

Mechanism of "Rhizoma Bletillae-Radix Notoginseng" Medicine in Treating Diabetic Foot Ulcer: A Review

Zhou Man^{1,a}, Wang Yaping^{1,b}, Lei Ting^{2,c,*}

¹Shaanxi University of Chinese Medicine, Xianyang, 712000, China

²Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang, 712000, China

^a329322665@qq.com, ^b1609442307@qq.com, ^c554631847@qq.com

*Corresponding author

Abstract: Modern Chinese medicine has a new understanding of the dialectical treatment of the etiology and pathogenesis of diabetic foot ulcer (DFU). "The surgical method is the most important for external treatment". Based on the traditional wound repair theory of "removing putrefaction and promoting granulation", the combination of traditional Chinese and western medicine surgery in our hospital selected medicine pairs (Rhizoma Bletillae and Radix Notoginseng) to treat DFU, which was not only analyzed by genomics and protein genomics. Systematically and deeply reveal the functional material basis and mechanism of Rhizoma Bletillae -Radix Notoginseng drug pair, and flexibly apply the intervention strategy of "removing blood stasis and promoting regeneration" in traditional Chinese medicine surgery, and organically combine traditional Chinese medicine dosage forms with new dressings for modern wound repair, providing new technical methods for the treatment of DFU by traditional Chinese medicine. This paper focuses on the research on the TCM theory of Rhizoma Bletillae -Radix Notoginseng medicine in treating diabetic foot ulcer, and discusses the mechanism of Rhizoma Bletillae -Radix Notoginseng medicine in treating diabetic foot ulcer in combination with the previous experimental research of the research group.

Keywords: Rhizoma Bletillae; Radix Notoginseng; Drug pair; Diabetic foot ulcer; Theoretical study on drug pair

1. Introduction

Chronic skin ulcers are local skin tissue damage and ulceration caused by various causes, most of which are associated with chronic inflammation, vascular damage and neuropathy. Chinese medicine also known as "stubborn sore", "sore", "pulse" and other names. Its pathogenesis is mostly the imbalance of Yin and Yang, disharmony of the viscera, deficiency of vital qi, stagnation of qi and blood, and obstruction in the meridians. Treatment and improvement of circulation is the key, the nutritional nerve is the foundation, and the prevention of infection is the most critical. Local external treatment, remove saprophytic muscle, warm Yang and blood circulation for the method, plaster external application is the most commonly used. Lu Jingshan, a master of traditional Chinese medicine, mentioned a prescription "medicine pair" (white and Panax notoginseng) in "Shiji Ink Medicine pair", which is mostly used for the treatment of acute and chronic lower limb skin ulcers[1]. In particular, diabetic foot ulcer (DFU) has remarkable clinical efficacy. Combined with the clinical practice and experimental research of the research group, the efficacy material basis and mechanism of action of bai and Panax notoginseng medicine have been preliminarily explored, but the theoretical exploration of traditional Chinese medicine is insufficient, so this paper is designed to clarify this.

2. Main etiology and therapeutic principles of DFU

The treatment of chronic skin ulcers by traditional Chinese medicine has a long history. Diabetic foot ulcers belong to the category of "gangrene" and "eliminating thirst" in traditional Chinese medicine. The "Neijing" has the name of "occurring in the foot toe called gangrene". In the "Health Treasure Jian" of the Song Dynasty, "thirsty patients have severe sores on the foot and knee until they die", which described the poor prognosis of DFU co-infection.

DFU patients are often divided into Yin cold blood stasis type and damp heat blood stasis type. Yin cold blood stasis type is ischemic type, Presmanifested as chills and low skin temperature, Pale, flushing,

or cyanosis at the ends of the limbs, With some numbness and pain, In aggravated during the cold, Lameness is obvious; Less pus in the ulcer surface, The granulation is lighter, And slow growth; The tongue is pale or dark, May have pechymosis, Moss is thin and white, Pulture or delay, Treatment with warm Yang and scattered cold, Promoting blood circulation and removing blood stasis as the method; Wet-heat and blood stasis type is the infection type, Presmanifested as localized redness, heat and pain, High amount of exudation from the ulcer surface, Odor smell foul, The lesions developed rapidly, In severe cases, the full foot and calf skin color is black and dark, Red tongue drops, Yellow and greasy moss, Pulse slip number or string number, Treatment to clear the heat and remove dampness, Promote blood circulation and remove blood stasis[2].

"Outline of the department of sore" pointed out: "sore is a disease, found outside, external medicine is particularly important." TCM external treatment is widely used in the three periods of diabetic foot, namely debridement period, granulation period and epithelial formation period[3]. The commonly used dosage forms include lotion, wet dressing, ointment, powder, rub, etc. At present, the topical drugs for the treatment of diabetic foot ulcer include Sanhuang ointment, Qilong capsule and wet burn cream. Due to the unique appearance and smell of external Chinese medicine, some patients have poor compliance, local ulcer drugs cannot be stored for a long time, insufficient purification of Chinese medicine ingredients, poor efficacy and other shortcomings, which has been restricting the play of external treatment of Chinese medicine. In short, it is urgent to develop an artificial skin Chinese medicine dressing with the effect of microenvironment homeostasis regulation, which can be applied to local wound repair of DFU.

In the long-term clinical practice, it is found that the traditional treatment of "removing saprophytic muscle" can not solve all types of diabetic foot ulcers. For acute skin ulcer, "decay muscle" in line with the clinical law; and in chronic skin ulcer, the common situation is "rot, new", although the pus is clean, the wound is clean and smooth, but the stiffness around the wound, dark red color, wound granulation color light, it is difficult to produce new meat, accompanied by rough skin, dry, dark tongue, etc. This kind of clinical manifestation is in line with the pathogenesis of "stasis" in traditional Chinese medicine, mainly due to the local deficiency of qi and blood in the wound, skin loss (namely "deficiency"), so that the carrion does not take off, blood stasis does not go, so that the new meat is not born, often "due to deficiency stasis, due to stasis deficiency", mutual cause and effect. During treatment, attention should be paid to "removing stasis", promoting muscle and long skin, and on this basis, the traditional theory of "removing sepsis" should be developed into "removing stasis and producing muscle". In view of "blood stasis", the key pathological factor of chronic difficult ulcer such as DFU, the TCM intervention strategy of "removing blood stasis and removing new blood" was given, that is, the dynamic sequential diagnosis and treatment plan of "promoting blood circulation and removing blood stasis" was adopted in the early, middle and late stages of the course of the disease.

3. Analysis of the compatibility characteristics of white and Panax notoginseng drugs

"Medicine has the specialty of personality, and only the party has the wonderful use of the society." Drug pair is the basic form of Chinese medicine compatibility in traditional Chinese medicine. It is an organic combination of relatively fixed, complementary or complementary following the characteristics of drugs and according to the theory of compatibility. It is not only the minimum unit used for prescription, but also the basis of the connecting party and single medicine. The word "medicine pair" was first seen in Xu Zhicai's book *Lei Gong Medicine pair in the Northern Qi Dynasty*. Zhang Zhongjing of the Eastern Han Dynasty had many experiences in treating typhoid diseases, many of which are in use today. The composition of traditional Chinese medicine is complex, so it is necessary to combine the basic theory of traditional Chinese medicine, clinical medication experience and modern experimental research technology, and comprehensively clarify the characteristics of multi-component-multi-target-multi-pathway.

3.1 "Smell-seeking"

"Smell" is the theory of drug compatibility, in clinical drug compatibility, for the same or similar Chinese medicine, between them often can play a synergistic effect, for the taste effect of different Chinese medicine, because they a efficacy can be suitable for a disease needs, also can seek common ground while putting aside differences, complementary to help[4]; For traditional Chinese medicine with opposite taste effects, on the one hand, it can antagonize and inhibit the bias and toxicity of drugs through compatibility; on the other hand, the characteristics of comprehensive cooperation of drugs with opposite

properties can be used to achieve the effect of "opposite effect"[5]. White and cold, bitter, sweet, astringent, warm, sweet, slightly bitter, white and notoginseng, can alleviate the nature of white and cold, that is, the effect of "opposite".

3.2 "Seven feelings and harmony"

In the Western Han Dynasty, Shennong Materia Medica first summarized the law of traditional Chinese medicine compatibility, pointing out that there were seven feelings: "single line, beard, phase, fear, evil, opposite and killing". The theory of "seven emotions and harmony" is closely related to the compatibility of drug compatibility, which reveals that "efficiency enhancement and attenreduction" is the core purpose of drug compatibility, and mutual interaction, two-way regulation, drug introduction, and new use are all "efficiency enhancement"[6]. On the one hand, "collaborative interoperability" uses the analogy of Chinese medicine to accumulate medicinal power; on the other hand, it uses the different pathological links of the disease or the internal connection between the treatment. White and notoginseng are to hemostatic drugs, which can accumulate drug strength and enhance the function of hemostasis, and meanwhile, the efficacy of chronic skin ulcer can accumulate drug strength and use each other in different stages of the disease. "Two-way regulation" is to use the opposite characteristics of the two drugs in the taste and function, two-way intervention to dynamically balance, and then regulate the rise and decline of viscera functions and the peace of Mingyang qi and blood[7]. Bai and Panax notoginseng are opposite in sexual taste, and the comprehensive efficacy of the two drugs can make the treatment achieve dynamic balance. "Medicine into the" is with the choice of medicine and guidance, help medicine to the whole medicine to direct disease, the meridian reflects the natural viscera meridian lesions selective effects of the body, clinical optional under the same Chinese medicine, but clinical more often based on the relationship between the viscera selected belonging to different meridians of traditional Chinese medicine. Bai He and Panax notoginseng together to the lung, liver, stomach meridian, lung main fur, spleen and limbs muscles, and the spleen and stomach as the source of qi and blood biochemistry, the combination of the two drugs can better play the effect of its muscle growth. In short, the above many compatibility ideas are designed to enhance the efficacy of traditional Chinese medicine and improve the efficacy of treatment to achieve the purpose of "increasing efficiency".

3.3 "Walking together"

Zhang Jingyue, a doctor in the Ming Dynasty, described in Jingyue Encyclopedia that "the sex moves is Yang, the sex is quiet and the Yin", "the quiet is moving, the walk is feasible, and the guard can be safe", clearly pointing out that drugs have the difference of walking and arguing Yin and Yang with movement. Both the dynamic and static behavior are the induction of various properties of Chinese medicine on the basis of the static discharge, which emphasizes the trend force. The dynamic behavior includes not only the tendency of drugs, but also the tendency of drugs, which is a comprehensive induction of the trend of drugs[8]. The operation and play of medicine and its role depend on the promotion of medicine, which can use the relaxation of medicine, so that the efficacy is maintained for a long time. White and Panax notoginseng belong to the hemostatic medicine, Panax notoginseng promote blood circulation and stasis hemostasis, go but not keep, white and convergence hemostasis, keep but do not go, love evil stasis, so white and Panax notoginseng two, the combination of the two drugs can make hemostasis without stasis, in order to enhance the hemostatic effect, can not only make the drug quickly reach the disease, but also can prolong the action time.

3.4 "Traditional Chinese medicine and treatment"

"Chinese medicine treatment" is the main basis for the compatibility of drug combination. Treatment cooperation can combine traditional Chinese medicine with similar treatment effects, so as to better highlight the effect of a certain treatment, and two drugs with different treatment effects can be used to form a drug pair, starting from the disease certificate, combining different treatment methods for synergy. It has the effect of astringent and hemostasis, reducing swelling and producing muscle, external use, internal use can relieve ulceration, discharging pus and discharging blood, and has the wonderful use of supporting the old and creating new; Panax notoginseng has the function of removing blood stasis and creating new, stopping bleeding and relieving pain. The use of white and Panax notoginseng medicine can not only support the old, but also effectively promote the healing of ulcer wounds, so it has a good repair effect on chronic refractory diseases such as diabetic foot. Therefore, white and panax notoginseng, as a medicine, are the same, and follow the law of "removing blood stasis and new", regulate the body qi, blood and Yang Yin and Yang, make the body keep Yin and Pingyang secret, qi and blood harmony,

and finally promote the healing of the wound.

4. Research on the modern pharmacological mechanism of white and *Panax notoginseng* medicine

4.1 Chemical composition and mechanism of action of Baibaihe and *Panax notoginseng*

Modern pharmacological studies show that white and contain sugars, bibenzyl, Philippines, monohydrofield, dihydrophenofurans, bifield, diphenoxane derivatives, steroids and triterpenoids[9]. These components make white and effective to promote wound repair. As a traditional Chinese medicine commonly used in wound repair, modern studies show that it has the effects of hemostasis, anti-inflammation, antioxidant and immune regulation, and can play a role in promoting cell proliferation, microangiogenesis and inhibiting scar hyperplasia in all stages in the process of wound repair[10]. The mechanism of action runs through the whole process of wound repair, which can avoid excessive blood loss and accelerate hemostasis and coagulation. In the inflammation period, the transformation from the inflammation period to the proliferation period can be reduced by the regulation of collagen[11].

The main chemical components of *Panax notoginseng* are saponins with complex chemical structure, which contain saponins, flavonoids, sterols, sugars, volatile oils, polyylene alcohols, amino acids and organic acids[12]. Very high medicinal value. Among them, *Panax notoginseng* total saponins can improve vascular endothelial function, inhibit platelet aggregation and have anti-thrombosis effect; ginsenosides can have immune regulation, pro-growth promotion, liver preservation, repair, analgesia and anti-atherosclerotic plaque formation[13]; Polysaccharides have anti-inflammatory, haemostatic and immunomodulatory activities, stimulate macrophage activation, produce and activate cytokines, and promote the proliferation of T lymphocytes[14]; Flavonoids can improve blood circulation, dilate coronary arteries, reduce myocardial oxygen consumption, reduce cardiac load, improve myocardial blood supply, increase vascular elasticity and other effects[15]. *Panax notoginseng* has obvious pharmacological effects on the blood system, cardiovascular and cerebrovascular system, central nervous system and immune system. It has the functions of hemostasis and enriching blood, promoting blood circulation and removing blood stasis, anti-arrhythmia, anti-myocardial ischemia, protecting brain tissue, calming and relieving pain, improving memory and enhancing resistance[16].

4.2 Pharmacological mechanism of diabetic foot ulcer

Modern medical research show that the main components of white and DFU healing are white and polysaccharide (*Bletilla striata* polysaccharide, BSP), and BSP promoting DFU healing may inhibit the hyperactivation of macrophages in the ulcer area[17], Promote new blood vessel formation, regulate inflammation, and promote the process of epithelialization[18], The synthesis and release of increased hydroxyproline content, and the proliferation of fibroblasts[19]. besides, Wang Annan et al. found that white and may play anti-apoptosis, promote cell proliferation, angiogenesis and inhibit inflammation through multiple components, multiple targets and multiple pathways, Thus achieving the purpose of treating the diabetic foot, Its mechanism of action may interact with the active components of white and, In particular, white and polysaccharide, white and phenol and white and dihydrofield, The expression of epidermal growth factor (EGFR), threonine kinase 1 (AKT 1), vascular endothelial growth factor (VEGF A), tumor necrosis factor (TNF), mitogen-activated protein kinase 3 (MAPK 3), caspase 3 (CASP 3), and oncogene (HRAS) are regulated by PI3K-AKT, MAPK and VEGF signaling pathways[20].

The main component of DFU healing in *Panax notoginseng* is total saponin, which may be the upward regulation of miR-146a expression, downregulation of the target gene IRAK 1 and TRAF 6 expression, thus reducing inflammation[21], Reducing the expression of monocyte chemotactic protein-1[22], Reduce the expression of tumor necrosis factor- α (TNF- α)[23]And decreased the expression of endothelin-1 (ET-1) in DSU rats[24]. Deng Xiaoyan showed through clinical trials that *Panax notoginseng* total glycoside can significantly improve the ischemia of diabetic foot patients and shorten the course of patients[25]. Little through network pharmacology research found that notoginseng may participate in the biological process of regulation of cell proliferation, inflammatory response, oxidative stress response treatment, the mechanism may be through the PI3K-AKT signaling pathway, MAPK signaling pathway, IL-17 signaling pathway biological effect, and determine the AKT 1, CHUK, MYC therapeutic targets[26].

4.3 Mechanism of white and Panax notoginseng medicine on the treatment of diabetic foot ulcer

TCM has the characteristics of overall regulation and multi-target efficacy, and plays an important role in regulating the environmental homeostasis of the wound surface. TCM regulation of microenvironment is a hot topic in scientific research at present. According to the theoretical guidance of traditional Chinese medicine, the research group dialectically applied traditional Chinese medicine to the diabetic foot ulcer, which can directly act on the wound surface, form the barrier effect of "artificial skin", restore the relative independence of the internal environment, and is conducive to maintaining the steady state of a balanced and moist micro-environment. Through animal model experiments, the research group preliminarily confirmed that the material can promote the healing of the wound, and the mechanism of action may be related with the high expression of VE GF in the wound, as well as the up-regulation of β -catenin and RSPO-3 expression and the downregulation of GSK-3 β protein expression in the Wnt / β -catenin pathway[27][28]. Group also further cell experiments on the drug, confirmed that white and glue / micron notoginseng containing serum TNF- α , IL-6 and NO in the model of inflammation and inhibition, reduce the DFU local inflammatory reaction, reduce vascular and nerve damage, improve local tissue immunity, improve the inflammatory microenvironment, promote wound healing[29]. Ph / micron Panax notoginseng-containing serum can also inhibit the secretion of inflammatory factors by the macrophages, which may be related with inhibition of NF- κ B pathway activation, reduction of NF- κ B p65 into the nucleus and inhibition of I κ B α phosphorylation[30].

Around the two key points of "angiogenesis remodeling" and "inhibition of inflammatory response", The research group carried out a systematic study on the efficacy components, key targets and related signal pathways of P, It further revealed the molecular mechanism of the regulation of diabetic foot ulcer (DFU): the effective components of white and Panax notoginseng on the treatment of DFU are quercetin, paronin, di-octyl phthalate, 3, 4-dimethylbenzoic acid etc, These components mainly regulate proteins such as TNF, TP 53, NOS 3, IL-6, Wnt, NF- κ B, Notch and other signaling pathways can inhibit inflammatory response, promote cell proliferation and differentiation, anti-apoptosis, pro-vascular endothogenesis, participate in immune regulation, So as to achieve the effect of treating the disease[31]. In addition, in vitro experiments showed that white and polysaccharide in high fat and high glucose can regulate cytoplasm and nucleus β -catenin, inhibit cytosolic Gsk-3 β expression, activate Wnt / β -catenin pathway expression, promote the downstream target gene c-Myc, promote HUVEC proliferation, VE GF and bF GF, repair the integrity of HUVEC barrier and improve cell status, so as to achieve the role of promoting angiogenesis, repair of diabetic foot ulcer wound. In addition, Notch pathway activator Jagged-1 promotes the release of IL-6, IL-1 β , TNF- α , and Notch1 mRNA by regulating the expression of NICD, promote the nuclear displacement of NICD, activate the Notch pathway and promote the inflammatory response, while notoginseng total saponin can play the anti-inflammatory effect by inhibiting the expression of NICD and HES 1, reduce Notch1 and the release of inflammatory factors IL-6, TNF- α , IL-6 β mRNA and inhibiting the nuclear displacement of NICD.

Based on the above research basis, White and glue / microns sponge dressing acts on the wound of diabetic foot ulcer, Will form a homeostasis of a balanced moist vascular and inflammatory microenvironment, Under key signaling pathways and network patterns in the regulation of vascular structure and function homeostasis, Not only can it provide local repair cells for trauma, Can also improve the network imbalance between the cytokines, Promote their proliferation and inhibit their apoptosis, Involved in multiple processes including inflammatory regulation, angiogenesis, tissue repair and structural remodeling in trauma, The dual effect of homeostatic regulation of DFU microenvironment can be networked at the overall level, Promote chronic wound healing.

5. Summary and outlook

In recent years, more research on bai and Panax notoginseng has promoted wound healing, Bai He and Panax notoginseng have multiple ways in the treatment of wound surface, Multiple targets, The function characteristics of multi-level comprehensive regulation, This is also the advantage of traditional Chinese medicine treatment, However, the complexity of its components involves the safety and adverse effects of clinical medication, Although possible mechanisms can be analyzed by observing changes in cells or molecules, However, subsequent researchers need to carry out more thorough pharmaceutical trials and clinical studies to carry out more thorough and systematic validation, And combined with the practice of the clinicians, To improve the analysis of the wound repair and healing mechanism of bai and Panax notoginseng, To provide a more perfect theoretical support for the clinical adoption of its therapeutic wounds, Give further play to its characteristics and advantages of promoting wound healing.

To sum up, bai He and Panax notoginseng are effective in the treatment of diabetic foot ulcer. From the theory of traditional Chinese medicine, bai He and Panax notoginseng match the same smell, combining traditional Chinese medicine, and the two drugs achieve the effect of promoting blood circulation, removing blood stasis, reducing swelling and creating muscle, and promoting the wound healing of diabetic foot ulcer. In addition, network pharmacology revealed that the possible mechanisms of white and Panax notoginseng drugs in the treatment of diabetic foot ulcer were inhibiting inflammatory response, promoting cell proliferation and differentiation, fighting apoptosis, promoting vascular endothelogenesis, and participating in immune regulation. Through in vivo and in vitro experiments, the research group verified that white and panax notoginseng played a role in the mechanism of improving local inflammation, promoting proliferation and promoting angiogenesis, but the mechanism of cell apoptosis and immune regulation needs to be further verified by experiments. Traditional Chinese medicine itself has various ingredients, and the combination of drugs is more complex, and the metabolic process of different ingredients is not the same, and the content of some active ingredients may be too low to be tested, which is also the challenge of future research. In this regard, multi-omics joint analysis can combine genomics, lipidomics, proteomics and other technologies, which is helpful to systematically and deeply reveal the effective substance basis and action mechanism of bai and Panax notoginseng drug. In addition, from the perspective of life science, mechanical principles can also be used to make a new subversive interpretation of the action mechanism of sponge dressing, promote the transformation of clinical achievements, and finally form the benign development of the industrial chain of specialized disease of diabetic foot ulcer.

References

- [1] Li Zhi, Qi Zheng. *A brief analysis of thirst elimination disease pathogenesis [J]. Beijing Traditional Chinese Medicine*, 2012, 31 (01): 28-29 + 72.
- [2] Cui Yan, Han Lili, Li Yufeng. *Cui Gongang's experience of treating diabetic foot ulcer [J]. Traditional Chinese Medicine Journal*, 2010, 03: 404-405.
- [3] Niu Yaoxiang, Gao Lu, Jiang Wenyue. *Treatment of diabetic foot [J]. Ginseng Research*, 2015, 01: 49-54.
- [4] Gao Hansen. "Drug pair" and the mobilization of drug properties [J]. *Journal of Guangzhou College of Traditional Chinese Medicine*, 1988, 5 (4): 184-188.
- [5] Xi-Ji'an zhang. *On the ideological origin and historical evolution of the prescription [J]. The Journal of Practical Traditional Chinese Medicine*, 2005, 21 (4): 240-242.
- [6] Zan Shujie, Wang Kai, Li Lin, etc. *Drug pair compatibility theory [J]. Journal of Traditional Chinese Medicine*, 2023, 64 (17): 1729-1733.
- [7] Ma Juntian, Zhang Ying, Wang Xianling, et al. *On the compatibility and effect of drug combination [J]. Traditional Chinese Medicine Research*, 2013, 26 (7): 58-60.
- [8] Zhao Wanlu, Pan Yi, Xu Shihui, Qin Luping, Zhang Lu. *Take aconite, cassia bark and dried ginger as examples to discuss the research progress of walking compatibility [J]. Chinese Journal of Traditional Chinese Medicine*, 2022, 12: 7240-7243.
- [9] Kong Weihua, Xu Jianbo, Cui Qi, et al. *Progress in white and chemical composition, pharmacological effects and white and polysaccharide extraction process [J]. Traditional Chinese Medicine Information*, 2021, 38 (9): 69-78.
- [10] Kong Weihua, Xu Jianbo, Cui Qi, et al. *Progress in its chemical composition, pharmacological action and polysaccharide extraction process [J]. Information on Traditional Chinese Medicine*, 2021, 38 (9): 69-78.
- [11] Xu Dongmin, Du Juanjiao, Yang Ying. *Progress in the mechanism of action in wound repair [J]. Chinese Journal of Integrated Traditional Chinese and Western Medicine Surgery*, 2023, 01: 125-129.
- [12] Zhu Yaling, Yang Ziwei, Gao Jiahui, Chen Jianmei, Chen Lu, Kong Yazhen, Diao Yong. *Network pharmacological analysis of the mechanism of action of Panax notoginseng-white and drugs [J]. Journal of Huaqiao University (Natural Science Edition)*, 2020, 41 (04): 501-509.
- [13] Kang S Y, Kim S H, S Chini V B, et al. *Dietary ginsenosides improve endothelium-dependent relaxation in the thoracic aorta of hypercholesterolemic rabbit [J]. Gen Pharmacol*, 1995, 26 (3) : 483-487.
- [14] LI Y. *Immunomodulating Chinese herbal medicines [J]. Mem Inst Oswaldo Cruz*, 1991, 86(Suppl2): S159-164
- [15] Yin Jian, Guo Li Gong. *Modern research and clinical application of traditional Chinese medicine [M]. Beijing: Xueyuan Publishing House, 1993: 35-36.*
- [16] Zhang Jie. *Pharmacological effects and research progress of traditional Chinese medicine Panax notoginseng [J]. Health Industry in China*, 2017, 14 (28): 40-41.

- [17] Zhao Yan. *Study on the healing mechanism of NLRP 3 inflammasome-diabetic foot ulcer [D]. Hubei College of Medicine, 2022.DOI:10.27913/d.cnki.ghyby.2021.000095.*
- [18] Li xiaomei. *Application study of BPS hydrogel to promote diabetic wound healing [D]. Dalian Medical University, 2022.DOI:10.26994/d.cnki.gdlyu.2021.000316.*
- [19] Yu Linhua, Nie Xuqiang, Pan Huijun and so on. *Effect of white and polysaccharides on wound healing of diabetic ulcers [J]. Chinese Journal of Traditional Chinese Medicine, 2011, 36 (11): 1487-1491.*
- [20] Wang Anan, Fan Shuyuan, Hou Tiejun and so on. *Exploring the mechanism of white and treating diabetic foot based on network pharmacology and molecular docking methods [J]. Journal of Liaoning University of Traditional Chinese Medicine, 2022, 24(05):161-169.DOI:10.13194/j.issn.1673-842x.2022.05.032.*
- [21] Du Yuqing. *To explore the mechanism of the treatment of total saponin and bone marrow stem cells based on miR-146a [D]. Beijing University of Traditional Chinese Medicine, 2021.DOI:10.26973/d.cnki.gbjzu.2021.000204.*
- [22] Guo Zhenhua, Wu Shengji, Shan Nana, etc. *Effect of Panax notoginseng total glycoside on chemotactic protein-1 levels of monocytes in rats with diabetic skin ulcers [J]. Journal of Xinxiang Medical College, 2013, 30 (08): 598-599 + 605.*
- [23] Yu Xin, Dong Huajiang, Shan Nana, etc. *Effect of Panax notoginseng total glycoside on tumor necrosis factor- α levels in rats with diabetic skin ulcers [J]. Journal of Xinxiang Medical College, 2012, 29 (12): 893-895.*
- [24] Xu Hahuan, Dong Huajiang, Shan Nana, etc. *Effect of Panax notoginseng total glycoside on endothelin-1 levels in diabetic skin ulcer rats [J]. Journal of Xinxiang Medical College, 2012, 29 (11): 815-817.*
- [25] Deng Xiaoyan. *Efficacy of 31 cases [J]. Hainan Medical Science, 2010, 21 (01): 73-75.*
- [26] Liddle, Sun Guanwen, Bao Huhe, etc. *Exploring the mechanism of Panax notoginseng in the treatment of diabetic foot based on network pharmacology and molecular docking technology [J]. Traditional Chinese medicine bulletin, 2023, 22(06):46-51+60.DOI:10.14046/j.cnki.zyytb2002.2023.06.006.*
- [27] Thunder, Si Mingming, Zhou Jun, etc. *Experimental study on the effect of gelatin / bletilla gum-micron notoginseng sponge material on wound healing [J]. Clinical Medicine Research and Practice, 2016, 1 (11): 1-5 + 8.*
- [28] Thunder, Yu Jinwen, Zhou Jun, etc. *Effect of gelatin / bletilla gum-notoginseng porous material on wound repair and expression of β -catenin, GSK-3 β , and RSPO-3 expression in rats with diabetic ulcers [J]. Journal of Modern Integrated Traditional Chinese and Western Medicine, 2019, 28 (19): 2057-2062.*
- [29] Thunder, Qu Jian, Zhou Jun, etc. *Molecular mechanism of inflammatory microenvironment of diabetic foot ulcer in rats [J]. Western Medicine, 2020,32 (3): 339-343,349.*
- [30] Jie Yu, Zhang Kang, Zhang Jinmei, etc. *Effect of white and gum / micrometer Panax notoginseng cream-containing serum on LPS-induced nuclear factor- κ B signaling pathway in macrophages [J]. Chinese Journal of Integrated Traditional Chinese and Western Medicine Surgery, 2022, 28 (01): 12-16.*
- [31] Jie Yu, Zhang Jinmei, Zhang Min, etc. *Exploring the mechanism of white and Panax notoginseng on the repair of diabetic foot based on network pharmacology and molecular docking method [J]. Journal of Modern Integrated Traditional Chinese and Western Medicine, 2022, 31 (17): 2400-2409.*