

Research Progress of Traditional Chinese Medicine in the Treatment of Diabetes Complicated with Osteoporosis

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Keywords: Diabetes with Osteoporosis, Traditional Chinese Medicine, Research Progress, Overview

Abstract: Diabetes mellitus combined with osteoporosis (OP) is characterized by hyperglycemia and decreased bone density. The slight decrease of bone density causes systemic progressive bone pain, and the severe one causes brittle fracture of hip and lumbar spine. With the acceleration of aging process, the incidence rate also increases year by year, which increases the medical burden of the society. In recent years, the understanding of TCM and TCM treatment of this disease are more and more abundant, and the clinical effect is remarkable. This article reviews the research progress of TCM treatment of diabetes with osteoporosis in order to better guide the clinical practice.

1. Introduction

In the past three decades, the prevalence of diabetes in China has risen rapidly. Research data show that ^[1] among diabetes patients, nearly half of them are accompanied by sarcopenia and bone mass reduction, and about one-third of them are accompanied by osteoporosis, which is significantly higher than that of normal people. Osteoporosis increases the risk of bone fragility and fracture ^[2]. The most frequently fractured parts are hip, thoracolumbar and distal radius and distal ulna, and the above parts are weight-bearing structures, once a fracture occurs, it will not be able to move freely, restrict the labor force, and deteriorate the quality of life. The serious consequences of fracture make the patients and the society unbearable. The incidence of fracture in patients with diabetes mellitus increases, and because of the presence of diabetes after fracture, it is difficult to heal and the risk of infection increases, which makes the clinical treatment more difficult. As China enters the age of aging, its threat to the life and health of the middle-aged and old people can not be ignored.

At present, western medicine treatment is mainly based on long-term lifestyle intervention such as mood adjustment, diet restriction, moderate exercise and the sun shines, combined with comprehensive treatment such as hypoglycemic drugs, calcium and vitamin drugs, drugs that inhibit bone absorption and drugs that promote bone formation, so as to control blood sugar, promote bone mineralization and inhibit bone absorption. Western medicine treatment requires long-term medication and good cooperation between patients and medical personnel. Therefore, some patients have poor dependence and poor efficacy. In addition, western medicine has many adverse reactions,

and some patients refuse to take it. However, at present, there is no drug that can completely prevent or cure. Therefore, exploring effective and long-term treatment has become a clinical problem that needs to be solved, and it is extremely critical to improve the quality of life of patients. Traditional Chinese medicine has a long history, and the theory of medicine and food homology also reflects the universality and low toxicity of traditional Chinese medicine in treating diseases. Traditional Chinese medicine starts from the whole. The characteristics of syndrome differentiation and treatment, address both symptoms and root causes, internal and external considerations, and regulation of visceral functions determine that TCM treatment not only improves symptoms, but also has the advantages of regulating the body's overall condition, enhancing immunity, accurate efficacy, and regulating emotions. The time of taking medicine is relatively free, the price is relatively cheap, the patient's dependence is good, the adverse reactions are less, and the acceptance is also increased.

2. Disease Name, Etiology and Pathogenesis

There is no clear record of "diabetes with osteoporosis" in the ancient Chinese medical books, and there is no disease name completely consistent with it. Now most doctors think that this disease belongs to the category of "Xiao Ke" combined with "bone paralysis" ^[3]. The disease is mainly deficiency, and the disease is located in the bone, but the incidence is closely related to the liver, spleen and kidney ^[4]. According to traditional Chinese medicine, in normal physiological state, the five viscera and six viscera perform their respective functions, the physiological function of the body is normal, the Qi and blood are abundant, the muscles are full, and the muscles and bones are favorable. The spleen is the foundation of the day after tomorrow. It controls the four limbs and muscle. It is the source of qi and blood production. The generated essence, Qi and blood nourish the limbs and bones, and replenish the kidney essence; the kidney stores essence and generates marrow, and the marrow nourishes bone. The essence in the kidney is sufficient to nourish the bone marrow, the bone is strong, the spleen function is normal, and the muscles of the limbs are strong and flexible. The liver stores blood and governs the tendons, while the kidney stores essence and governs the bones. The sufficiency of liver blood depends on the gasification of kidney essence, while the sufficiency of kidney essence also needs the nourishment of liver blood. The two interact to jointly nourish the tendons and bones, and the bones are strong. In pathological state, various factors make the viscera dysfunctional, Yin and Yang imbalance of the body. Irregular diet, emotional disorder, excessive overwork and other causes spleen and stomach injury, the transformation and transfer of fine substances are affected. The muscles of the limbs are not fully nourished, and the muscles are thin, which further affects the normal function of the bones. The muscles of the limbs are not fully nourished, and the muscles are thin, thus affecting the normal function of the bones. The spleen function is damaged, the generation of Qi and blood is lacking, and the innate essence in the kidney cannot be fully nurtured, resulting in the deficiency of kidney essence. Therefore, kidney essence cannot produce a bone marrow, which can not nourish bone to maintain the physiological function of bone, bone weakness, fragility and easy to break, causing bone paralysis. Old age, weak body, kidney deficiency and deficiency of kidney essence lead to deficiency of liver yin and liver blood. The two cause and effect each other, so the tendons cannot be fed, the bone marrow cannot be nourished, the tendons and bones are damaged, and the tendons of the limbs are lack of nourishment, and the limbs are weak and even lose their functions. Blood stasis runs through Xiao Ke, which not only affects the patency of qi, hinders the operation of Qi and blood, causes unbearable bone pain, but also affects the generation of new blood, make the musculoskeletal nutrition insufficient, and affect its function ^[5]. Chu Shufang^[6] and others believe that the etiology and pathogenesis of "Xiao Ke" complicated with "bone paralysis" are yin

deficiency and internal heat of Xiao Ke, the course of disease is prolonged, and the kidney qi and kidney essence are insufficient over a long period of time, so bone growth, development and function are affected, and eventually the bone loss and becomes "bone paralysis". Liu Juntong^[7] and others collated the academic ideas of various doctors to conclude that splenic function damage, deficiency of Qi and blood, kidney weakness, deficiency of essence, deficiency of liver deficiency and loss of blood, phlegm and blood stasis as the etiological mechanisms. Chen Guoxun^[8] and others believe that the essence of the disease is deficiency syndrome, with the dysfunction of the spleen and kidney two organs as the cause and the stasis blood blocking collaterals as the symptom. Fang Zhaohui^[9] believed that the etiology and mechanism of this disease was based on deficiency of kidney essence, related to liver and spleen, insufficiency of liver and kidney essence and blood, and lack of nutrition of muscles, bones and blood vessels, resulting in limb and joint pain and difficulty in flexion and extension. Some experts^[10] believe that the main pathogenesis of this disease is the deficiency of Yin and Yang of the kidney and the stasis of blood collaterals.

3. TCM Treatment

3.1. Single Medicine and Active Ingredients

3.1.1. *Drynaria Rhizome*

Drynaria Rhizome is a commonly used medicine in orthopedics and traumatology. It is bitter and warm in nature and belongs to the liver and kidney meridians. It has the effects of healing pain, tonifying the kidney and strengthening the bone, eliminating wind and removing spots. Doctors in the past dynasties have been widely used to treat low back pain caused by kidney deficiency, muscle and bone damage caused by trauma, bone weakness and other diseases, and the therapeutic effect is obvious. Jiang et al.^[11] verified that the active ingredients of *Drynaria* can exert the therapeutic effect of anti OP through metabolic pathways such as arachidonic acid metabolism and lipid metabolism. Modern studies have found^[12] that *Drynaria* and its active components share common gene and protein targets with fractures, and have strong binding efficiency with key targets. They play the role of fracture repair through multiple signaling pathways such as MAPK, PI3K/Akt, RAS and VEGF. Among them, MAPK, PI3K/Akt signaling pathways are involved in osteoblast formation, Ras signaling pathway is involved in enhancing the migration of mesenchymal stromal cells, and VEGF signaling pathway is related to angiogenesis. Zhao Dun^[13] et al. Found that the total flavonoids of *Rhizoma Drynariae* pass through PI3K/Akt/HIF-1 α /VEGF signaling pathway can regulate osteogenesis and angiogenesis in rats with tibial bone defect, and it is dose-dependent. In addition, the combination of total flavonoids of *Drynaria* and calcium carbonate can improve the repair of bone loss and trabecular fracture, prevent the reduction of collagen fibers in the femoral tissue of ovariectomized rats, regenerate new bone or cartilage tissue, and activate Wnt3a/ β -Catenin pathway, alleviating the loss of bone mass^[14]. In short, *Drynaria* and its effective active ingredients can regulate bone metabolism through multiple signal pathways, strengthen bone formation, increase bone strength, weaken bone absorption, maintain the balance of bone remodeling cycle, and have a good anti osteoporosis effect.

3.1.2. *Epimedium*

Epimedium was first recorded in Shennong materia medica. It belongs to the medicine of tonifying kidney and warming yang in traditional Chinese medicine. It is sweet and spicy in taste, warm in nature, and belongs to the liver and kidney channels and collaterals. It is often used to treat various syndromes caused by kidney yang deficiency. Wu^[15] and others found that 62 of the unique

targets of Epimedium overlapped with those of osteoporosis through systematic bioinformatics research, and epimedium has good binding activity to key targets. These targets have regulatory effects on cell cycle and cell senescence, suggesting that Epimedium has the characteristics of multiple targets and multiple pathways in the treatment of osteoporosis. Cell and animal experiments have found that a variety of effective extracts of Epimedium have good anti osteoporosis effects in the bone remodeling cycle through different signal pathways, among which the total flavonoids of epimedium and icariin are mostly studied^[16]. Wang Xiaofei et al.^[17] found that the total flavonoids of Epimedium can regulate bone metabolism and enhance bone density in rats, which may be related to stimulating the proliferation and osteogenic differentiation of osteoblasts and inhibiting bone resorption by affecting Notch1, smad4 and smad7 pathway proteins. Moreover, the structure of flavonoids in Epimedium has estrogen like effect, which can avoid adverse reactions and effectively prevent and treat osteoporosis. Bone marrow mesenchymal stem cells are pluripotent stem cells, which can differentiate into bone cells, chondrocytes, adipocytes, etc. after differentiation, the balance between various cells is destroyed, resulting in various diseases, such as osteoporosis caused by the imbalance of differentiation between bone cells and adipocytes^[18]. Wei et al.^[19] found that a certain concentration of icariin can promote the proliferation of bone marrow mesenchymal stem cells and the expression of osteogenic genes, and its mechanism may be related to the activation of $Er\ \alpha$ And Wnt/ β - Catenin signaling pathway. Clinical studies have found^[20,21] that the extract of Epimedium can significantly reduce the levels of alkaline phosphatase and Ca^{2+} in the serum of patients with osteoporosis, and can promote calcium deposition and calcium influx. On the basis of oral Chinese patent medicine, the combination of epimedium can significantly increase the bone density of the femoral neck and lumbar spine, regulate the bone metabolism index, and alleviate the pain symptoms of osteoporosis. In addition, the content of zinc, manganese and other trace elements in Epimedium is high, which can promote the growth of bone and is beneficial to the rehabilitation of osteoporosis^[22].

3.1.3. Fructus Psoraleae

Fructus Psoraleae, which belongs to the kidney and spleen channels and collaterals, has the effects of Tonifying the kidney and strengthening yang, consolidating the essence and shrinking urine, warming the spleen, treating diarrhea, receiving Qi and relieving asthma. It is clinically used to treat various diseases caused by kidney yang deficiency. Pharmacological studies have found that isopsoralen and psoralen, as the main active components of Fructus Psoraleae, have obvious anti osteoporosis and anti-inflammatory effects. Isopsoralen has certain intervention effect on osteoporosis caused by various reasons, such as estrogen reduction, vitamin A deficiency, oxidative stress reaction and osteoporosis caused by diabetes^[23]. Isopsoralen can increase the content of osteocalcin and tartaric acid phosphatase in serum of ovariectomized rats, and improve bone quality and bone strength by regulating Runx 2 / MMP13 signaling pathway in bone tissue of osteoporosis rats^[24,25]. Chai^[26] et al found that psoralen and subtilisol can improve the differentiation and bone resorption of mouse osteoclasts induced by M-CSF and RANKL in vitro, and the intrinsic mechanism may be related to the inhibition of Akt and AP-1 pathway activation. Wang Jian^[27] also found that psoralen can activate Wnt / β -Catenin signaling pathway regulates some indexes of bone metabolism, such as reducing the level of osteocalcin, improving the bone density of osteoporosis rats, increasing the thickness and number of trabeculae in bone tissue, and reducing the separation of trabeculae. Psoralen can significantly inhibit the expression of marker genes of osteoclast formation such as trap, cathepsin K and Oscar, and affect the formation of osteoclasts. At the same time, psoralen can also reduce the expression of c-fos and NFATc1 transcription factors and slow down the degradation of bone^[28].

3.2. Chinese Herbal Compound

Wei Ruoyu et al. [29] found that Qishu Tanggu Decoction can improve blood glucose level, reduce bone pain and increase bone density without obvious toxic and side effects. It has strong clinical practicability and has obvious therapeutic effect on postmenopausal diabetes patients with OP. Zhang Zhenhua [30] et al found that on the basis of improving lifestyle, drug control of blood sugar and taking calcitriol to promote bone mineralization, diabetes patients with OP were treated with Bushen Jianpi Huoxue Decoction, which could significantly reduce blood sugar and osteocalcin levels, increase blood calcium and bone alkaline phosphatase levels, and increase bone strength and quality. The above treatment effects were better than the basic treatment; in addition, based on the molecular level research findings [31], Bushen Jianpi Huoxue Decoction can activate Wnt signaling pathway and inhibit NF- κ B signaling pathway can improve diabetes with Op. Lou Yan [32] et al. Studied the mechanism of Qi Kui granule (composed of raw Astragalus membranaceus, prepared Polygonum multiflorum and Huangshu sunflower) in the treatment of type 2 diabetes complicated with osteoporosis, and found that Qi Kui granule can reduce blood glucose and increase bone density in model rats, significantly induce mesenchymal stem cells (MSCs) to differentiate into osteogenic direction, promote the formation of calcium nodules, and reduce the differentiation of MSCs into adipose direction. The effect of intervention on MSCs is obvious. At the same time, it was confirmed by ELISA that Qikui granule could significantly increase the expression level of osteocalcin and bone alkaline phosphatase, the key proteins of osteogenesis induction. In addition, MTT test confirmed that Qikui granule could significantly improve the passage and proliferation activity of MSCs and maintain the cell stemness. Lu [33] et al. found that in Liuwei Dihuang pills the key active ingredients such as β -sitosterol, stigmasterol, diosgenin and kaempferone can promote insulin secretion, increase estrogen level and stimulate angiogenesis by acting on corresponding targets. Li et al. [34] confirmed that Zishen Jiangtang pill can improve the blood glucose level of rats induced by STZ, prevent the changes of fasting blood glucose and fasting insulin to a certain extent, inhibit bone calcium, serum bone alkaline phosphatase, osteocalcin and other bone metabolism indexes, and significantly change the metabolism of blood and urine levels, suggesting that this prescription can treat diabetes with OP from metabolomics, glucose and bone metabolism; another study found that [35] Zishen Jiangtang pill may reduce the expression of inflammatory factors, reduce the activation of corresponding pathways, affect the differentiation of osteoclasts, and weaken bone resorption.

4. Conclusion

Traditional Chinese medicine is guided by the concept of integrity and syndrome differentiation, based on the viscera and meridians, and characterized by the combination of four diagnoses, both symptoms and signs, and both internal and external treatment. With the development and progress of technology and the convergence and integration of Chinese and Western medicine, the understanding and treatment of diseases in traditional Chinese medicine are no longer limited to seeing, hearing, asking, and making prescriptions. It has moved from the macro world to the micro world, from the subjective and fuzzy to the objective and standard, from the medicinal materials to the molecular mechanism, and from the whole to the therapeutic target and signal pathway. This is the ancient Chinese medicine and modern western medicine, the experience of the predecessors and the exploration of the future generations, the intersection of primitive methods and advanced technology. In recent years, many doctors have explored the etiology and pathogenesis of diabetes combined with osteoporosis from multiple angles and levels, and have achieved certain research results in syndrome differentiation, treatment and treatment methods, in the prevention and treatment of diabetes complicated with osteoporosis, tonifying the kidney is the main thing,

regulating the liver and spleen is the secondary, and promoting blood circulation, unblocking the collaterals and relieving pain throughout. It is found that TCM treatment can improve the symptoms of patients with diabetes, regulate glucose metabolism, improve bone metabolism, reduce the expression of inflammatory factors, increase bone density, enhance bone strength, reduce bone pain, reduce the adverse effects of some Western medicines, regulate emotion and enhance immunity. The patients have high acceptance and good dependence. Cooperation with western medicine can improve the clinical efficacy and achieve certain clinical effects. However, the current study is short-term, small sample, and the region is also limited. Therefore, the study of TCM pathogenesis of this disease is not perfect, and there is no unified standard for syndrome differentiation and prescription of TCM treatment. Most of the studies on the treatment of this disease by traditional Chinese medicine focus on the role and mechanism of a single component of traditional Chinese medicine, which is inconsistent with the overall concept of traditional Chinese medicine. Most of the studies on traditional Chinese medicine are focused on the effects on bone mineral density, blood sugar and some bone metabolism indexes of the subjects, while the studies on cellular molecules, proteins and pathways are relatively lacking. Therefore, the mechanism and metabolic mechanism of the treatment of this disease by Chinese herbal compound are not clear, there is no unified standard for clinical promotion. In addition, most of the current studies are internal treatments, and there are few clinical and experimental studies on external treatments such as acupuncture and acupoint application. However, acupuncture and acupoint application have a certain effect on diabetes complicated with osteoporosis, and the mechanism is still unclear.

In future research, we can use advanced technologies such as metabolomics and network pharmacology to study the mechanism of action of Chinese herbal compound on the disease at the molecular level and cell level, and design multi center and large sample experimental research, to sum up and improve the etiology and pathogenesis of this disease, so as to make the syndrome differentiation and classification and prescription medicine more unified, so as to combine theory and practice, clinical and basic, internal and external treatment, excavate the advantages of traditional Chinese medicine, find a new entry point for traditional Chinese medicine to prevent and treat diabetes with osteoporosis, provide more objective basis for clinical treatment, and promote the development of traditional Chinese medicine.

References

- [1] Liang, Yanhong. *Effect of liraglutide plus alfacalcidol on BALP, OPG, apelin-13 levels in diabetic patients with osteoporosis [J]. Jilin Medical Science*, 2022, 43 (07): 1891-1893.
- [2] Ying Dawen, Liu Fang. *Development of a correlation between diabetes and osteoporosis [J]. Practical preventive medicine*, 2015, 22 (10): 1275-1278.
- [3] Xu Wenxia, Shu Yiqiong. *Therapeutic advances in Chinese medicine for diabetic osteoporosis [J]. Journal of clinical Chinese medicine*, 2018, 30 (12): 2322-2324.
- [4] Shi Fanfan, Zhao Jirong, Ma Tong, et al. *The mechanism of TCM treatment of diabetes osteoporosis based on "Spleen Kidney Theory" [J]. Shaanxi traditional Chinese medicine*, 2022,43 (05): 604-607.
- [5] Jin Yixi, Feng Xingzhong. *Discussion on the pathogenesis and treatment of osteoporosis in elderly patients with diabetes [J]. Guide to traditional Chinese medicine*, 2015,21 (16): 96-99.
- [6] Chu Shufang, Zhao hengxia, Liu Deliang, et al. *TCM prevention and treatment of type 2 diabetes complicated with osteoporosis [J] World traditional Chinese medicine*, 2018,13 (7): 1804-1808.
- [7] Liu juntong, Yang Yufeng, Cao Bin, et al. *Research on theoretical framework of TCM etiology and pathogenesis of diabetes osteoporosis [J]. Journal of Liaoning University of traditional Chinese medicine*, 2019, 21 (06): 110-113.
- [8] Chen Guoxun, Wang Mingchao, Xu Changpeng, et al. *Research progress of traditional Chinese medicine in treating type 2 diabetes with osteoporosis [J]. Hebei Traditional Chinese medicine*, 2017,39 (6): 941-944.
- [9] Wang Sihai, Fang Zhaohui, Zhao Jindong. *Fang Zhaohui's experience in treating type 2 diabetes with osteoporosis [J]. Chinese Journal of clinical health care*. 2020, 05: 679-682.
- [10] Liu Ju, Mei qunchao, Zhang Linying, et al. *Effect of Bushen Huoxue Recipe on bone metabolic markers and bone mineral density in elderly patients with type 2 diabetes complicated with osteoporosis [J]. Journal of traditional*

Chinese medicine, 2018,33 (07): 1226-1229.

- [11] Yi-chang Jiang et al. UPLC-MS metabolomics method provides valuable insights into the effect and underlying mechanisms of *Rhizoma Drynariae* protecting osteoporosis [J]. *Journal of Chromatography B*, 2020, 1152.
- [12] Lin Haixiong, Wang Xiaotong, Wang Ligang et al. *Drynariae Rhizoma* Identified the Synergistic Mechanism of for Treating Fracture Based on Network Pharmacology. [J]. *Evid Based Complement Alternat Med*, 2019, 2019: 7342635.
- [13] Zhao Dun, Fang bin, Yi Chunzhi, et al. Effects of total flavonoids of *Drynaria* on bone tissue remodeling, bone morphogenetic protein 2, vascular endothelial growth factor and CD31 [J]. *China tissue engineering research*, 2022,26 (29): 4638-4642.
- [14] Hu Yimei, Mu Panyun, Ma Xu et al. *Rhizoma drynariae* total flavonoids combined with calcium carbonate ameliorates bone loss in experimentally induced Osteoporosis in rats via the regulation of *Wnt3a/β-catenin* pathway. [J]. *J Orthop Surg Res*, 2021, 16: 702.
- [15] Wu Keliang, Han Linjing, Zhao Ying et al. Deciphering the molecular mechanism underlying the effects of epimedium on osteoporosis through system bioinformatic approach. [J]. *Medicine (Baltimore)*, 2022, 101: e29844.
- [16] Liu Yaoyao, Liu Xiangning, Tian Yinping, et al. Research progress of pharmacological mechanism of *Icariin* on skeletal system [J]. *New Chinese medicine and clinical pharmacology*, 2020,31 (12): 1516-1520.
- [17] Wang Xiaofei, Li Jingjing. Effect of total flavonoids of *Epimedium* on the expression of notch and Smads pathway proteins in aged osteoporosis rats [J]. *Chinese Journal of orthopedics and traumatology*, 2019,27 (02): 1-5.
- [18] Huang Di, Zi Hui. Research progress of epimedium and its active ingredients in the prevention and treatment of osteoporosis [J]. *Journal of practical Chinese medicine*, 2022,36 (06): 54-57.
- [19] Wei QiuShi, He MinCong, Chen MeiHui et al. *Icariin* stimulates osteogenic differentiation of rat bone marrow stromal stem cells by increasing TAZ expression. [J]. *Biomed Pharmacother*, 2017, 91: 581-589.
- [20] Liu Haiyan. Clinical observation on the treatment of osteoporosis with *Epimedium* [J]. *Inner Mongolia traditional Chinese medicine*, 2019,38 (01): 16-17.
- [21] Tu Yan, Xiong Lina, Liu Xiangjie, et al. Observation on the clinical effect of *Epimedium* combined with *danxiankanggu* capsule in treating senile osteoporosis [J]. *Anhui medicine*, 2018,22 (09): 1814-1817.
- [22] Liu Bo, Zhang Rui, Xu Peng, et al. Effect of *Epimedium* on osteoporosis in ovariectomized rats [J]. *Chinese Journal of experimental formulary*, 2013, 19 (07): 178-181.
- [23] Yang Kuo, Gao Rong, Shen Baode, et al. Research Progress on pharmacological effects and mechanism of liver and kidney injury of isopsoralen [J]. *evaluation and analysis of drug use in Chinese hospitals*, 2021, 21 (11): 1399-1403+1408.
- [24] Liu Rui, Yang Xiaojie, Li Xin, et al. Study on the effect of isopsoralen on bone metabolism in ovariectomized rats [J]. *Chinese Journal of osteoporosis*, 2017,23 (06): 807-811.
- [25] Shang Yanchun, Zhang Haiying, Chai Weiwei. Discussion on the effect of isopsoralen on improving bone metabolism in osteoporosis rats [J]. *Chinese Journal of osteoporosis*, 2021,27 (02): 220-224.
- [26] Chai Lijuan, Zhou Kun, Wang Shaoxia et al. *Psoralen* and *Bakuchiol* Ameliorate M-CSF Plus RANKL-Induced Osteoclast Differentiation and Bone Resorption Via Inhibition of AKT and AP-1 Pathways in Vitro. [J]. *Cell Physiol Biochem*, 2018, 48: 2123-2133.
- [27] Wang Jian, Zhang Chi. Based on *Wnt/β*- Study on the effect of psoralen on osteoporosis rats through the catenin pathway [J/OL]. *World traditional Chinese medicine*: 1-6 [2022-08-09].
- [28] Kong Lingbo, Ma Rui, Yang Xiaobin et al. *Psoralidin* suppresses osteoclastogenesis in BMMs and attenuates LPS-mediated osteolysis by inhibiting inflammatory cytokines. [J]. *Int Immunopharmacol*, 2017, 51: 31-39.
- [29] Wei Ruoyu, Zhang Zengjian. Clinical observation of *Qishu Tanggu* Decoction in treating postmenopausal women with diabetes and osteoporosis [J]. *New world of diabetes*, 2020, 23 (07): 63-65.
- [30] Zhang Zhenhua, Rong Fang, Li Fang, et al. Study on the application of *Bushen Jianpi Huoxue* Decoction in diabetes patients with osteoporosis [J]. *Electronic Journal of modern medicine and health research*, 2022,6 (03): 90-93.
- [31] Zhang Yongqing, Liu Mingming, Li Haisheng et al. Traditional Chinese medicine *Bushen-Jianpi-Huoxue* decoction prevents diabetic osteoporosis in rats via *Wnt* and nuclear factor-kappa B signaling pathways. [J]. *Int J Rheum Dis*, 2017, 20: 941-948.
- [32] Lou Yan, Yu Xu, Sun Xinyi, et al. Experimental study on the intervention of *Qikui Granule* on type 2 diabetes rats with osteoporosis [J]. *Western traditional Chinese medicine*, 2022, 35 (06): 25-28.
- [33] Lu Zhaoqi, Huang Minling, Lin Haixiong et al. Network pharmacology and molecular docking approach to elucidate the mechanisms of *Liuwei Dihuang* pill in diabetic osteoporosis. [J]. *J Orthop Surg Res*, 2022, 17: 314.
- [34] Li Huilin, Chu Shufang, Zhao Hengxia et al. Effect of *Zishen Jiangtang* Pill, a Chinese Herbal Product, on Rats with Diabetic Osteoporosis. [J]. *Evid Based Complement Alternat Med*, 2018, 2018: 7201914.
- [35] Lian Lirong, Chu Shufang, Liang Jiachang, et al. Exploration on the mechanism of *Zishen Jiangtang* pill in treating osteoporosis in diabetes [J]. *Chinese Journal of osteoporosis*, 2022, 28 (04): 551-557.