ISSN 2706-6819 Vol.8, Issue 1: 1-13, DOI: 10.25236/IJFM.2026.080101

Exploration on the Active Ingredients and Pharmacological Mechanisms of Bushen Zhuanggu Granules in Treating Osteoporosis Based on Network Pharmacology

Li Wenyang[1,a], Zhang Yu[2,b,*]

[1]*Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, 610075, China*
[2]*Chengdu First People's Hospital, Chengdu, Sichuan, 610041, China*
[a]*3279401531@qq.com,* [b]*52032849@qq.com*
[*]*Corresponding author*

Abstract: *This study aimed to systematically explore the effective active ingredients, key targets, and potential molecular mechanisms of Bushen Zhuanggu Granules (BSZGP) in the treatment of osteoporosis (OP) using network pharmacology. Active ingredients and corresponding targets of BSZGP were screened from the TCMSP database, while OP-related targets were obtained from the GeneCards database. A protein-protein interaction network was constructed using the STRING database to identify key targets, followed by GO and KEGG pathway enrichment analysis via the DAVID platform. Resultly, the findings suggest that BSZGP may primarily exert its effects through core active ingredients such as quercetin, luteolin, kaempferol, and beta-sitosterol, acting on key targets including TNF, IL6, AKT1, and HIF1A. These interactions likely regulate pathways such as the TNF signaling pathway, contributing to anti-inflammatory and antioxidant effects. In conclusion, this study preliminarily reveals that BSZGP treats OP through a synergistic mechanism involving "multiple components, multiple targets, and multiple pathways," providing a theoretical basis for further experimental validation and clinical application.*

Keywords: *Osteoporosis, Bushen Zhuanggu Granules, Network Pharmacology, Mechanism of Action*

1. Introduction

Osteoporosis (OP) is a systemic skeletal disease characterized by reduced bone mass and deterioration of bone microarchitecture, leading to increased bone fragility and a significantly heightened risk of fractures [1]. Its clinical manifestations primarily include bone pain, spinal deformities, and fragility fractures, with chronic low back pain being particularly common [2]. Epidemiological surveys indicate a strong correlation between the prevalence of OP in China and age: it is approximately 15%–50% in individuals under 50 years old, rising to about 56% in those over 60 [3]. The overall prevalence ranges from 6.6% to 19.3%, with an average of around 13% [4]. The pain and functional impairment caused by osteoporosis and its resultant fractures severely affect patients' quality of life, making it a significant chronic disease threatening the health of middle-aged and elderly populations [5]. Currently, modern medicine primarily employs calcium and vitamin D supplementation as a foundation for treatment. This is combined with interventions targeting bone resorption and formation processes, utilizing drugs that inhibit or promote related mechanisms for anti-osteoporotic therapy [6]. Although these methods show certain efficacy, they are still plagued by issues such as noticeable adverse drug reactions and poor long-term patient compliance. In contrast, Traditional Chinese Medicine (TCM), with its multi-component, multi-target, and multi-system regulatory effects, demonstrates significant advantages in treating osteoporosis.

In TCM theory, osteoporosis falls under the categories of "bone wilting" (Gu Wei) and "bone desiccation" (Gu Ku). Its core pathogenesis is attributed to deficiency of the liver and kidney. The kidney, considered the congenital foundation, governs bones and generates marrow. The liver governs tendons, stores blood, and shares a common source with the kidney, enabling the mutual transformation of essence and blood. For women, who are said to "take the liver as their congenital foundation," the postmenopausal period involves liver-kidney yin deficiency. The exhaustion of Tian Gui (a TCM concept roughly analogous to reproductive essence) leads to depletion of essence and blood, which are then insufficient

ISSN 2706-6819 Vol.8, Issue 1: 1-13, DOI: 10.25236/IJFM.2026.080101

to nourish the bone marrow. Over time, this results in diminished marrow and desiccated bones, manifesting as this disease. Therefore, the fundamental treatment principle is to tonify the liver and kidney, replenish essence, and strengthen bones.

Bushen Zhuanggu Granules (BSZGP) is an empirical formula for osteoporosis treatment developed by the orthopedic research team at Chengdu Hospital of Integrated Traditional Chinese and Western Medicine. Formulated under the guidance of TCM theory and based on years of clinical practice, it consists of eight herbal medicines: Taxilli Herba (Sangjisheng), Angelicae Pubescentis Radix (Duhuo), Cinnamomi Ramulus (Guizhi), Eucommiae Cortex (Duzhong), Dipsaci Radix (Xuduan), Drynariae Rhizoma (Gusubu), Epimedii Folium (Yinyanghuo), and Alpiniae Oxyphyllae Fructus (Yizhiren). Preliminary clinical application has demonstrated its promising therapeutic potential. However, due to the complex composition of this formula and its characteristic multi-component, multi-target, multi-pathway synergistic actions, the specific pharmacodynamic material basis and systematic molecular mechanisms underlying its treatment of osteoporosis remain incompletely understood. Network pharmacology, integrating multidisciplinary technical approaches, can systematically reveal the potential mechanisms of drug intervention in diseases. It provides an effective strategy for elucidating the active components, targets, and related signaling pathways of TCM formulas. Therefore, this study intends to employ network pharmacology methods to construct a "component-target-pathway-disease" interaction network. This will enable the systematic prediction and analysis of the potential active ingredients and mechanistic pathways of BSZGP in treating osteoporosis, aiming to provide a scientific basis for the clinical application and subsequent experimental research of this formula.

2. Materials and Methods

2.1. Collection of BSZGP Active Ingredients and Target Prediction

The active ingredients and corresponding targets for the eight herbal medicines composing BSZGP (Taxilli Herba [Sangjisheng], Angelicae Pubescentis Radix [Duhuo], Cinnamomi Ramulus [Guizhi], Eucommiae Cortex [Duzhong], Dipsaci Radix [Xuduan], Drynariae Rhizoma [Gusubu], Epimedii Folium [Yinyanghuo], and Alpiniae Oxyphyllae Fructus [Yizhiren]) were predicted using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP: http://tcmspw.com/tcmsp.php). Effective active ingredients and targets were screened based on the criteria of oral bioavailability (OB) $\geq$ 30% and drug-likeness (DL) $\geq$ 0.18. All obtained compound targets were integrated and deduplicated, and then the target gene names were standardized using the Uniprot database (https://www.uniprot.org/).

2.2. Acquisition of OP-Related Targets

The GeneCards database (https://www.genecards.org/) was utilized to comprehensively search for disease-related targets using the keyword "Osteoporosis". Targets with a relevance score equal to or greater than the median value were selected as disease-related targets.

2.3. Acquisition of Drug-Disease Intersection Targets

The obtained BSZGP component targets and disease targets were cross-mapped. Intersection target genes were identified by using the Jvenn online platform (https://www.bioinformatics.com.cn/static/others/jvenn_en/example.html).

2.4. Construction of the Herb-Active Ingredient-Disease-Target Network and Screening of Key Active Ingredients

Files named "network.xlsx" and "type.xlsx", containing the drug components and the aforementioned intersection targets, were created. These files were imported into Cytoscape 3.10.1 to construct a herb-active ingredient-disease-target network. Network topology analysis was performed, and the key active ingredients of BSZGP for treating osteoporosis were screened based on their degree values.

2.5. Construction of Protein-Protein Interaction (PPI) Network and Screening of Key Targets

To further investigate the protein-protein interactions involved in BSZGP's treatment of osteoporosis, the intersection genes of the drug's core components and the disease were uploaded to the STRING

ISSN 2706-6819 Vol.8, Issue 1: 1-13, DOI: 10.25236/IJFM.2026.080101

database (https://string-db.org/) to construct a PPI network. The species was set to "Homo sapiens", the minimum interaction score was set to 0.4, and discrete nodes were hidden in the interaction network while keeping other parameters at default settings. The results were saved in TSV format. The TSV file was imported into Cytoscape 3.10.1, and the CytoHubba plugin was used to screen genes based on three algorithms: degree, closeness, and betweenness. Finally, the intersection of the results from these three algorithms was taken to obtain the core targets for the drug's treatment of the disease.

2.6. GO and KEGG Pathway Enrichment Analysis

To gain deeper insights into the potential mechanism of BSZGP in treating osteoporosis, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed on the intersection targets of the drug's action targets and the disease-related targets. The intersection targets were uploaded to the DAVID database (https://david.ncifcrf.gov/summary.jsp) for visualization. The gene identifier was set to OFFICIAL_GENE_SYMBOL, and the species was specified as Homo Sapiens. GO functional annotation was conducted from three aspects: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF), describing the roles of the target proteins in gene function concerning the drug's treatment of the disease. The top 10 terms for BP, CC, and MF were selected based on p-values. Additionally, the top 20 KEGG pathway entries related to the disease were selected as key signaling pathways for the drug's treatment, based on p-values, to predict the drug's mechanism of action. Finally, visualization analysis was performed using a bioinformatics online platform (http://www.bioinformatics.com.cn/).

3. Results

3.1. Collection of BSZGP Active Ingredients and Prediction of Drug and Disease Targets

A total of 77 active compounds were screened using the TCMSP database. After standardizing the target gene names via the Uniprot database, 231 potential drug targets were obtained. A search of the GeneCards database identified 3655 osteoporosis-related targets. An intersection analysis of drug-disease targets revealed 142 common targets (Figure 1), suggesting their potential role as therapeutic targets for BSZGP in treating osteoporosis.

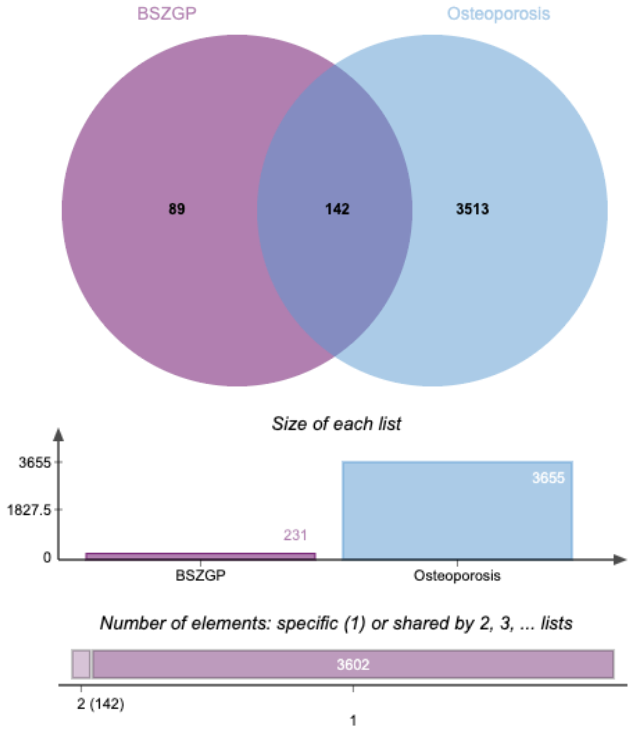


Figure 1: Venn diagram of intersecting targets between drugs and diseases

ISSN 2706-6819 Vol.8, Issue 1: 1-13, DOI: 10.25236/IJFM.2026.080101

3.2. Construction of the "Herb-Active Ingredient-Disease-Target" Network and Identification of Key Active Ingredients

Based on the correspondence between active ingredients and intersection targets, an interaction network comprising 229 nodes and 1246 edges was constructed using Cytoscape 3.10.1 (Figure 2). Network topology analysis revealed that key components with a Degree value ≥ 21 included: quercetin, luteolin, kaempferol, beta-sitosterol, and naringenin. These components are likely to function as pivotal bioactive components in the treatment of osteoporosis with BSZGP.

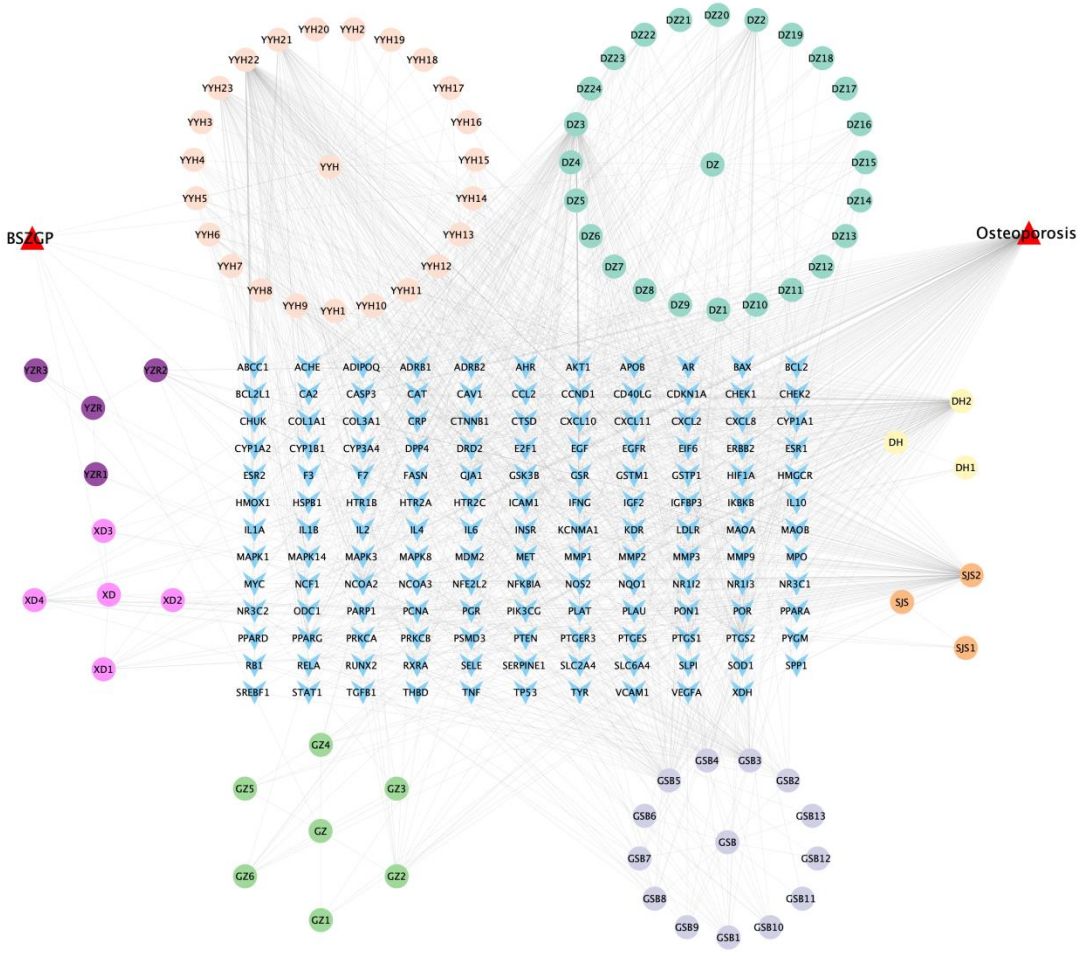


Figure 2: "Traditional Chinese Medicine–Active Component–Disease–Target" network

Note: In the figure, "triangles" represent herbs and the disease, "circles" represent the various herbal components, and "diamonds" represent the corresponding targets of the components

3.3. Construction of the Protein-Protein Interaction (PPI) Network and Screening of Key Targets

A preliminary PPI network was constructed using the 142 intersection targets via the STRING database (Figure 3). Visualization with Cytoscape yielded an interaction diagram containing 142 nodes and 3274 edges. The CytoHubba plugin within Cytoscape was then employed to perform degree, closeness, and betweenness centrality calculations. This analysis identified the top 10 targets based on each metric: degree (Figure 4), closeness (Figure 5), and betweenness (Figure 6). The intersection of these three sets of targets yielded 9 core targets: TP53, TNF, IL1B, EGFR, IL6, AKT1, HIF1A, ESR1, and PTGS2 (Figure 7). These hub genes are predicted to play pivotal regulatory roles within the network.

ISSN 2706-6819 Vol.8, Issue 1: 1-13, DOI: 10.25236/IJFM.2026.080101

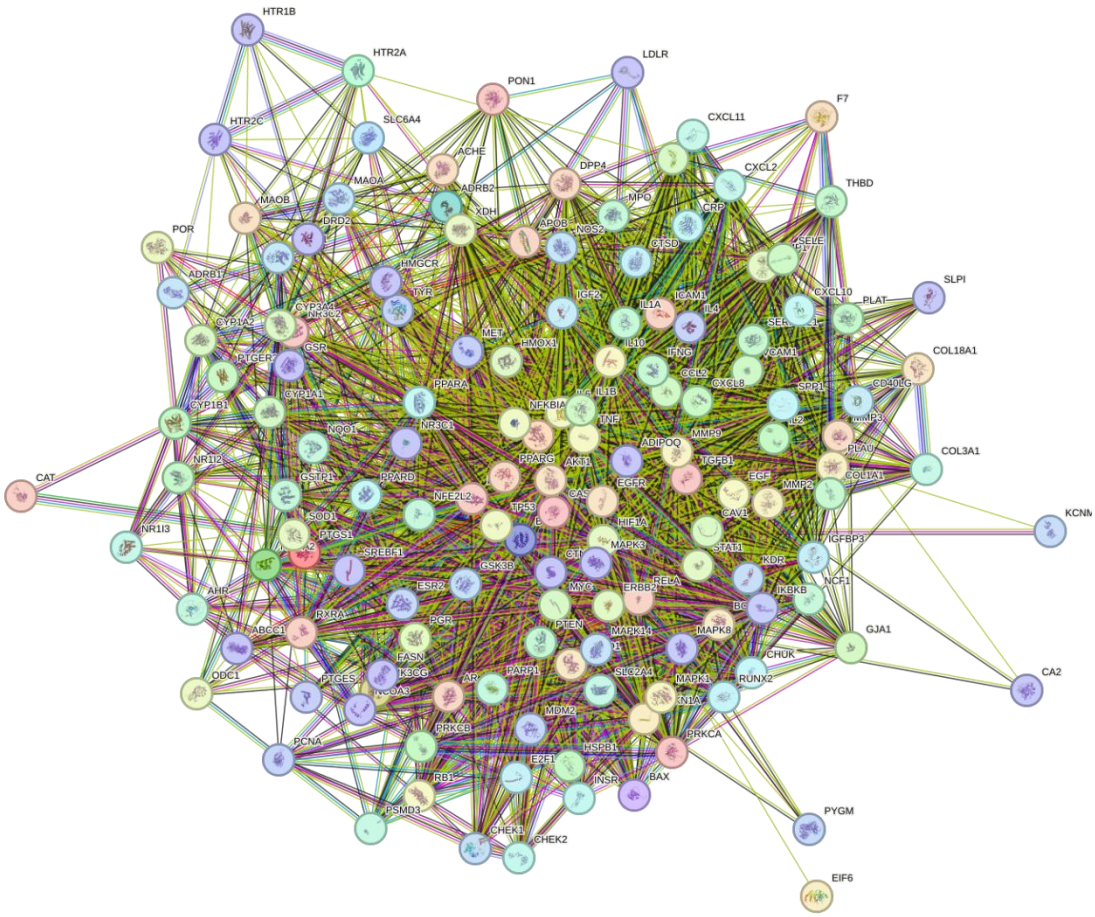


Figure 3: STRING Preliminary Protein-Protein Interaction Network

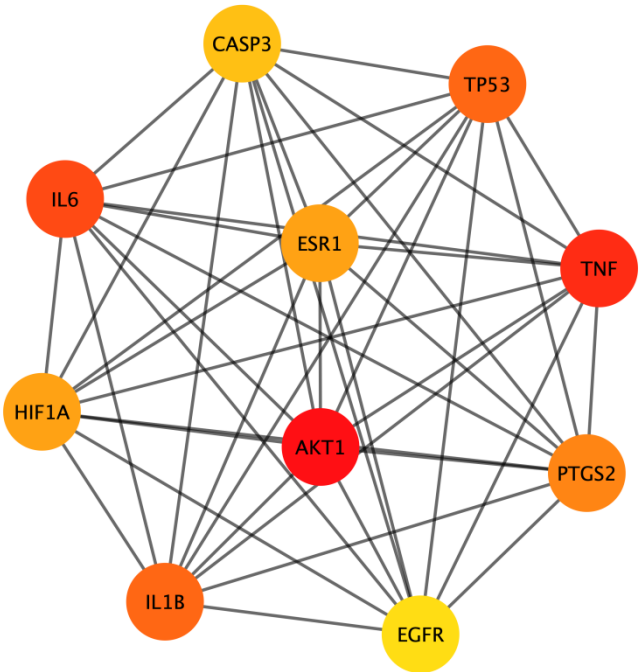


Figure 4: Degree Algorithm

ISSN 2706-6819 Vol.8, Issue 1: 1-13, DOI: 10.25236/IJFM.2026.080101

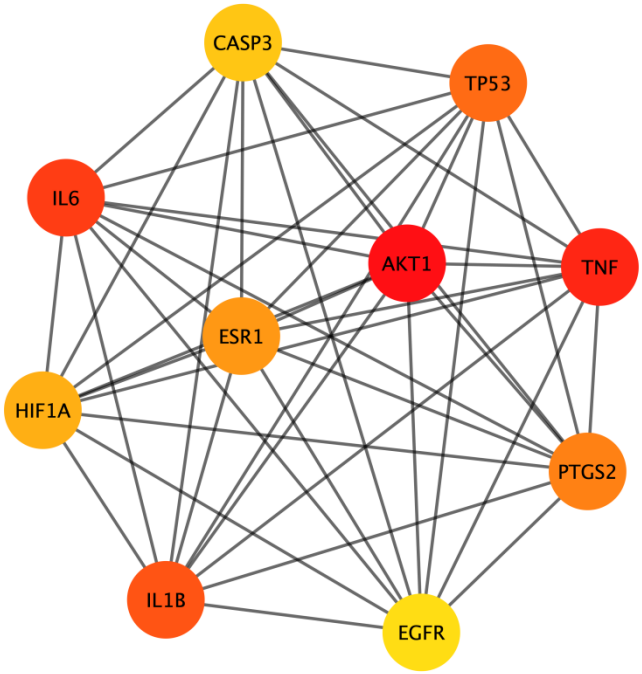


Figure 5: Closeness Algorithm

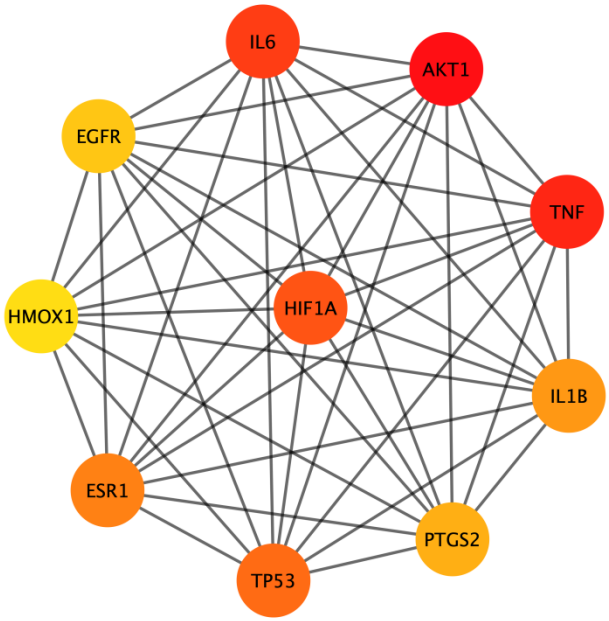


Figure 6: Betweenness Algorithm

ISSN 2706-6819 Vol.8, Issue 1: 1-13, DOI: 10.25236/IJFM.2026.080101

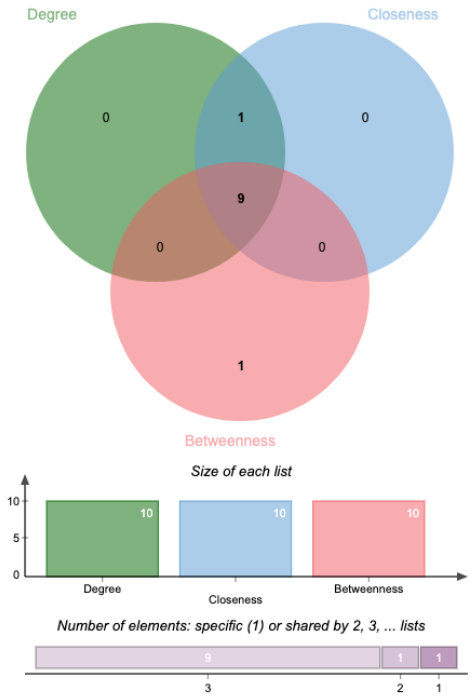


Figure 7: Venn diagram of the intersection among three algorithms

3.4. Enrichment Analysis of Biological Functions

3.4.1. GO Gene Functional Enrichment Analysis

GO analysis of the drug-disease intersection genes identified a total of 2892 significantly enriched terms ($P < 0.05$). Among these, 2613 terms belonged to Biological Processes (BP), which were primarily associated with responses to xenobiotic stimulus, lipopolysaccharide, nutrient levels, and molecules of bacterial origin (Figure 8). Cellular Components (CC) comprised 94 terms, showing significant enrichment in structures such as membrane raft, membrane microdomain, caveola, and plasma membrane raft (Figure 9). Molecular Functions (MF) included 185 terms, key among them being nuclear receptor activity, ligand-activated transcription factor activity, DNA-binding transcription factor binding, and RNA polymerase II-specific DNA-binding transcription factor binding (Figure 10).

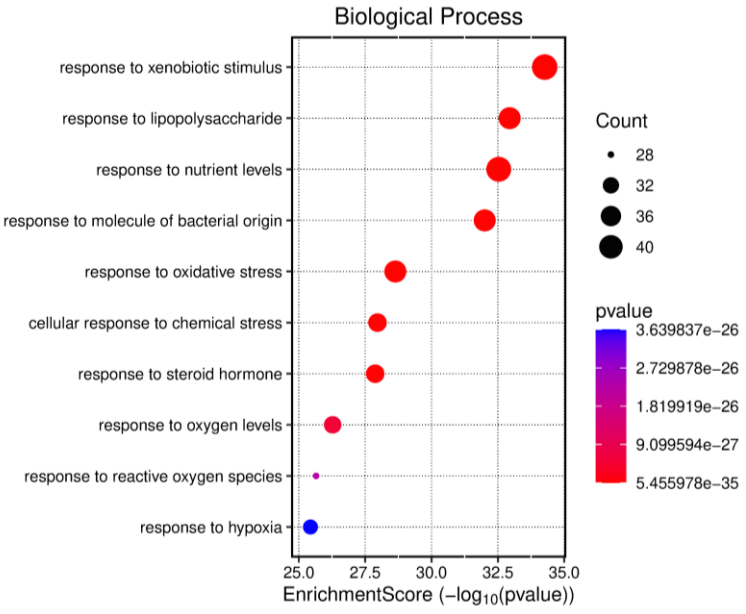


Figure 8: Bubble Chart of Top 10 BP Enrichment Analysis

ISSN 2706-6819 Vol.8, Issue 1: 1-13, DOI: 10.25236/IJFM.2026.080101

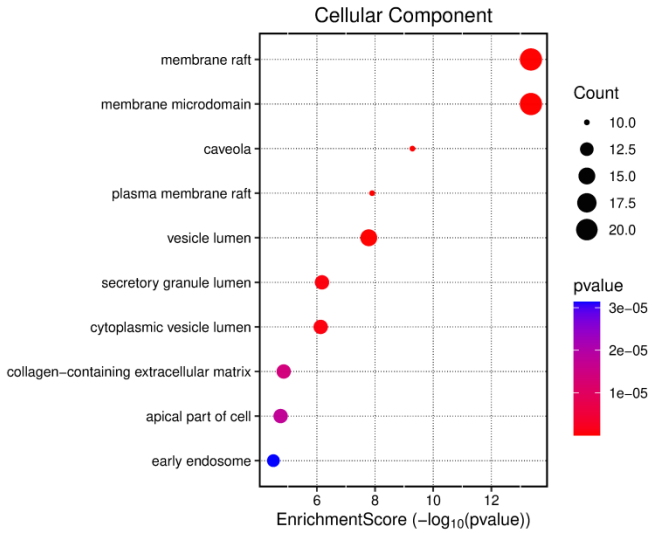


Figure 9: Bubble Chart of Top 10 CC Enrichment Analysis

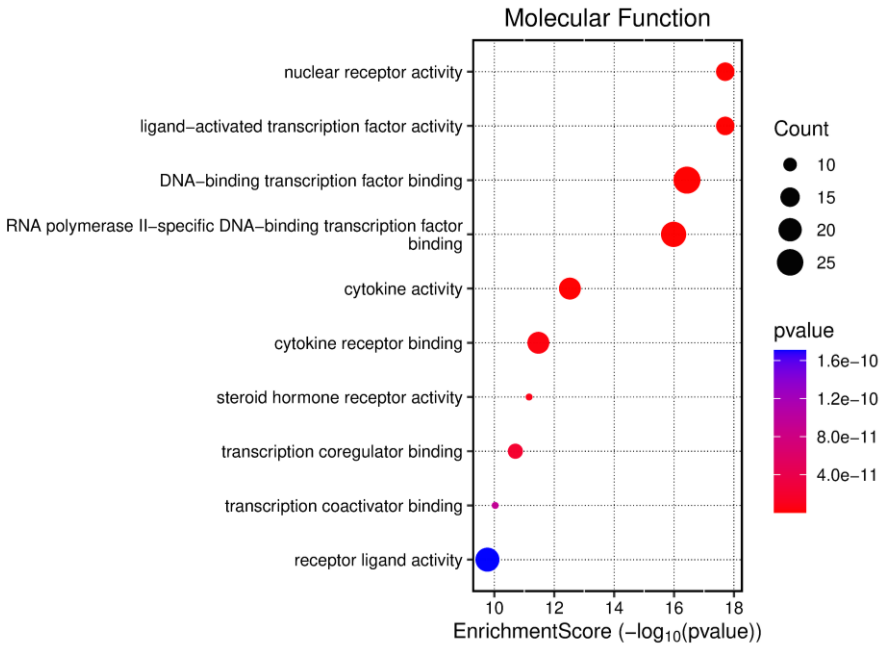


Figure 10: Bubble Chart of Top 10 MF Enrichment Analysis

3.4.2. KEGG Pathway Enrichment Analysis

KEGG pathway analysis of the intersection targets identified 186 significantly enriched pathways ($P < 0.05$). Figure 11 displays the top 20 core pathways ranked by P-value, including the IL-17 signaling pathway, TNF signaling pathway, among others. The mechanisms of action for these key signaling pathways are illustrated in Figure 12.

ISSN 2706-6819 Vol.8, Issue 1: 1-13, DOI: 10.25236/IJFM.2026.080101

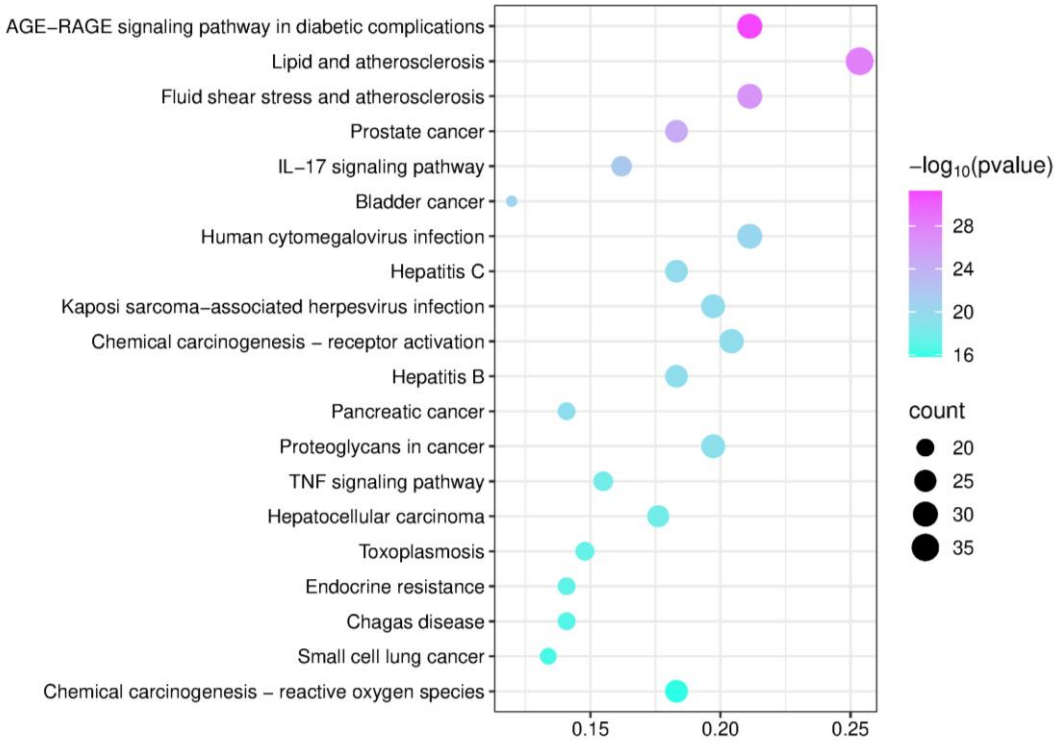
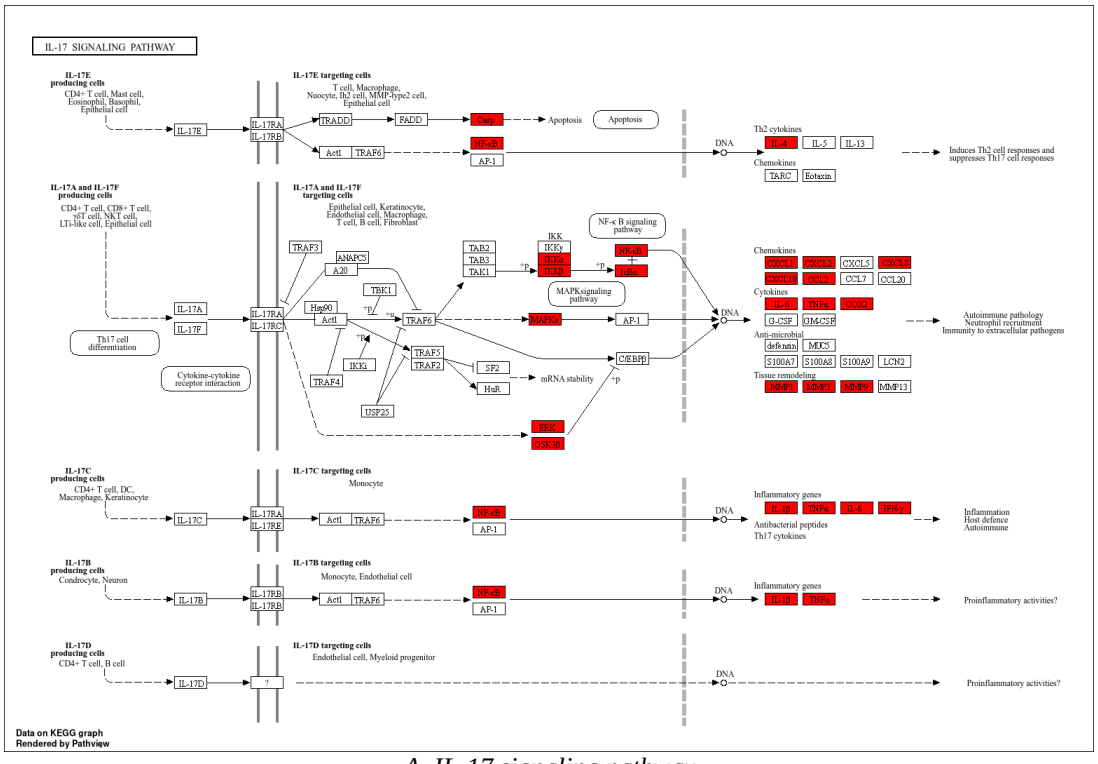
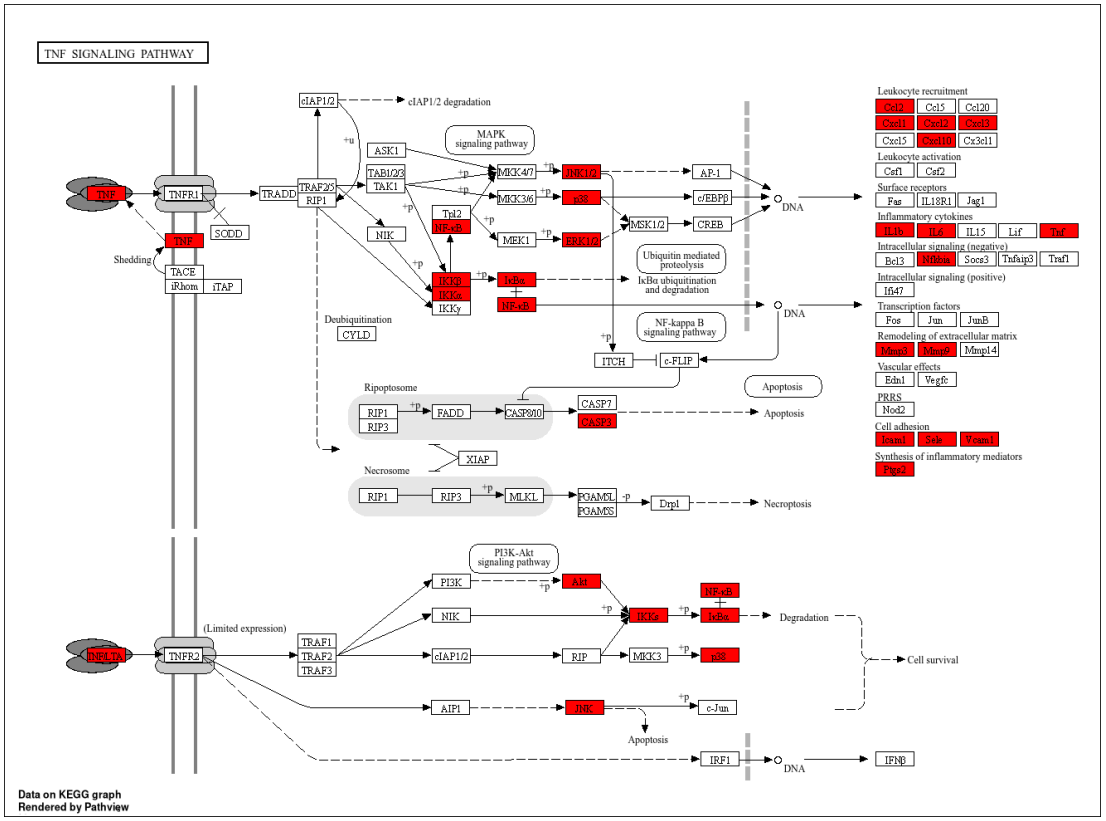


Figure 11: Top 20 KEGG Pathway Enrichment Analysis Chart



A. IL-17 signaling pathway

ISSN 2706-6819 Vol.8, Issue 1: 1-13, DOI: 10.25236/IJFM.2026.080101



B. TNF signaling pathway

Figure 12: Mechanism of action of the core signaling pathways. Core targets are highlighted in red.

4. Discussion

With the acceleration of population aging in China, the incidence of OP continues to rise. Characterized by progressive declines in bone mineral density and bone quality, its clinical manifestations include low back pain, reduced height, and a significantly increased risk of fragility fractures. In Traditional Chinese Medicine (TCM), this disease falls under the categories of "bone wilting" (Gu Wei) and "bone desiccation" (Gu Ku). Its core pathogenesis is attributed to deficiency of kidney essence, meaning the kidney's functions of governing bones and generating marrow are diminished, leading to a lack of nourishment for the bones and resulting in fragility and porosity. Based on the therapeutic principle of "tonifying the kidney and strengthening bones", the clinical empirical formula BSZGP is commonly used in our hospital. The complete formula consists of eight herbal medicines: Taxilli Herba (Sangjisheng), Angelicae Pubescentis Radix (Duhuo), Cinnamomi Ramulus (Guizhi), Eucommiae Cortex (Duzhong), Dipsaci Radix (Xuduan), Drynariae Rhizoma (Gusubu), Epimedii Folium (Yinyanghuo), and Alpiniae Oxyphyllae Fructus (Yizhiren). In this formula, Eucommiae Cortex, Dipsaci Radix, Drynariae Rhizoma, and Epimedii Folium serve as the monarch herbs, collectively tonifying the liver and kidney and strengthening bones and sinews. Taxilli Herba assists the monarch herbs in tonifying the liver and kidney while dispelling wind-dampness, and Cinnamomi Ramulus warms and unblocks the channels and vessels while assisting yang transformation; together they act as minister herbs. Angelicae Pubescentis dispels wind, eliminates dampness, unblocks impediment, and relieves pain, while Alpiniae Oxyphyllae Fructus warms the kidney and secures essence; both serve as assistant and envoy herbs. All herbs work synergistically to achieve the effect of nourishing the liver and kidney, replenishing essence, and strengthening bones. Based on network pharmacology methods, this study systematically explored the potential active ingredients, action targets, and related signaling pathways of Bushen Zhuanggu Granules (BSZGP) in treating osteoporosis, aiming to explain its synergistic mechanism of "multi-component, multi-target, multi-pathway" from a systems level.

TCM formulas, by virtue of their multi-component, multi-target synergistic mechanisms, can effectively intervene in key pathological processes such as anti-inflammatory, antioxidant, tissue metabolism, and apoptosis by regulating multiple signaling pathways, thereby achieving therapeutic effects against OP [7]. Based on network pharmacology analysis, this study preliminarily screened out

ISSN 2706-6819 Vol.8, Issue 1: 1-13, DOI: 10.25236/IJFM.2026.080101

components such as quercetin, luteolin, kaempferol, beta-sitosterol, and naringenin, which may be the core active substances in BSZGP for treating OP. Among them, quercetin, a natural flavonol, possesses significant anti-inflammatory, antioxidant, and antibacterial properties. Studies indicate that quercetin can inhibit osteoclastogenesis by affecting the OPG/RANK/RANKL mechanism through inhibiting RANKL activation, thereby reducing bone resorption and stabilizing bone mass balance [8,9]. Furthermore, quercetin can effectively inhibit premature senescence in osteoblastic MC3T3-E1 cells, and through this pathway, it can effectively reduce bone loss in ovariectomized osteoporotic mouse models, exerting estrogen-like effects [10]. Luteolin is a plant flavonoid with antioxidant activity. Research has found that it can promote osteoblast proliferation by alleviating oxidative stress and promote osteoblast differentiation by regulating the ERK/LRP-5/GSK-3β pathway, playing an important role in the treatment of glucocorticoid-induced OP [11]. Kaempferol can activate estrogen receptor activity, enhance the proliferation and differentiation capacity of osteoblastic MG-63 cells, and promote osteoblast mineralization [12]. Beta-sitosterol, widely present in various TCM ingredients, possesses physiological functions such as anti-inflammatory, antioxidant, and anti-androgenic effects [13]. Studies have found that beta-sitosterol can promote and enhance osteogenesis by increasing the osteoprotegerin/osteoclast differentiation factor (OPG/ODF) ratio in osteoblasts and stimulating estradiol function through ovarian granulosa cell differentiation [14].

Through the intersection of three network pharmacology algorithms, key targets for BSZGP in treating OP were identified, including TP53, TNF, IL1B, EGFR, IL6, AKT1, HIF1A, ESR1, and PTGS2. Among these, TNF plays a pivotal role in the imbalance of bone homeostasis. It directly promotes the differentiation and maturation of osteoclast precursors, enhances bone resorption activity, and simultaneously inhibits the generation and function of osteoblasts, thereby impeding bone formation [15]. Particularly in the estrogen-deficient state postmenopause, elevated levels of TNF-α in the body are significantly associated with reduced bone density, making it a key inflammatory driver of osteoporosis progression [16]. IL6, another core inflammatory mediator, acts synergistically with TNF-α. Elevated IL-6 levels are linked not only to aging and declining estrogen but also amplify inflammatory responses. By stimulating the expression of factors like RANKL, IL6 creates a favorable bone marrow microenvironment for osteoclast differentiation and activation [17,18]. Clinical studies confirm that serum IL-6 levels are significantly elevated in postmenopausal osteoporosis patients and positively correlate with the rate of bone loss [16]. AKT1 regulates osteoblast (OB) differentiation and osteoclast (OC) growth by activating downstream effector proteins such as mTORC1/S6K1. Knockout of the AKT1 gene in mice delays ossification and severely disrupts bone development [19]. HIF-1, one of the core targets regulating bone metabolism, plays a key role in balancing bone formation and resorption. On one hand, through the osteogenic-angiogenic coupling mechanism, it promotes the osteogenic and angiogenic differentiation of bone marrow mesenchymal stem cells in hypoxic environments, coordinating bone regeneration [20]. On the other hand, HIF-1 activation can directly promote osteoclast differentiation and function, while conditions like osteoporosis (e.g., estrogen deficiency) weaken physiological inhibition of its activation, thereby exacerbating bone resorption [21]. Studies have confirmed that inhibiting the HIF-1 signaling pathway can effectively delay the progression of postmenopausal osteoporosis, highlighting its significance in the pathological process [22]. Thus, these core targets likely profoundly influence the balance between osteogenesis and osteoclastogenesis primarily by modulating the bone immunoinflammatory microenvironment and oxidative stress.

Further KEGG pathway enrichment analysis revealed that the key mechanisms of BSZGP in treating OP may involve biological effects such as anti-inflammatory actions through pathways like the IL-17 signaling pathway and TNF signaling pathway. Among these, the TNF signaling pathway mediates chronic inflammation-related bone remodeling, which is a critical therapeutic target for osteoporosis. Core genes in this pathway, such as TNF and IL6, regulate the balance between bone resorption and bone remodeling by connecting TNF with the RANK/RANKL/OPG signaling transduction [23]. Additionally, inhibiting TNF receptor binding reduces matrix metalloproteinases, thereby suppressing pathological responses like chondrocyte apoptosis and cartilage destruction [24,25]. Therefore, it is hypothesized that BSZGP may treat OP by targeting TNF, IL6, AKT1, HIF1A, and other key targets, and regulating signaling pathways such as the TNF signaling pathway to exert anti-inflammatory and antioxidant effects.

5. Conclusion

In summary, this study, utilizing network pharmacology, indicates that the active components of BSZGP exert therapeutic effects on OP through a multi-target, multi-pathway approach. The specific molecular mechanism involves core components such as quercetin, luteolin, kaempferol, and beta-sitosterol likely targeting TNF, IL6, AKT1, and HIF1A. By regulating signaling pathways like the TNF

ISSN 2706-6819 Vol.8, Issue 1: 1-13, DOI: 10.25236/IJFM.2026.080101

signaling pathway, these components achieve anti-inflammatory and antioxidant effects, thereby treating OP. This provides a theoretical basis for the clinical application of this formula. However, this study has certain limitations, and further experimental validation is required to explore the specific mechanisms involving these core targets and pathways.

References

[1] Amin Usman, McPartland Aoife, O'Sullivan Miriam, et al. An overview of the management of osteoporosis in the aging female population [J]. Women's health (London, England), 2023, 19:17455057231176655.
[2] Ensrud KE, Crandall CJ. Osteoporosis [J]. Annals Of Internal Medicine, 2017, 167(3):ITC17-ITC32.
[3] Mart ń-Merino E, , Petersen I, et al. Risk of venous thromboembolism among users of different anti-osteoporosis drugs: a population-based cohort analysis including over 200,000 participants from Spain and the UK [J]. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 2018, 29(2):467-478.
[4] Li Chong, Lv Weihua, Wang Tingting, et al. The study of prevalence of osteoporosis in 1088 medical workers [J]. Chinese Journal of Osteoporosis, 2015, 21(10):1217-1220.
[5] Qaseem Amir, Forciea Mary Ann, et al. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians [J]. Annals of internal medicine, 2017, 166(11):818-839.
[6] Liu Xingxing, Guo Yikun, Ai Qi, et al. Study on the mechanism of Liuwei Dihuang Pills in the treatment of osteoporosis based on network pharmacology and molecular docking [J]. Natural Product Research and Development, 2021, 33(9):1593-1602+1538.
[7] Zhang Huihao, Zhou Chengcong, Zhang Zhiguo, et al. Integration of Network Pharmacology and Experimental Validation to Explore the Pharmacological Mechanisms of Zhuanggu Busui Formula Against Osteoporosis [J]. Frontiers in Endocrinology, 2022, 12:841668.
[8] Zhang Xiao, Zhang Guoqing, Gu Bolin, et al. Current advance in the effect of salvia miltiorrhiza and its effective components on bone metabolism [J]. Chinese Journal of Osteoporosis. 2015, 21(1):112-116.
[9] Jian Huang, Lan Yuan, et al. Icaritin and its glycosides enhance osteoblastic, but suppress osteoclastic, differentiation and activity in vitro [J]. Life Sciences, 2007, 81(10):832-840.
[10] Gu Yijing, Fu Jiayao, Wu Wenjing, et al. Quercetin alleviates estrogen deficiency-induced osteoporosis through anti-senescence effect on bone cells [J]. Journal of Tongji University (Medical Science), 2019, 40(3):274-280.
[11] Jing Zheng, Wang Changyuan, et al. Luteolin attenuates glucocorticoid-induced osteoporosis by regulating ERK/Lrp-5/GSK-3β signaling pathway in vivo and in vitro [J]. Journal of cellular physiology, 2019, 234(4):4472-4490.
[12] Zeng Yirong, Zeng Jianchun, Fan Yueguang, et al. Effect of kaempferol on proliferation and differentiation of osteoblast MG-63 [J]. Lishizhen Medicine and Materia Medica Research, 2012, 23(6):1463-1465.
[13] Rajavel Tamilselvam, , Packiyaraj Pandian, et al. β-Sitosterol targets Trx/Trx1 reductase to induce apoptosis in A549 cells via ROS mediated mitochondrial dysregulation and p53 activation [J]. Scientific reports, 2018, 8(1):2071.
[14] Lin Mingzhu, Zhao Yan, Cai Enbo, et al. Anti-tumor effect of β-sitosterol in H22 tumor-bearing mice [J]. Chinese Journal of Public Health, 2017, 33(12):1797-1800.
[15] Wang Shaoyi, Zhang Hengyan, Zhu Yanbin, et al. Progranulin Protects Against Osteoporosis by Regulating Osteoclast and Osteoblast Balance via TNFR Pathway [J]. Journal of cellular and molecular medicine, 2025, 29(3):e70385.
[16] He Yong, Liu Shuqin, Wang Changjiang, et al. Effects of interleukin-6, tumor necrosis factor alpha on the pathogenesis of postmenopausal osteoporosis [J]. Chinese Journal of Clinical Healthcare, 2007, 10(1):41-43.
[17] Srivastava Rupesh K, Sapra Leena. The Rising Era of "Immunoporosis": Role of Immune System in the Pathophysiology of Osteoporosis [J]. Journal of inflammation research, 2022, 15:1667-1698.
[18] Yang Xufeng, Hao Yanming, Lu Ke, et al. Study on the mechanism of inflammatory bone marrow microenvironment affecting the occurrence and development of osteoporosis [J]. Chinese Journal of Osteoporosis, 2022, 28(11):1614-1619.
[19] Peng Xiaoding, Xu Peizhang, et al. Dwarfism, impaired skin development, skeletal muscle atrophy, delayed bone development, and impeded adipogenesis in mice lacking Akt1 and Akt2 [J]. Genes & development, 2003, 17(11):1352-1365.
[20] Wang Ying, Wan Chao, Deng Lianfu, et al. The hypoxia-inducible factor α pathway couples

ISSN 2706-6819 Vol.8, Issue 1: 1-13, DOI: 10.25236/IJFM.2026.080101

angiogenesis to osteogenesis during skeletal development [J]. The Journal of Clinical Investigation, 2007, 117(6):1616-1626.
[21] Chen Wei, Wu Panfeng, Yu Fang, et al. HIF-1α Regulates Bone Homeostasis and Angiogenesis, Participating in the Occurrence of Bone Metabolic Diseases [J]. Cells, 2022, 11(22):3552.
[22] Zhong Hang, Cao Can, Yang Jing, et al. Research on Relationship of HIF-1 Signaling Pathway and Postmenstrual Osteoporosis [J]. Journal of Sichuan University (Medical Sciences), 2017, 48(6):862-868.
[23] Ji Yafeng, Jiang Xuesheng, et al. Impact of interleukin-6 gene polymorphisms and its interaction with obesity on osteoporosis risk in Chinese postmenopausal women [J]. Environmental Health and Preventive Medicine, 2019, 24(1):1-6.
[24] Gao Shichao, Yin Haibo, Liu Hongxiao, et al. Research progress on MAPK signal pathway in the pathogenesis of osteoarthritis [J]. China Journal of Orthopaedics and Traumatology, 2014, 27(5):441-444.
[25] Wang Dongyan, Qiao Jiutao, et al. Thymoquinone Inhibits IL-1β-Induced Inflammation in Human Osteoarthritis Chondrocytes by Suppressing NF-κB and MAPKs Signaling Pathway [J]. Inflammation, 2015, 38(6):2235-2241.