Therapeutic effects of *Astragali Radix* on diabetic foot: a clinical randomized controlled trial

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**Author contributions**

All authors contributed equally to this research. Zhengju Du conducted the experiments and wrote the manuscript. Lidan Zhang performed the data analysis. Hanggang Ni and Qian Guo designed the study and amended the paper. All authors have read and agreed to the published version of the manuscript.

**Competing interests**

The authors declare no conflicts of interest.

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**Abbreviations**

VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; MMP-2, matrix metalloproteinase-2; TNF-α, Tumor necrosis factor-alpha; IL-6, Interleukin-6; NURF3, Nucleotide-binding oligomeric structural domain-like receptor protein 3.

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**Abstract**

**Objective:** This study was conducted to evaluate the efficacy of *Astragalus* on diabetic foot, as well as the effects on the levels of serum VEGF, bFGF, MMP-2, and inflammatory factors in patients, and to provide a scientific basis for the treatment of diabetic foot with the traditional Chinese medicine *Astragalus*. **Methods:** By taking 100 cases of diabetic foot patients who were admitted to the metabolic internal medicine division of the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine and met the criteria of natriuresis during April 2021–April 2023 as the study subjects, and according to the random number method, all patients were divided into the control group and the observation group, with 50 cases in each group. In the control group, only basic treatment was carried out, while in the observation group, *Astragalus* injection was added based on the control group. After 8 weeks of treatment, the clinical efficacy, serum VEGF, bFGF, MMP-2, and inflammatory factor levels of the patients in the two groups were compared, respectively. **Results:** The total clinical efficiency of patients in the observation group was significantly better than that in the control group ($\chi^2 = 5.01, P < 0.05$). The inflammatory factor indexes decreased substantially in both groups. However, the decrease in the observation group was significantly higher than in the control group ($P < 0.05$). Compared with the control group, serum VEGF and bFGF were considerably higher in the observation group, while MMP-2 was significantly lower ($P < 0.05$). **Conclusion:** *Astragali Radix* is clinically effective in the diabetic foot, which can induce vascular endothelial repair and reduce the level of inflammatory factors, to improve the inflammatory state of patients and promote the restoration of ulcerated wound tissue, which is worth promoting in clinical practice.

**Keywords:** Astragali Radix; diabetic foot; VEGF; bFGF; inflammatory factor
**Introduction**

The diabetic foot and its complications are one of the world’s most critical public health problems, which refers to the development of foot infections, ulcers, or tissue destruction in people with diabetes, and are the most common reason for hospitalization of people with diabetes [1]. According to data from the Global Diabetic Foot Epidemiology Survey, the global prevalence of diabetic foot is 5% to 10%. The diabetic foot has a very high mortality and disability rate, which seriously threatens the life safety and quality of life of diabetic patients [2, 3]. According to statistics, amputations caused by diabetic foot are eight times more common in non-diabetic patients. The pathogenesis of the disease includes neuropathy, vasculopathy, skin lesions, and disorders of inflammatory response [4]. Due to the complex pathogenesis of diabetic foot, the treatment is mainly comprehensive, including control of blood glucose, blood lipids, blood pressure, wound replacement, infection control, improvement of lower extremity perfusion, and internal and external treatment of Chinese medicine [5]. However, the efficacy of Western medicine still shows poor performance, therefore, the combination of Chinese and Western medicine that integrates the advantages of Chinese and Western medicine has become one of the research hotspots for the prevention and treatment of diabetic foot [7-9]. Astragalus Radix (AR) is one of the most widely used herbal medicines in traditional Chinese medicine. It was first published in Sheng Nong’s herbal classic, according to Chinese medicine, it has the effects of tonifying qi and raising yang, alleviating sweating and stopping bleeding, relieving edema, reducing water retention, mitigating sepictemia, promoting pus drainage and enhancing ulcer wound repair, and is also commonly used in traditional Chinese medicine to treat sores and ulcers that do not heal. Modern pharmacological research found that Astragalus Radix is rich in flavonoids, saponins, polysaccharides, amino acids, and various trace elements, with immune function, antioxidant effect, improved body metabolism, and lower blood glucose [10, 11]. It has been widely used in treating cardiomyopathy, cognitive diseases, tumors, diabetes, and related complications [12, 13]. Unfortunately, few clinical studies are related to treating diabetic feet with Astragalus Radix. This study aimed to investigate the efficacy of AR on diabetic foot and the effects on serum VEGF, bFGF, MMP-2, and inflammatory factor levels in patients with diabetic foot. Providing scientific evidence for the treatment of diabetic foot by traditional Chinese medicine.

**Materials and methods**

**General information**

One hundred patients with diabetic foot admitted to the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine between April 2021 and April 2023 were selected as study subjects, and all patients were divided into control and observation groups according to the random number method, with 50 cases in each group. In the control group, there were 26 males and 24 females, aged 45–85 years, with a mean age of (63.17 ± 8.84) years, duration of disease 8–25 years, with a mean period of (13.86 ± 8.31) years, 16 cases of Wanger grade I, 20 cases of grade II, and 14 cases of grade III. In the control group, there were 22 males and 28 females, aged 46–83 years, mean age (61.93 ± 7.54), duration of disease 7–23 years, mean duration of illness (11.25 ± 6.5) years, 18 cases of Wanger grade I, 19 cases of grade II, and 13 cases of grade III. There was no significant difference in gender, age, disease duration, and Wanger grade between the two groups (P > 0.05). The Ethics Committee of the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine approved the study, and all patients signed an informed consent form.

**Inclusion & Exclusion Criteria**

**Inclusion criteria.** ① Diabetic foot needs to meet the diagnostic criteria of “Guidelines of the international writing group on the diabetic foot on diagnosis” (2020 edition); ② The patient’s condition is stable; ③ The patient gives informed consent.

**Exclusion criteria.** ① Combined with severe cardiopulmonary disease; ② Severe malnutrition; ③ Type 1 diabetes mellitus; ④ Severe anemia; ⑤ Malignant tumor; ⑥ Poor compliance. The process of inclusion and exclusion of study subjects is shown in Table 1.

**Treatment method**

The control group was given essential treatments such as blood pressure control, blood glucose, lipid control, regular debridement and dressing change, anti-inflammation, etc., and the clinical dietitian guided the diet and kept the albumin level above 30g/L. The targets of blood pressure control were < 140/90mmHg, blood glucose control: fasting blood glucose 4.4–7.0mmol/L, non-fasting blood glucose < 10.0mmol/L, lipid control: total cholesterol < 4.5mmol/L, triglycerides < 1.7mmol/L, HDL < 1.0mmol/L for men, and HDL < 1.3mmol/L for women. The observation group was treated with Astragalus Radix based on the control group, and the Astragalus Radix preparation solution was selected from Astragalus Radix injection (Heilongjiang ZBD Pharmaceutical Co., Ltd., Production batch number: A63210401056, A63221101072, Heilongjiang, China) which only contains Astragalus Radix component. The method of use and the course of treatment were as follows: Astragalus Radix injection 20 ml was added to 0.9% sodium chloride injection 250 ml, intravenous drip once a day. All patients were treated for 8 weeks.

**Observed indicators**

**Determination of efficacy.** The clinical efficacy of the patients was determined at the end of the 8-week course of treatment. The clinical efficacy was divided into (1) Notably effective: the symptoms of foot ulcer infection completely disappeared, and the damaged tissues and ulcers were completely healed. (2) Effective: the symptoms of foot ulcer infection were basically reduced, and the damaged tissues and ulcers were basically healed. (3) Ineffective: the symptoms of foot ulcer infection, damaged tissues, and ulcers were not significantly improved or even aggravated. Total effective rate = (number of effective + number of effective)/complete × 100%.

**Measurement of serum VEGF, bFGF, and MMP-2 levels.** Overnight fasting venous serum was collected from all study subjects before and after drug treatment, and serum VEGF, bFGF, and MMP-2 levels were measured using an enzyme-linked immunosorbent assay (Jiangsu Enzyme Immunity Industry Co. MM-51120H2, Jiangsu, China).

**Inflammatory factor determination.** Overnight fasting venous serum was collected from all study subjects before and after drug treatment. TNF-α levels were measured by enzyme-linked immunosorbent assay (Jiangsu Enzyme Immunity Industry Co. MM-3693802, Jiangsu, China), and IL-6 levels were measured by electrochemoluminescence assay (Jiangsu Enzyme Immunity Industry Co. MM-3522602, Jiangsu, China), respectively.

**Statistical methods**

All data were analyzed using SPSS26.0 statistical software, measurement data were expressed as (± s), and categorical data were expressed as (%). T-test was used for measurement data conforming to the normal distribution, and the χ² test was used for comparison between groups. P < 0.05 was statistically significant.

**Results**

**Clinical efficacy**

The treatment efficiency of patients in the observation group was significantly higher than that of the control group (χ² = 5.01, P < 0.05), as shown in Table 1. In Summary, the efficacy of the observation group was considerably superior to that of the control group.

**Serum VEGF, bFGF and MMP-2 levels**

The serum VEGF and bFGF levels in the observation group increased significantly (P < 0.05) after treatment with Astragalus Radix compared with those before treatment, and the increase was considerably higher.
than that in the control group (P < 0.05) (Table 2 and 3). The serum MMP-2 levels in the observation group were significantly lower after Astragalus Radix treatment than before (P < 0.05). However, the serum MMP-2 levels in the control group after treatment were not statistically significant compared with the pre-treatment levels (t = 1.03, P = 0.3) (Table 4). Therefore, serum VEGF, bFGF and MMP-2 levels in the observation group were markedly favorable to those in the control group.

Levels of inflammatory factors
Before treatment, there was no statistically significant difference in the levels of all inflammatory factors between the two groups (P > 0.05). After treatment, the levels of TNF-α and IL-6 decreased significantly in both groups. However, compared with the control group, the decrease in the observation group was significantly greater than that in the control group (P < 0.05) (Table 5 and 6). In conclusion, the level of inflammatory factors in patients treated with Astragalus was significantly lower than that in the control group.

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**Table 1** Comparison of clinical efficacy between two groups of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>Notably effective (%)</th>
<th>Effective (%)</th>
<th>Ineffective (%)</th>
<th>Total efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50</td>
<td>18 (36.0)</td>
<td>23 (46.0)</td>
<td>9 (18.0)</td>
<td>41 (82.0)</td>
</tr>
<tr>
<td>Observation group</td>
<td>50</td>
<td>22 (44.0)</td>
<td>26 (52.0)</td>
<td>2 (4.0)</td>
<td>48 (96.0)</td>
</tr>
</tbody>
</table>

χ² = 5.01

<table>
<thead>
<tr>
<th>Group</th>
<th>pre-treatment</th>
<th>post-treatment</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>54.67 ± 16.78</td>
<td>87.68 ± 22.34</td>
<td>-7.72</td>
<td>0.00</td>
</tr>
<tr>
<td>Observation group</td>
<td>55.12 ± 18.50</td>
<td>18.98 ± 25.50</td>
<td>4.33</td>
<td>0.00</td>
</tr>
</tbody>
</table>

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Table 3 Comparison of bFGF levels before and after treatment in two groups (pg/ml)

<table>
<thead>
<tr>
<th>Group</th>
<th>pre-treatment</th>
<th>post-treatment</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>102.35 ± 22.78</td>
<td>145.23 ± 18.21</td>
<td>10.65</td>
<td>0.00</td>
</tr>
<tr>
<td>Observation group</td>
<td>104.13 ± 19.28</td>
<td>153.45 ± 15.37</td>
<td>12.36</td>
<td>0.00</td>
</tr>
<tr>
<td>t</td>
<td>0.42</td>
<td>2.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.67</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4 Comparison of MMP-2 levels before and after treatment between the two groups (ug/L)

<table>
<thead>
<tr>
<th>Group</th>
<th>pre-treatment</th>
<th>post-treatment</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>2.73 ± 0.67</td>
<td>2.58 ± 0.74</td>
<td>1.03</td>
<td>0.30</td>
</tr>
<tr>
<td>Observation group</td>
<td>2.69 ± 0.27</td>
<td>2.29 ± 0.22</td>
<td>8.21</td>
<td>0.00</td>
</tr>
<tr>
<td>t</td>
<td>0.39</td>
<td>2.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.7</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5 Comparison of TNF-α levels before and after treatment between the two groups (pg.L)

<table>
<thead>
<tr>
<th>Group</th>
<th>pre-treatment</th>
<th>post-treatment</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>22.4 ± 9.75</td>
<td>13.96 ± 5.58</td>
<td>4.95</td>
<td>0.00</td>
</tr>
<tr>
<td>Observation group</td>
<td>24.15 ± 8.66</td>
<td>8.54 ± 6.77</td>
<td>4.2</td>
<td>0.00</td>
</tr>
<tr>
<td>t</td>
<td>0.95</td>
<td>4.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.35</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6 Comparison of IL-6 levels in the two groups before and after treatment (pg. L)

<table>
<thead>
<tr>
<th>Group</th>
<th>pre-treatment</th>
<th>post-treatment</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>23.16 ± 11.62</td>
<td>11.20 ± 6.93</td>
<td>6.3</td>
<td>0.00</td>
</tr>
<tr>
<td>Observation group</td>
<td>21.08 ± 13.57</td>
<td>8.54 ± 6.77</td>
<td>6.26</td>
<td>0.00</td>
</tr>
<tr>
<td>t</td>
<td>0.83</td>
<td>2.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.41</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Risk factors and pathogenesis of diabetic foot
The development of diabetes results from a combination of factors; in both empirical studies, peripheral neuropathy, vascular disease, and foot infections are risk factors for diabetes [14]. The risk of diabetic foot disease and amputation is also closely related to the duration of diabetes (≥ 15 years), glycated hemoglobin, renal insufficiency, nutritional status, advanced age, and diabetic comorbidities [15, 16]. The pathogenesis of the diabetic foot is complex. It includes chronic inflammatory demyelinating lesions of the peripheral nerves in diabetic foot patients due to hyperglycemia, hyperlipidemia, accumulation of advanced glycosylation end products, and microvascular dysfunction caused by activation of polyol and oxidative stress pathways [5, 17, 18]. In addition, the synthesis and dysfunction of macrophages, fibroblasts, and vascular endothelial cells, resulting in a low anti-inflammatory response and vascular tissue repair capacity, is another important mechanism for developing diabetic foot [19].

Treatment and healing of diabetic foot
In clinical practice, it is observed that the early manifestations of diabetic foot patients are decreased tactile sensation, numbness of the limb, reduced ability to perceive temperature, pain, vibration, slower nerve conduction, weakened knee jump response, or even disappearance [20]. In the late stage, the disease develops into tissue degeneration and necrosis, infection, formation of ulcerated wounds, and even destruction of bone structure. Therefore, the treatment of
diabetic foot is based on comprehensive treatment, including self-education and management, debridement, anti-infection, topical dressing, revascularization, hyperbaric oxygen therapy, stem cell therapy, and emerging internal and external Chinese medicine treatment. Diabetic foot Ulcer wound repair is a highly complex process in which inflammatory factors, vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (PGF-2), and matrix metalloproteinase-2 (MMP-2) play a significant role in coordinating with each other. VEGF is a potent angiogenic and vascular permeability-inducing factor that promotes endothelial cell proliferation through endothelial cell-specific mitogens. bFGF is a trace substance found in mammals and humans. bFGF receptors are distributed in various tissues and cells; thus, its physiological effects are extensive, and it is a multifunctional cell growth factor. When injured, the tissues or cells around the injury site secrete bFGF. bFGF can promote the proliferation and division of fibroblasts, vascular endothelial cells, smooth muscle cells, epithelial cells, and neural cells and accelerate wound healing by stimulating the rapid expansion of epithelial cells and covering the center of the wound. bFGF is a gelatinase-type IV collagen, which can degrade the arterial wall. MMP-2 is present in endothelial cells, fibroblasts, and other cells, and when MMP-2 is successfully activated, it can be used in the degradation of extracellular matrix; therefore, stable expression of MMP-2 facilitates wound healing [21]. In diabetic ulcers, chronic prolonged inflammation accompanied by protein hydrolysis leads to a chronic migratory state, which in turn leads to poor recovery of diabetic ulcer wounds, and the coordinated interaction of VEGF and bFGF plays an essential role in the process of vascular renewal and skin wound repair. In contrast, overexpression of MMP-2 decreases VEGF levels, inhibits fibroblast function, and increases extracellular matrix breakdown, thereby affecting the healing of diabetic foot wounds. Therefore, in diabetic foot treatment, inhibiting inflammatory response, promoting VEGF and bFGF levels, and reducing MMP-2 levels are essential for the repair of diabetic foot ulcer wounds.

The effect of Astragalus Radix on TNF-α and IL-6

TNF-α is an important pro-inflammatory cytokine that can play an essential role in the immune system during inflammation, cell proliferation, differentiation, and apoptosis by promoting oxidative stress at the site of inflammation. Previous studies have also found that AR can reduce the inflammatory response and increase renal indexes by inhibiting the TLR4 / NF-kB signaling pathway [22]. In animal experiments, it was found that astragaloside in Astragali Radix could reduce IL-6 and TNF-α levels by regulating the expression of NLRP3 inflammatory vesicle-related proteins, thereby regulating lipid and inflammatory factor levels in rats with early diabetic atherosclerosis and achieving vascular protection [23]. The same was observed for Astragali polysaccharide in the acute infection model induced by glucoceolic acid to inhibit the level of TNF-α caused by staphylococci. These findings suggest that Astragali inhibits inflammatory factor levels and reduces the inflammatory response in acute and chronic inflammatory conditions.

Effect of Astragali Radix on ulcerated wounds

Astragali Radix is rich in several chemicals and, therefore, can promote the repair of ulcer wounds in several ways. Astragali polysaccharide, the main active component of Astragali Radix, can promote wound recovery, collagen secretion, and structural reconstruction and reduce oxidative damage to wounds [24]. Secondly, astragaloside can regulate vascular endothelial growth factors on EA-hy926 cells by activating the ERK1/2 signaling pathway to promote their proliferation and angiogenesis [25]. The effects of astragaloside on EA-hy926 cells were observed in animal models. In animal models, it was also observed that Astragali could promote endothelial repair in diabetic wounds by improving the function of endothelial progenitor cells (EPCs) [26, 27]. Qiu et al. found that Astragali extract was associated with the activation of the Wnt/β-Catenin signaling pathway and could regulate the action of the Wnt/β-Catenin signaling pathway through the regulation of Wnt1, Wnt3a, β-Catenin, GSK, and upregulation of β-Catenin, C-myc, Cyclin D1, and other proteins, thus promoting the epidermal stem cell proliferation and differentiation, accelerating the healing of diabetic ulcers [28]. Meanwhile, significant improvements in ulcer healing and pain relief were observed in clinical studies following treatment of diabetic foot ulcers with herbs containing astragalia [29]. Therefore, Astragali Radix has a definite effect on the prognosis of sore wounds and has excellent potential for application in treating diabetic foot [30, 31]. In the present study, we not only observed that the total treatment efficiency of patients in the Astragulus-treated group was significantly higher than that of the control group. Moreover, the serum VEGF and bFGF levels of diabetic foot patients were significantly increased after treatment with Astragali Radix, and the increase was substantially higher than that of the control group after treatment. MMP-2 levels were significantly lower in the observation group after treatment, but in the control group, there was no statistically significant difference in MMP-2 levels before and after treatment. We also observed that the levels of inflammatory factors (TNF-α, IL-6) in diabetic foot patients were significantly reduced after treatment with Astragali Radix. The magnitude of the reduction was also considerably higher than that in the control group, indicating that Astragali Radix can effectively inhibit the levels of inflammatory factors, increase the levels of serum VEGF and bFGF, and effectively reduce the levels of MMP-2, thus promoting the repair of ulcer wounds in diabetic foot patients.

Conclusion

In conclusion, we found through this study that Astragali Radix has definite efficacy on diabetic foot, can effectively inhibit the level of inflammatory factors in diabetic foot patients, can promote the elevation of serum VEGF and bFGF, and reduce the level of MMP-2, which can effectively promote the ulcer wound repair of diabetic foot. Therefore, Astragali Radix can be applied to treating diabetic feet in clinical practice.

Limitations

In this study, the antibiotic regimen was not kept consistent due to differences in the bacterial class of infection between patients, and the grace and dose of antibiotics may have impacted the experimental results.

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