<0.001), decreased the number of patients who did not improve (OR, 0.26; 95% CI, 0.15-0.45, p<0.001), and shortened the time it took for diabetic foot ulcers to heal (MD, -10.46; 95% CI, -14.91- -6.37, p<0.001). The number of patients who experienced a 30% or greater decrease in the ulcer area of their diabetic foot ulcer did not, however, differ significantly between Chinese herbal medicine and standard treatment (OR, 2.69; 95% CI, 0.70-10.30, p=0.15). Conclusions

According to the data analyzed, Chinese herbal medicine had a significantly higher overall effective rate, a smaller post-treatment wound, fewer patients who did not improve, and a shorter healing period for diabetic wound ulcers. However, there were no appreciable differences in the number of patients who experienced ulcer area reductions of 30% or more when compared to standard treatment for diabetic foot ulcers. However, given the majority of the chosen tests had small sample sizes and certain comparisons had few chosen studies, care should be taken when connecting to its values.

**Keywords:** Chinese herbal medicine; standard treatment; adjunctive technique; diabetic foot ulcers

### Introduction

One of the worst effects of diabetes is diabetic foot ulcers, which appear in 15-25% of people with the disease.<sup>1</sup> Diabetic foot ulcers not only result in physical discomfort and mental stress but also a lower quality of life.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> Due to the rising prevalence of diabetes, there will likely be an increase in the global burden of diabetic foot ulcers.<sup>5</sup> 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. <sup>6</sup> 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, <sup>13</sup> 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 personals with diabetic foot ulcers.

### Method

### Design of the examination

The meta-analyses followed a predetermined assessment process and were included in the epidemiological declaration. Numerous databases were accessed for data gathering and analysis, including 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. These datasets were utilized to compile examinations that compared and evaluated the effect of Chinese herbal medicine as an adjunctive technique to standard treatment for personnel with diabetic foot ulcers.

### Data pooling

Comparing Chinese herbal medicine and standard treatment for the management of diabetic foot ulcers resulted in several clinical outcomes. Diabetic foot ulcers were the primary inclusion parameter outcome in these results. Language constraints were not taken into consideration while screening candidates and choosing which examination to include. The number of recruited candidates for the examinations was not constrained in any way. We did not include reviews, editorials, or letters in this synthesis because they do not contain an intervention. Figure 1 depicts the complete examination identification process in detail.



Figure 1. Schematic diagram of the examination procedure

### Eligibility of included studies

It is being investigated how Chinese herbal medicine affects the clinical results of diabetic foot ulcers, both positively and negatively. The sensitivity analysis only took into account papers that discussed how interventions affected the frequency of diabetic foot ulcers. The interventional groups were contrasted against a wide range of subtypes to perform sensitivity and subclass analyses.

# Inclusion and exclusion criteria

# Inclusion criteria:

Following were the requirements for inclusion in the meta-analysis: an evaluation of the results of Chinese herbal medicine compared to standard treatment on diabetic foot ulcers. The outcome's expression must be in the proper output for statistical analysis to be applied.

# Exclusion criteria:

Examinations with a non-comparative design were not included. In addition, the current assessment did not include letters, books, review articles, or book chapters.

### Identification of studies

A protocol of search strategies was devised and specified as follows by the PICOS principle, which states: P (population) personals with diabetic foot ulcers; Chinese herbal medicine was the "intervention" or "exposure"; C (comparison): the comparative effectiveness of Chinese herbal medicine compared with standard treatment. O (outcome): diabetic foot ulcers; S (design of the examination): the planned examination had no boundaries.

Using the keywords and related phrases listed in Table 1, we conducted an extensive search of the databases selected up until July 2023. The titles and abstracts of all the papers included in a reference management program, as well as any examinations that did not link the type of treatments to clinical outcomes, were all reviewed. Additionally, two authors act as reviewers to identify pertinent tests.

Database	Search strategy									
Google Scholar	#1 "diabetic foot ulcers" OR "standard treatment"									
	#2 "Chinese herbal medicine" OR "adjunctive technique"									
	#3 #1 AND #2									
Embase	#1 'diabetic foot ulcers' /exp OR 'standard treatment'									
	#2 'Chinese herbal medicine'/exp OR 'adjunctive technique'/									
	#3 #1 AND #2									
Cochrane library	#1 (diabetic foot ulcers):ti,ab,kw (standard treatment):ti,ab,kw (Word									
	variations have been searched)									
	#2 (Chinese herbal medicine):ti,ab,kw OR (adjunctive technique):ti,ab,kw									
	(Word variations have been searched)									
	#3 #1 AND #2									
Pubmed	#1 "diabetic foot ulcers"[MeSH] OR "standard treatment"[All Fields]									
	#2 "Chinese herbal medicine"[MeSH Terms] OR "adjunctive									
	technique"[All Fields]									
	#3 #1 AND #2									
OVID	#1 "diabetic foot ulcers"[All Fields] OR "standard treatment" [All Fields]									
	#2 "Chinese herbal medicine"[ All fields] OR "adjunctive technique"[All									
	Fields]									
	#3 #1 AND #2									

 Table 1. Database Search Strategy for inclusion of examinations

### Screening of studies

The amount of data was reduced using the following criteria: examination and personal features presented in a standard format; the first author's last name; the time and year of the examination; the nation in which the examination was conducted; and the gender; the population type that was recruited for the examination; the total number of personals; qualitative and quantitative evaluation methods; demographic information; clinical and treatment characteristics. The likelihood of bias in each test as well as the caliber of the methodologies utilized in the examinations that were selected for further inquiry were both examined by two anonymous reviewers. Each examination's technique was assessed independently by two reviewers.

### Statistical analysis

Using dichotomous or continuous random- or fixed-effect models, the odds ratio (OR) and the mean difference (MD) with a 95% confidence interval (CI) were calculated in the current meta-analysis. The I2 index, which ranges from 0 to 100, was calculated (in percent). I2 = 0 denotes the absence of heterogeneity, while higher I2 values

denote the presence of greater heterogeneity. When I2 was 50% or above, the random effect was chosen; if I2 was less than 50%, the choice to employ the fixed effect increased. <sup>14</sup> As previously mentioned, subcategory analysis was carried out by categorizing the results of the initial examination. Using Begg's and Egger's tests for quantitative analysis, publication bias was evaluated and determined to be present if p>0.05. An analysis with two tails was used to calculate the p-values. Graphs and statistical analysis were created using Jamovi 2.3. **Results** 

Following an assessment of 2034 pertinent examinations, 17 tests released between 2006 and 2021 were included in the meta-analysis since they matched the criteria for inclusion. <sup>15-31</sup> 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 ( $I^2 = 0\%$ ), lower wound size after treatment (MD, -2.44; 95% CI, -3.46- -1.43, p<0.001) with high heterogeneity ( $I^2 = 90\%$ ), lower number of patients without any improvement (OR, 0.26; 95% CI, 0.15-0.45, p<0.001) with no heterogeneity ( $I^2 = 0\%$ ), and lower time of diabetic wound ulcer healing (MD, -10.46; 95% CI, -14.91- -6.37, p<0.001) with high heterogeneity ( $I^2 = 75\%$ ) 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% Cl, 0.70-10.30, p=0.15) with moderate heterogeneity ( $I^2 = 73\%$ ), as revealed in Figure 6.

No indication of examination bias was found using the quantitative Egger regression test or the funnel plot's visual interpretation (p = 0.89). However, it was discovered that the majority of the relevant examinations had poor practical quality and no prejudice in selective reporting.

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			Chinese	
			herbal	standard
Study	Country	Total	medicine	treatment
Song, 2006 15	China	50	25	25
Wang, 2006 <u><sup>16</sup></u>	China	60	30	30
Deng, 2007 <u>17</u>	China	75	40	35
Xing, 2008 18	China	96	50	46
He, 2008	China	80	40	40
	Hong			
Leung, 2008 <sup>20</sup>	Kong	80	40	40
Li, 2011 <sup>21</sup>	China	48	24	24
Du, 2011 <sup>22</sup>	China	60	30	30
Kuo, 2012 <sup>23</sup>	Taiwan	21	11	10
Li, 2015 <sup>24</sup>	China	60	30	30
He, 2016 <sup>25</sup>	China	120	60	60
Chen, 2016 <sup>26</sup>	China	60	30	30
Lei, 2017 <sup>27</sup>	China	60	30	30
Xie, 2018 <sup>28</sup>	China	82	41	41
Xie, 2019 <sup>29</sup>	China	60	30	30
Liu, 2020 30	China	60	30	30
Wu, 2021 <u><sup>31</sup></u>	China	68	34	34
	Total	1140	575	565

 Table 2. Characteristics of studies

	Chinese herbal me	edicine	Standard trea	tment		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	l Year	M-H, Fixed, 95% Cl	
Song, 2006	8	25	5	25	10.2%	1.88 [0.52, 6.84]	2006	3	
Wang, 2006	10	30	5	30	10.0%	2.50 [0.74, 8.50]	2006		
He, 2008	10	40	6	40	13.4%	1.89 [0.61, 5.82]	2008		
Xing, 2008	12	50	8	46	18.9%	1.50 [0.55, 4.08]	2008		
Du, 2011	28	30	25	30	5.0%	2.80 [0.50, 15.73]	2011		
Li, 2011	19	24	14	24	8.7%	2.71 [0.76, 9.73]	2011		
Kuo, 2012	10	11	7	10	2.0%	4.29 [0.37, 50.20]	2012		
Li, 2015	29	30	25	30	2.5%	5.80 [0.63, 53.01]	2015	· · · · · · · · · · · · · · · · · · ·	
Chen, 2016	29	30	24	30	2.4%	7.25 [0.82, 64.46]	2016	· · ·	
He, 2016	58	60	56	60	5.6%	2.07 [0.36, 11.76]	2016		
Lei, 2017	30	30	25	30	1.2%	13.16 [0.69, 249.48]	2017	2 <b></b>	-
Xie, 2018	37	41	32	41	9.3%	2.60 [0.73, 9.26]	2018		
Liu, 2020	27	30	22	30	6.6%	3.27 [0.77, 13.83]	2020		
Wu, 2021	32	34	24	34	4.2%	6.67 [1.34, 33.28]	2021		
Total (95% CI)		465		460	100.0%	2.77 [1.89, 4.07]		•	
Total events	339		278						
Heterogeneity: Chi² =	5.95, df = 13 (P = 0.9	5); P = 0%						0.005 0.1 1 10	200
Test for overall effect:	Z = 5.22 (P < 0.0000)	1)						0.000 0.1 1 10 2	100

Figure 2. The effect's forest plot of the Chinese herbal medicine compared to standard treatment on total effective rate in personals with diabetic foot ulcers

	Chinese h	Standard treatment				Mean Difference		Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI Year	8	IV, Randor	m, 95% Cl	
Li, 2011	3.8	3.72	24	5.4	4.95	24	9.1%	-1.60 [-4.08, 0.88] 2011				
Kuo, 2012	3.92	4.87	11	4.47	6.45	11	3.7%	-0.55 [-5.33, 4.23] 2012				
He, 2016	2.1	2	60	4.1	1.22	60	18.5%	-2.00[-2.59, -1,41] 2016				
Xie, 2018	5.18	2.18	41	6.53	2.83	41	16.0%	-1.35[-2.44, -0.26] 2018	£			
Xie, 2019	0.75	0.08	30	5.83	2.07	30	17.8%	-5.08 [-5.82, -4.34] 2019	-	:		
Liu, 2020	4.23	2,22	30	5.62	2,49	30	15.5%	-1.39[-2.58, -0.20] 2020	12			
Wu, 2021	0.23	0.11	34	3,18	0.86	34	19.4%	-2.95[-3.24, -2.66] 2021		*		
Total (95% CI)			230			230	100.0%	-2.44 [-3.46, -1.43]		+		
Heterogeneity: Tau <sup>2</sup> =	1.37: Chi <sup>2</sup> = 5	7.95, df =	6 (P < 0.0	00001); P	= 90%				<u> </u>			
Test for overall effect (	Z = 4.71 (P <	0.00001)							22	-41 - <u>22</u> - 10	8 8 <b>2</b> 8 8 8	

Figure 3. The effect's forest plot of the Chinese herbal medicine compared to standard treatment on wound size after treatment in personals with diabetic foot ulcers

	Chinese herbal m	Standard trea	tment		Odds Ratio		Odds Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	Year		M-H	I, Fixed, 9	5% CI	
Song. 2006	2	25	12	25	19.8%	0.09 [0.02, 0.49]	2006	-		- 1		
Wang, 2006	3	30	11	30	17.8%	0.19 [0.05, 0.78]	2006			-		
Deng, 2007	4	40	11	35	19.0%	0.24 [0.07, 0.85]	2007			_		
Xing, 2008	3	46	6	50	9.7%	0.51 [0.12, 2.18]	2008				č	
He. 2008	6	40	12	38	18.8%	0.38 [0.13, 1.15]	2008			-		
Leung, 2008	3	40	9	40	15.0%	0.28 [0.07, 1.12]	2008			-		
Total (95% CI)		221		218	100.0%	0.26 [0.15, 0.45]			-			
Total events	21		61									
Heterogeneity: ChP =	2.97, df = 5 (P = 0.70	)); F = 0%						-	0.1		10	100
Test for overall effect:	Z = 4.86 (P < 0.0000	1)						0.01	0.1	9	10	100

Figure 4. The effect's forest plot of the Chinese herbal medicine compared to standard treatment on number of patients without any improvement in personals with diabetic foot ulcers

	Chinese h	erbal med	licine	Standard treatment				Mean Difference	Mean Difference					
Study or Subgroup	Mean SD Tota			Mean	SD	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% CI				
Lī, 2011	7	59.5	24	7.5	31.69	24	2.4%	-0.50 [-27.47, 26.47]	2011		-	-		
Lei, 2017	8.23	3.12	30	15.31	6.12	30	37.7%	-7.08 [-9.54, -4.62]	2017		-	-		
Xie, 2019	22.2	14.35	30	37,31	11.23	30	21.5%	-15.11 [-21.63, -8.59]	2019	_	-			
VAu, 2021	20.31	3.47	34	32.57	5.84	34	38,4%	-12.26 [-14.54, -9.98]	2021		+			
Total (95% CI)			118			118	100.0%	-10.64 [-14.91, -6.37]		3	٠			
Heterogeneity: Tau <sup>2</sup> =	10.99; Chi <sup>2</sup> =	11.99, df =	3 (P = 0	.007); F =	= 75%					-20	-10	0	10	20

Figure 5. The effect's forest plot of the Chinese herbal medicine compared to standard treatment on time of diabetic wound ulcer healing in personals with diabetic foot ulcers

	Chinese herbal n	standard trea	tment		Odds Ratio		Odds Ratio					
Study or Subgroup	Events Total		Events Total		Weight	M-H, Random, 95% C	Year		M-H,	Random, S	95% CI	
Song. 2006	23	25	13	25	22.8%	10.62 [2.05, 54.95]	2006			-		
He, 2008	34	38	26	40	27.0%	4.58 [1.35, 15.55]	2008			-	-	
Xing, 2008	43	50	44	46	23.0%	0.28 [0.05, 1.42]	2008			-		
Li, 2011	17	24	10	24	27.2%	3.40 [1.03, 11.26]	2011					
Total (95% CI)		137		135	100.0%	2.69 [0.70, 10.30]						
Total events	117		93									
Heterogeneity: Tau <sup>2</sup> =	1.35; ChiP = 11.00, (	#=3(P=	0.01); l <sup>2</sup> = 73%					-		-	1	
Test for overall effect:	Z = 1.44 (P = 0.15)							0.01	0.1	1	10	100

Figure 6. The effect's forest plot of the Chinese herbal medicine compared to standard treatment on number of patients with 30% or more reductions in the personals with diabetic foot ulcers

### Discussion

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. <sup>20</sup> 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. <sup>32, 33</sup> 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. <sup>34</sup> Additionally, only 1 examination utilized limb savage 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. <sup>35-37</sup>

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. The use of inaccurate or incomplete data from a previous analysis could have increased bias. The individual's nutritional status, together with their race, gender, and age, were probably the root reasons for discrimination. Due to incomplete data and some unpublished studies, values may inadvertently be affected.

### Conclusions

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. Hingorani, A., G.M. LaMuraglia, P. Henke, et al. *The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine.* Journal of vascular surgery **63**(2): p. 3S-21S (2016).
- 2. Al Ayed, M., M. Ababneh, A.A. Robert, et al. *Factors associated with health-related quality of life in patients with diabetic foot ulcer: a cross-sectional study from Saudi Arabia.* Cureus **12**(6) (2020).
- 3. McDonald, C.L., S. Westcott-McCoy, M.R. Weaver, et al. *Global prevalence of traumatic non-fatal limb amputation.* Prosthetics and orthotics international: p. 0309364620972258 (2021).
- 4. Edmonds, M., C. Manu, and P. Vas *The current burden of diabetic foot disease*. Journal of clinical orthopaedics and trauma **17**: p. 88-93 (2021).
- 5. Ampofo, A.G. and E.B. Boateng *Beyond 2020: Modelling obesity and diabetes prevalence.* Diabetes Research and Clinical Practice **167**: p. 108362 (2020).
- 6. Norman, G., M. Westby, K. Vedhara, et al. *Effectiveness of psychosocial interventions for the prevention and treatment of foot ulcers in people with diabetes: a systematic review.* Diabetic Medicine **37**(8): p. 1256-1265 (2020).
- 7. Pengzong, Z., L. Yuanmin, X. Xiaoming, et al. *Wound healing potential of the standardized extract of Boswellia serrata on experimental diabetic foot ulcer via inhibition of inflammatory, angiogenetic and apoptotic markers.* Planta Medica **85**(08): p. 657-669 (2019).
- 8. Kumar, S., A. Bharali, H. Sarma, et al. *Traditional complementary and alternative medicine (TCAM) for diabetic foot ulcer management: A systematic review.* Journal of Ayurveda and Integrative Medicine **14**(4): p. 100745 (2023).
- 9. zadeh Gharaboghaz, M.N., M.R. Farahpour, and S. Saghaie *Topical co-administration of Teucrium polium hydroethanolic extract and Aloe vera gel triggered wound healing by accelerating cell proliferation in diabetic mouse model.* Biomedicine & Pharmacotherapy **127**: p. 110189 (2020).

- 10. Abdullah, F.I., L.S. Chua, S.P. Mohd Bohari, et al. *Rationale of Orthosiphon aristatus for healing diabetic foot ulcer.* Natural Product Communications **15**(9): p. 1934578X20953308 (2020).
- 11. Jayalakshmi, M.S., P. Thenmozhi, and R. Vijayaraghavan *Plant leaves extract irrigation on wound healing in diabetic foot ulcers.* Evidence-Based Complementary and Alternative Medicine **2021**: p. 1-9 (2021).
- 12. Biram Chand Mewara, D.Y.R.N. and M. Sharma *A clinical study of the risk factors leading to complication in diabetic foot ulcer.* International Journal of Surgery **3**(2): p. 17-19 (2019).
- 13. Spanakis, M., M. Melissourgaki, G. Lazopoulos, et al. *Prevalence and clinical significance of drug–drug and drug–dietary supplement interactions among patients admitted for cardiothoracic surgery in greece.* Pharmaceutics **13**(2): p. 239 (2021).
- 14. 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).
- 15. Song, Y., M. Liu, Y. Li, et al. *Clinical observation of 25 cases of diabetes with diabetic foot treated by Simiao Yongan Tang.* J Sichuan Trad Chinese Med **24**: p. 64 (2006).
- 16. Wang, X. and J. Jiang *Clinical analysis of using intergrative medicine for patients with diabetic foot.* Jilin J Trad Chin Med **26**: p. 40–41 (2006).
- 17. Deng, J., J. Zhang, and G. Wang *Clinical observation of using Bu-yang-huan-wu decoction to treat diabetic foot.* J Sichuan Trad Chinese Med **25**: p. 81-82 (2007).
- 18. Xing, Y. Clinical observation of She-xiang-huo-xue capsule for patients with diabetic foot. J Liaoning Univ Trad Chin Med **10**: p. 142–143 (2008).
- 19. He, Z. *Clinical observation on 40 cases of diabetic gangrene treated with jiawei Taohong Siwu Tang.* Zhejiang J Trad Chinese Med **43**: p. 202–203 (2008).
- 20. Leung, P.-C., M.W. Wong, and W.-C. Wong *Limb salvage in extensive diabetic foot ulceration: an extended study using a herbal supplement.* Hong Kong Medical Journal **14**(1): p. 29 (2008).
- 21. Li, S., J. Zhao, J. Liu, et al. *Prospective randomized controlled study of a Chinese herbal medicine compound Tangzu Yuyang Ointment for chronic diabetic foot ulcers: a preliminary report.* Journal of Ethnopharmacology **133**(2): p. 543-550 (2011).
- 22. Du, J. and L. Li Chitosan Traditional Chinese Medicine Composite Film for Diabetic Foot Ulcer

*clinical controlled observation.* Infomation on TmdII onal Chinese Medicine **28**(3): p. 98-100 (2011).

- 23. Kuo, Y.-S., H.-F. Chien, and W. Lu *Plectranthus amboinicus and Centella asiatica cream for the treatment of diabetic foot ulcers.* Evidence-Based Complementary and Alternative Medicine **2012** (2012).
- 24. Li, Y. and B. Yang Intervention of "Chuanhuang powder" in the healing process of diabetic foot ulcer. Study on the correlation between AGEs and healing-promoting factors. World Science and Technology-Current Chinese Medicine Modernization **17**(2): p. 350-355 (2015).
- 25. He, C., L. Ye, and W. Li Moisture therapy traditional Chinese medicine hard plaster application in the treatment of diabetic foot ulcers

Clinical Observation. Beijing Journal of Traditional Chinese Medicine 35(10): p. 919-921 (2016).

26. Chen, D. Sanhuang ice wet compress in the treatment of Wagner grade 2-3 diabetic foot ulcers

Curative Effect Observation. Journal of Nurse Training 31(13): p. 1239-41 (2016).

27. Lei, W. *Clinical observation on external application of Zidan gauze in the treatment of diabetic foot.* Chinese Traditional Medicine Modern distance education of medicine **15**(21): p. 88-90 (2017).

- 28. Xie, J. and X. Zou *Clinical Observation on 41 Cases of Diabetic Foot Ulcer Treated with Xiangpi Shengji Ointment.* Hunan journal of traditional chinese medicine **34**(6): p. 60-62 (2018).
- 29. Xie, X., W. Guan, and X. Tang *Effect of Shenghongye wet compress on ulcer healing in patients with Wagner grade 1-3 diabetic foot.* Qilu Nursing Journal **25**(1): p. 127-128 (2019).
- 30. Liu, M., Clinical application of Huangjin Wanhong ointment in the treatment of diabetic foot ulcers with damp-heat toxin syndrome

Curative Effect Observation., in Kunming: Yunnan University of Traditional Chinese Medicine. p. 201.(2020).

- 31. Wu, D. *Clinical efficacy of saffron compatibility in treating diabetic foot ulcer.* Journal of Medicine and Pharmacy of Chinese Minorities **27**(7): p. 22-24 (2021).
- 32. Chen, C., N. Venketasubramanian, R.N. Gan, et al. *Danqi Piantang Jiaonang (DJ), a traditional Chinese medicine, in poststroke recovery.* Stroke **40**(3): p. 859-863 (2009).
- 33. Han, S.-Y., Z.-Y. Hong, Y.-H. Xie, et al. *Therapeutic effect of Chinese herbal medicines for post stroke recovery: a traditional and network meta-analysis.* Medicine **96**(49) (2017).
- Ramsey, S.D., K. Newton, D. Blough, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes care 22(3): p. 382-387 (1999).
- 35. Zhong, D., H. Cheng, and L. Li *The effects of Buyang Huanwu decoction combined with Western medicine in diabetic foot treatment: a systematic review and meta-analysis.* TMR Integr Med **7**: p. e23010 (2023).
- Wang, Y., H.-J. Cao, L.-Q. Wang, et al. *The effects of Chinese herbal medicines for treating diabetic foot ulcers: A systematic review of 49 randomized controlled trials.* Complementary Therapies in Medicine 44: p. 32-43 (2019).
- 37. Chen, M., H. Zheng, L.-P. Yin, et al. *Is oral administration of Chinese herbal medicine effective and safe as an adjunctive therapy for managing diabetic foot ulcers? A systematic review and meta-analysis.* The Journal of Alternative and Complementary Medicine **16**(8): p. 889-898 (2010).