Int J Clin Exp Med 2020;13(10):7427-7436
www.ijcem.com /ISSN:1940-5901/IJCEM0112741

Original Article

Utilizing network pharmacology to explore the underlying mechanism of wenshenxuanbi decoction in treating osteoarthritis

Tianwei Xia[1*], Dawei Huan[2*], Guoqing Mao[1], Jinzhu Liu[2], Jiayong Shi[2], Zhaofeng Yuan[2], Jirong Shen[1]

[1]Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing 210029, Jiangsu, China; [2]Nanjing University of Chinese Medicine, Nanjing 210008, Jiangsu, China. [*]Equal contributors.

Received April 17, 2020; Accepted June 27, 2020; Epub October 15, 2020; Published October 30, 2020

Abstract: Objective: The network pharmacology method was adopted in this study to establish the relationship between "Efficacy of ingredients-disease targets-biological pathway" and screening the targets of the wenshenxuanbi decoction of the treatments for osteoarthritis and clarifying its mechanism of treatment. Methods: Chemical components and selected targets related to eleven herbs were searched in the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform. In the GeneCards database, the OMIM database, and the DisGeNET database, osteoarthritis disease targets were searched. Then we screened the core targets between the drugs and the disease by identifying the intersections. Then an interaction network diagram of the targets was constructed using String. The GO Enrichment and KEGG enrichment analyses of the targets were analyzed based on the DAVID database. Results: Selecting oral bioavailability ≥ 30% and drug likeness ≥ 0.18 as search filters, 181 active ingredients and 134 corresponding protein targets were screened for the wenshenxuanbi decoction. There were 72 core genes that intersected with 2171 disease-related genes in OA. The GO analysis contained a total of 304 enrichment results, including 211 biological processes, 42 cell compositions, and 51 molecular functions. A total of 73 pathways were enriched by KEGG. This study predicted the main possible mechanisms of wenshenxuanbi decoction in treating OA, including anti-inflammation, regulating cellular proliferation, differentiation and apoptosis, promoting the balance between osteogenesis and osteoclasts, and antioxidation.

Keywords: Network pharmacology, Wenshenxuanbi decoction, osteoarthritis, target

Introduction

Osteoarthritis (OA) is a common chronic degenerative disease in adults [1, 2]. There are no effective drugs in modern medicine for treating OA [3-7]. Moreover, 10% of the global medical behaviors are related to OA [3]. OA is often referred to as "arthralgia" in traditional Chinese medicine [8]. Traditional Chinese medicine has certain advantages in treating OA. Wenshenxuanbi decoction has a good clinical effect on OA [9]. Wenshenxuanbi decoction consists of monkshood 10 g, cassia twig 10 g, woodwardia 10 g, asarum 6 g, poria cocos 12 g, coix seed 15 g, banksia rose 10 g, gastrodia elata 10 g, dogwood 10 g, alisma 10 g, stir-baked rhizoma atractylodes macrocephalae in bran 10 g, and licorice 10 g. However, the mechanism by which wenshenxuanbi decoction treats OA is unclear.

Nowadays, network pharmacology is widely used to explore the pharmacological mechanisms of traditional Chinese medicine, treating disease [10-12]. We utilized network pharmacology to explore the potential mechanism of wenshenxuanbi decoction in treating OA.

Methods

Screening the active compounds in wenshenxuanbi decoction and gathering potential targets

This study is based on the *traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform* (TCMSP, http://lsp.nwu.edu. cn/tcmsp.php), a pharmacology database and analysis platform of the TCM system, which retrieves all the chemical components of the twelve traditional Chinese medicines in the wenshenxuanbi decoction with keywords. In this study, oral availability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18 were used as the screening conditions for the active compounds. In combination with published studies, the chemi-

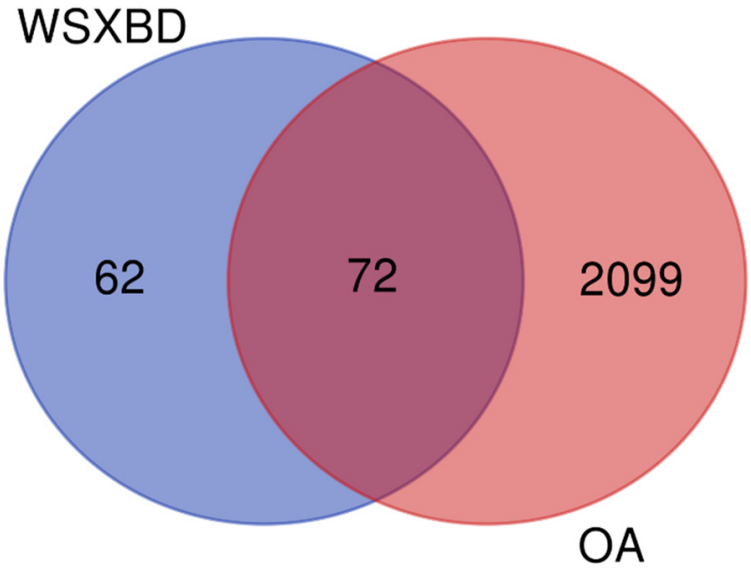

Figure 1. A Venn diagram showing the selection of the prescription and disease common targets.

cal components were screened, and the compounds with high activity in TCMSP were extracted by comprehensively considering their biological effects, content, research heat, and other factors. At the same time, the potential targets related to candidate compounds were collected on the TCMSP platform.

Identification of disease targets

The OA-associated disease targets were searched in GeneCards (https://www. genecards.org/), OMIM (http://www.omim.org/), and DisGeNET (http://www. disgenet.org/web/DisGeNET/menu/home), three disease-related databases, with "osteoarthritis" as a keyword.

Construction of the network

The relevant action targets of wenshenxuanbi decoction and the known disease targets of OA were intersected, and the intersection targets were uploaded to the STRING database (http://string-db.org/) [13] for building the protein-protein interaction (PPI) network.

Construction of the compound-target-disease network and screening the key genes

The selected core targets were uploaded to Cytoscape 3.2.1 software (https://cytoscape.org/) to generate a chemcompound-target-disease network graph to demonstrate the effect of the compound on the disease at the system level. At the same time, Cytoscape 3.2.1 software was used for the core network screening based on the topological parameters.

Enrichment analysis of the gene ontology (GO) function and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway

To illustrate the role of the target of the Chinese medicine compound protein in the gene function, the Database for Annotation, Visualization and Integrated Discovery (DAVID, https://david.ncifcrf.gov/, v.6.8) was used for the GO enrichment analysis [14]. The pathway enrichment analysis was accomplished using the *Kyoto Encyclopedia of Genes and Genomes* data (http://www.kegg.jp/) obtained from DAVID [15]. $P < 0.05$ was set as the basic screening condition for the GO enrichment analysis and the KEGG pathway enrichment analysis. The results of the enrichment analysis were then visualized through the OmicShare platform (http://www.omicshare.com/tools/home/report/koenrich.html), in order to reflect the main effect pathway of the wenshenxuanbi decoction for the treatment of osteoarthritis.

Results

Screening of the active compounds and targets

The compounds in the wenshenxuanbi decoction were collected using TCMSP, with OB ≥ 30% and DL ≥ 0.18 as the screening conditions. After we removed the duplicates, a total of 181 compounds were obtained, and they were considered as candidate compounds. In addition, 134 corresponding targets of the candidate compounds were obtained after we collected them and removed the duplicates on the TCMSP platform.

Screening of the core genes and the construction and analysis of the PPI graph network

A total of 2,307 targets were obtained by searching the Genecards, OMIM, and DisGeNET

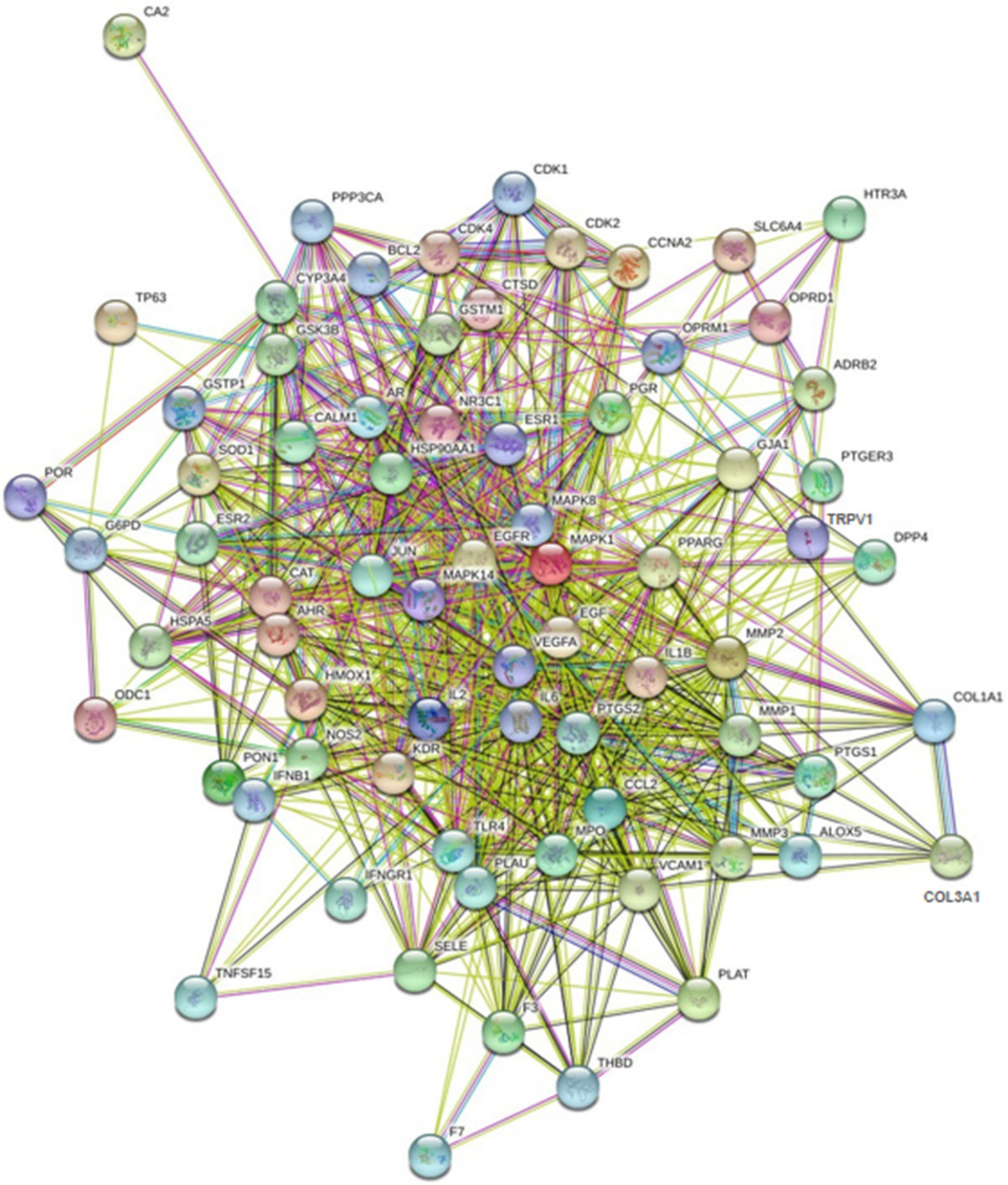

Figure 2. The core targets protein-protein interaction network. MMP2, matrix metalloproteinase 2; NOS2, nitric oxide synthase 2; COL1A1, collagen, type I, alpha 1; PPP3CA, protein phosphatase 3-catalytic subunit-alpha isoform (calcineurin A alpha); CDK1, cyclin-dependent kinase-1; BCL2, B-cell CLL/lymphoma 2; F7, coagulation factor VII; HTR3A, 5-hydroxytryptamine receptor 3A; GSTP1 glutathione S-transferase pi-1; AHR, aryl hydrocarbon receptor; EGF, epidermal growth factor; PTGS2, prostaglandin-endoperoxide synthase 2; ESR1, estrogen receptor alpha gene; CDK4, cyclin-dependent kinase 4; POR, P450 (cytochrome) oxidoreductase; VEGFA, vascular endothelial growth factor A; CCNA2, cyclin A2; GSK3B, glycogen synthase kinase 3 beta; MMP1, matrix metalloproteinase 2; TRPV1, transient receptor potential cation channel, subfamily V, member 1; HMOX1, heme oxygenase 1; MMP3, matrix metalloproteinase 3; GSTM1, glutathione S-transferase M1; MAPK1, mitogen-activated protein kinase 1; PLAT, plasminogen activator tissue; EGFR, epidermal growth factor receptor; SOD1, superoxide dismutase 1; G6PD, glucose-6-phosphate dehydrogenase; MAPK8, mitogen-activated protein kinase 8; CDK2, cyclin-dependent kinase 2; PGR, progesterone receptor; ODC1, ornithine decarboxylase 1; CAT, catalase; IL1B, interleukin 1, beta; CALM1, calmodulin 1; ESR2, estrogen receptor 2; PTGER3, prostaglandin E receptor 3; PLAU, plasminogen activator, urokinase; SLC6A4, solute carrier family 6, member 4; ALOX5, arachidonate 5-lipoxygenase; GJA1, gap junction protein, alpha 1, 43 kDa;

DPP4, dipeptidylpeptidase 4; PON1, paraoxonase 1; TNFSF15, tumor necrosis factor (ligand) superfamily, member 15; PPARG, peroxisome proliferative activated receptor, gamma; SELE, selectin E; THBD, thrombomodulin; NR3C1, nuclear receptor subfamily 3, group C, member 1; MAPK14, mitogen-activated protein kinase 14; MPO, myeloperoxidase; ADRB2, adrenergic, beta-2-, receptor, surface; CTSD, cathepsin D; CCL2, chemokine (C-C motif) ligand 2; IL6, Interleukin-6; HSP90AA1, heat shock protein 90 kDa alpha , class A member 1; COL3A1, collagen, type III, alpha 1; KDR, kinase insert domain receptor; IL2, Interleukin-2; HSPA5, heat shock 70 kDa protein 5; OPRD1, opioid receptor, delta 1; CA2, carbonic anhydrase II; OPRM1, opioid receptor, mu 1; TLR4, toll-like receptor 4; VCAM1, vascular cell adhesion molecule 1; IFNGR1, interferon gamma receptor 1; PTGS1, prostaglandin-endoperoxide synthase 1; F3, coagulation factor III; IFNB1, interferon, beta 1; JUN, v-jun sarcoma virus 17 oncogene homolog; AR, androgen receptor; CYP3A4, cytochrome -family 3-subfamily 4; TP63, tumor protein p63.

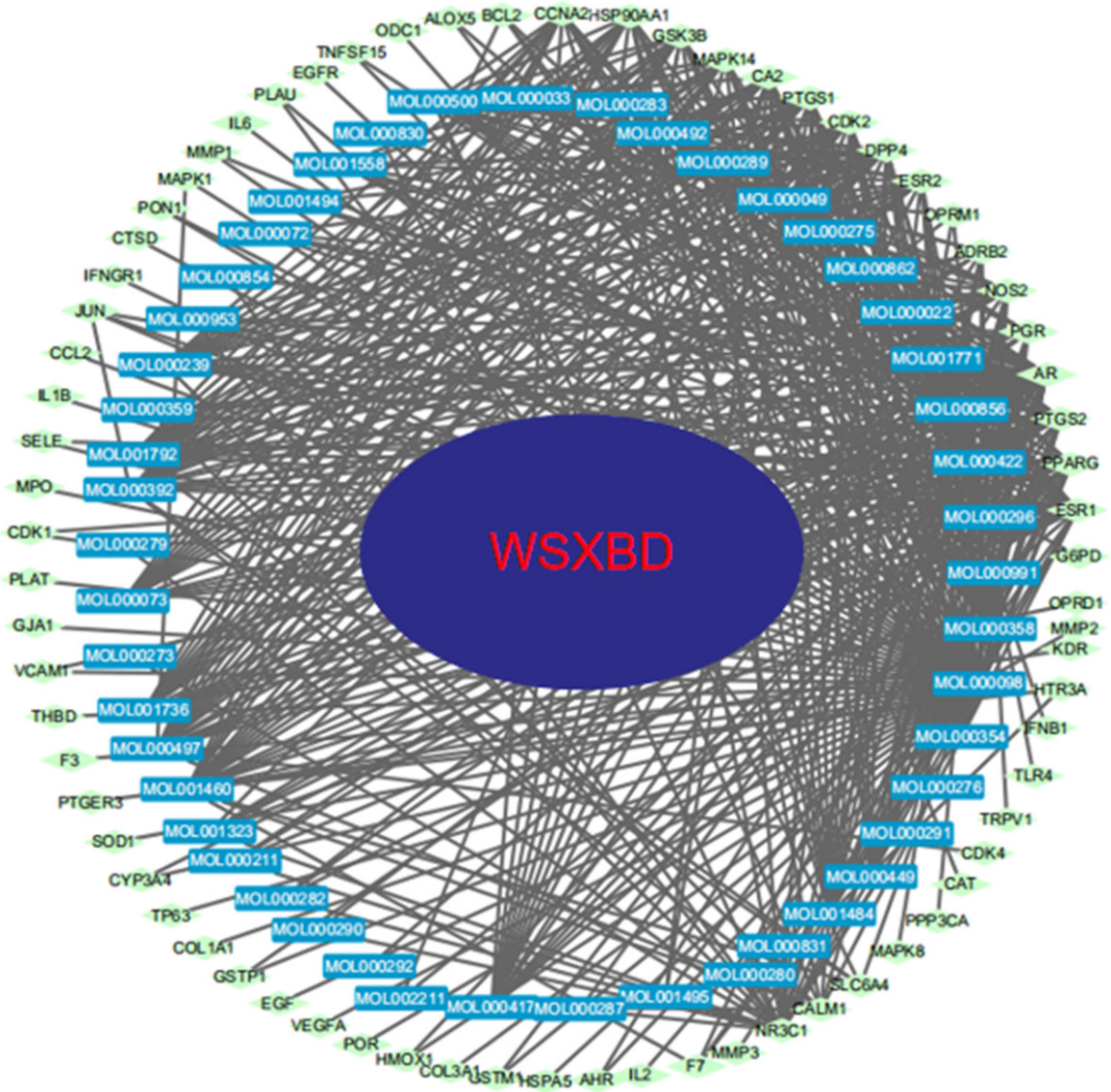

Figure 3. The compound-target-diseases of WSXBD.

databases, among which 2,139 targets were found in the Genecards database, 76 targets in the OMIM database, and 92 targets in the DisGeNET database. After removing the duplicates, there were 2,171 targets remaining. There are 72 intersections of action targets related to the wenshenxuanbi decoction (**Figure 1**). 72 targets were uploaded to the STRING database to draw the PPI network (**Figure 2**). There were 72 nodes (the isolated nodes were

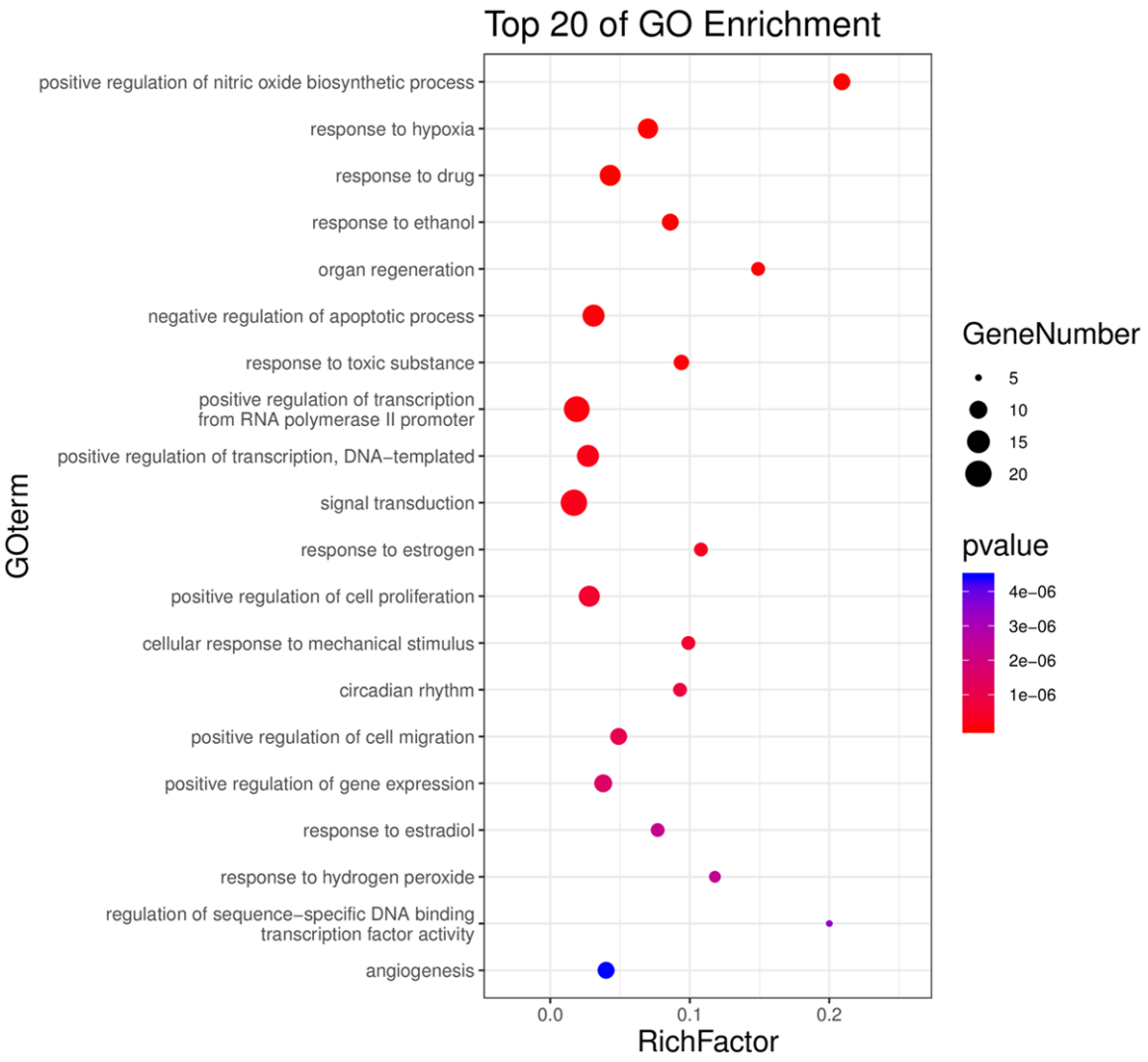

Figure 4. A biological process analysis of the GO pathway enrichment analysis for the active ingredient-potential targets of wenshenxuanbi decoction.

removed) and 770 sides (the network nodes represent the targets, and the lines represent the interactions of the targets). The average node degree was 21.4.

The compound-target-disease network

Cytoscape3.2.1 software was used to construct a chemical-target-disease network graph (**Figure 3**) of 72 targets, 181 compounds, WSXBD and OA. With an average of 7.2 degrees of freedom, 18 core targets with greater than average degrees of freedom were selected using the core network based on the topological parameters. The top 5 targets were DPP4, AR, PTGS2, PPARG, ESR1, and NR3C1. Therefore, the combined action mechanism of Wenshenxuanbi decoction with multiple components and multiple targets in the treatment of osteoarthritis reflects the characteristics of the traditional Chinese medicine compound.

Enrichment analyses of the GO function and KEGG pathway

A total of 211 biological process (BP) enrichment results, 42 cell composition (CC) enrichment results, and 51 molecular function (MF) enrichment results were obtained. The top 20 GO enrichment results are shown in **Figures 4-6**. In the BP correlation analysis results, the top 20 enrichment results are positive regulation of the nitric oxide biosynthesis process, response to hypoxia, response to the drug,

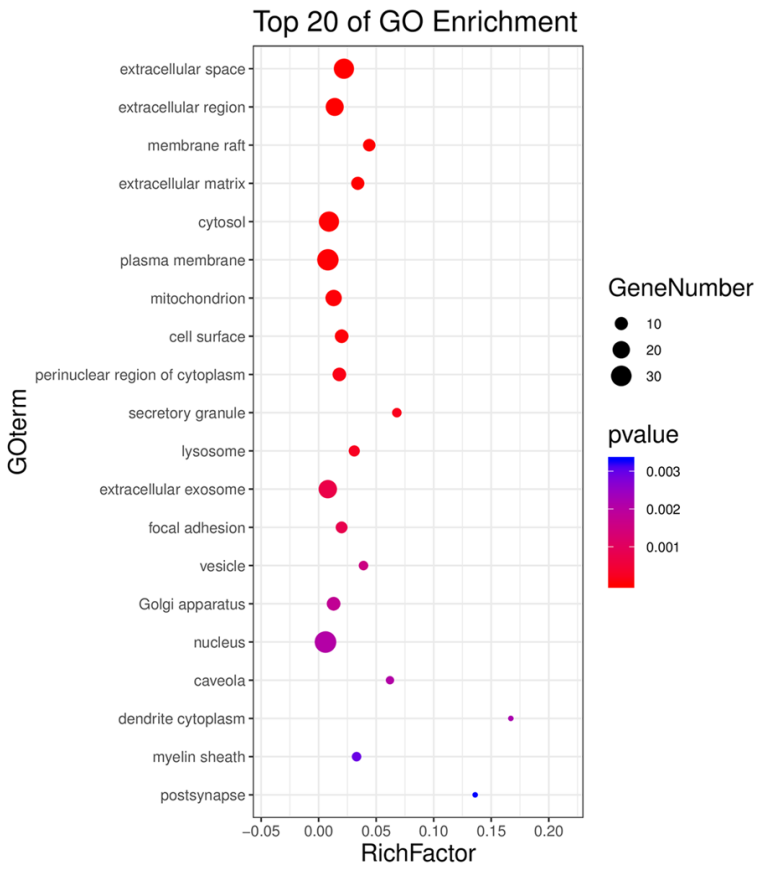

Figure 5. A cellular component analysis of the GO pathway enrichment analysis for the active ingredient-potential targets of wenshenxuanbi decoction.

response to ethanol, organ regeneration, negative regulation of the apoptotic process, response to toxic substances, positive regulation of the transcription from the RNA polymerase II promoter, positive regulation of the transcription-DNA-template, signal transduction, response to estrogen, positive regulation of cell proliferation, cellular response to mechanical stimuli, circadian rhythm, positive regulation of cell migration, positive regulation of gene expression, response to estradiol, response to hydrogen peroxide, regulation of sequence-specific DNA binding transcription factor activity, and angiogenesis (**Figure 4**). In the analysis results related to CC, the enrichment results of the top 20 are as follows: extracellular space, extracellular region, membrane raft, extracellular matrix, cytosol, plasma membrane, mitochondrion, cell surface, perinuclear region of cytoplasm, secretory granule, lysosome, extracellular exosome, focal adhesion, vesicle, Golgi apparatus, nucleus, caveola, dendrite cytoplasm, myelin sheath, and postsynapse (**Figure 5**).

In the analysis results related to MF, the enrichment results of the top 20 are enzyme binding, steroid binding, protein homodimerization activity, protein binding, steroid hormone receptor activity, nitric-oxide synthase regulator activity, serine-type endopeptidase activity, identical protein binding, RNA polymerase II transcription factor activity, ligand-activated sequence-specific DNA binding, receptor binding, heme binding, glycoprotein binding, NADP binding, cytokine activity, transcription factor binding, chromatin binding, sequence-specific DNA binding, MAP kinase activity, protein phosphatase binding, transcriptional activator activity, RNA polymerase II core promoter proximal region sequence-specific binding (**Figure 6**).

A total of 73 KEGG pathway enrichment results were obtained. The top 20 GO enrichment results are as follows (**Figure 7**). Pathways in cancer, Chagas disease (American trypanosomiasis), TNF signaling pathways, Tuberculosis, HIF-1 signaling pathway, Pertussis, PI3K-Akt signaling pathway, Salmonella infection, Bladder cancer, Estrogen signaling pathway, Leishmaniasis, influenza A, Hepatitis B, NOD-like receptor signaling pathway, Progesterone-mediated oocyte maturation, Rheumatoid arthritis, Prostate cancer, Focal adhesion, Osteoclast differentiation, Measles. This suggests that the treatment of osteoarthritis with wenshenxuanbi decoction may be regulated by the above signaling pathways.

Discussion

Considering the common signaling pathways of OA and excluding the pathways of unrelated diseases, we found that wenshenxuanbi decoction can effectively treat OA through its anti-inflammatory properties, affect proliferation, differentiation and apoptosis, and promote the balance between osteogenesis (OB) and osteoclasts (OC) and antioxidant.

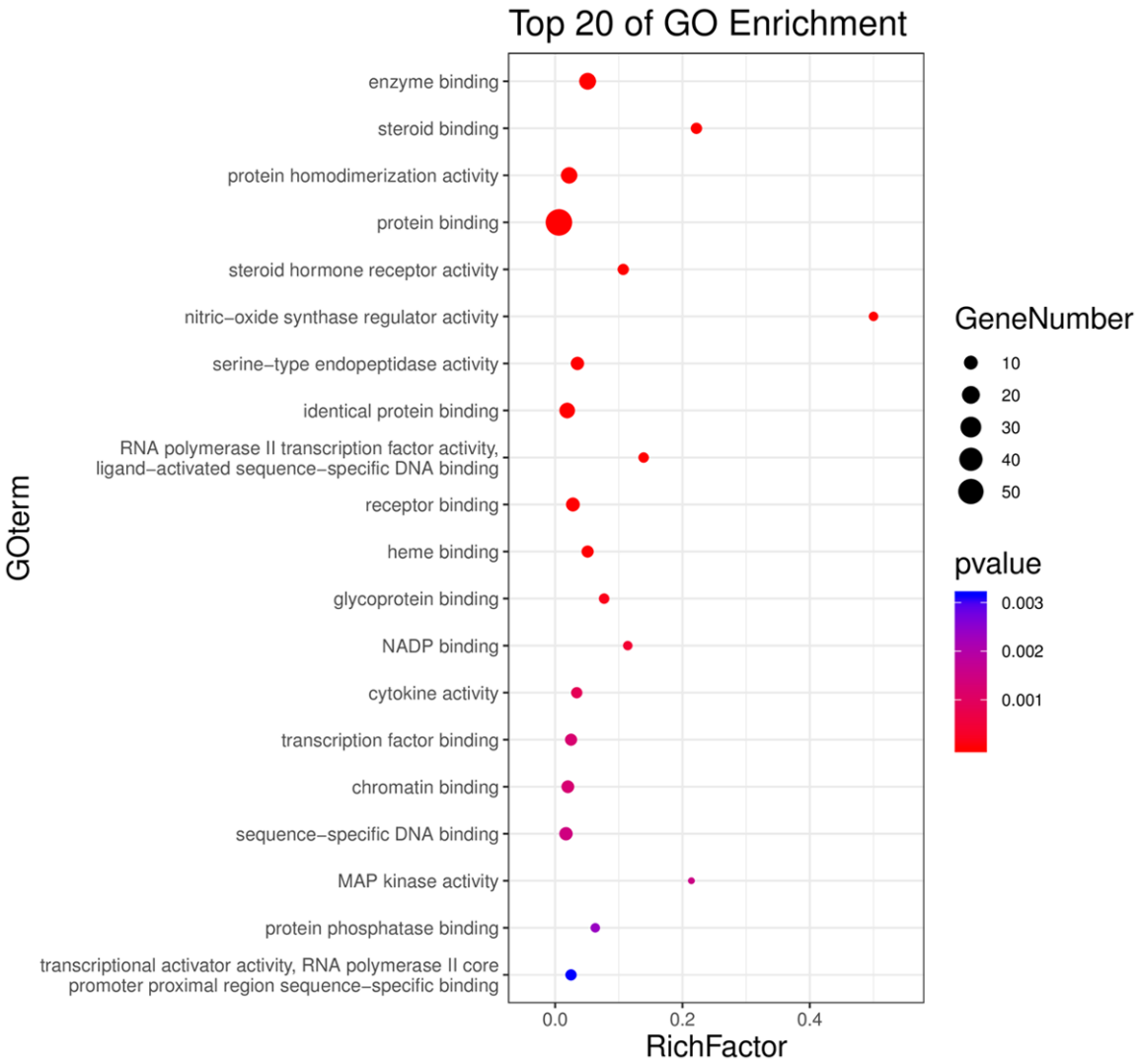

Figure 6. A molecular function analysis of the GO pathway enrichment analysis for the active ingredient-potential targets of wenshenxuanbi decoction.

(1) Anti-inflammatory. The enrichment analysis showed that the inflammation-related signaling pathways were enriched in the TNF related signaling and nod-like receptor pathways. Inflammatory factors [16, 17] exacerbate the inflammation, increase the protease expression of MMP-1, MMP-3, MMP-13, ADAMTS-4, and ADAMTS-5, accelerate the degradation of cartilage by activating NF-κB, extracellular protein kinase (Erk)-c-Jun amino-terminal kinase (Jnk)-protein kinase p38 lightning (p38), mitogen activated protein kinase (MAPK), and the TNF signaling pathways [18-22]. β-sitosterol, the active components of cornus, inhibits the activity of IL-6 and reduces the secretions of IL-1, TNF-α by reducing the synthesis of NO [23, 24]. Quercetin, the active component of licorice root,, plays a protective role on cartilage by inhibiting the NF-κB and TNF signaling pathways [25, 26]. Our previous study found that cinnamaldehyde, the active component of cassia twig, protects articular cartilage by inhibiting inflammation through the NF-κB and p38-JNK signaling pathways [20]. Proanthocyanidin, the active component of cassia twig, also decreases the expression of MMP-3 and MMP-13 by inhibiting the p38MAPK signaling pathway to protect cartilage. When hypoxia occurs in joints, HIF-1α will be transferred into the nuclei. It increases the expression of VEGF and angiogenesis, leading to synovitis [27, 28]. Our KEGG enrichment analysis suggests that wenshenxuanbi decoction plays an important role in treating OA by affecting HIF-1 signaling path-

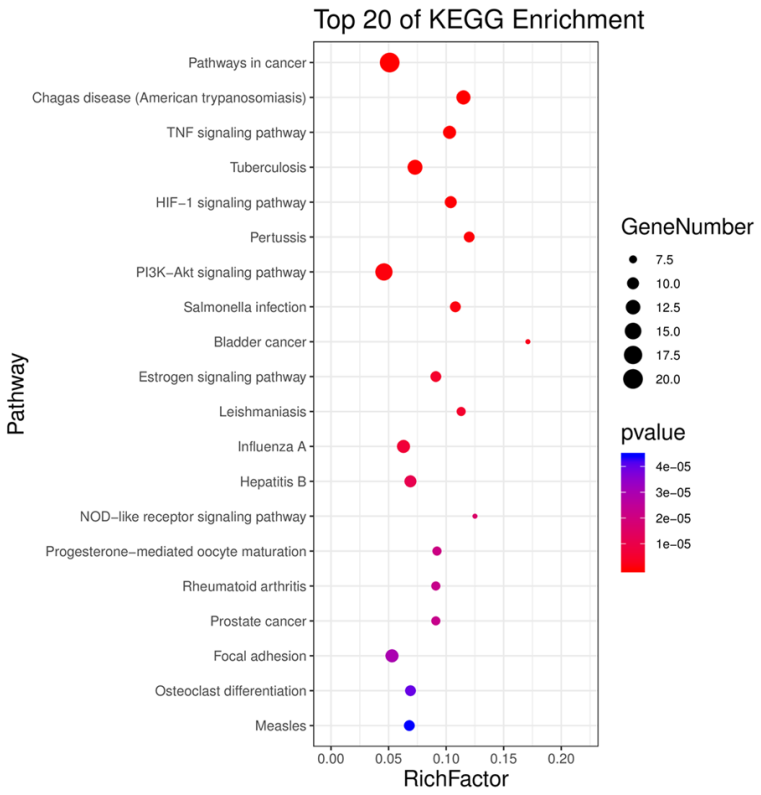

Figure 7. A KEGG pathway enrichment analysis of the active ingredient-potential targets of wenshenxuanbi decoction.

way. (2) It affects the proliferation, differentiation, and apoptosis of cells, and promotes the balance between OB and OC. According to the enrichment results, the PI3K/Akt signaling pathway, the osteoclast differentiation related pathway, the estrogen signaling pathway, and the downstream pathways of the cancer signaling pathway, such as Wnt [29] and the MAPK signaling pathway [30], play important roles in treating OA. The PI3K/Akt signaling pathway is related to the estrogen signaling pathway [31], which is not only an important pathway for regulating chondrocyte apoptosis and growth [32], it also participates in subchondral bone remodeling by regulating the proliferation, differentiation, and apoptosis of osteoblasts and osteoclasts [33-37]. Quercetin promotes osteogenic differentiation of rat bone marrow mesenchymal stem cells (BMSCs) [25, 26]. Low concentrations of cinnamaldehyde significantly improve the activity of alkaline phosphatase in osteoblasts, and promote the proliferation, differentiation, and osteoblast functions of osteoblasts [38]. Cinnamic acid blocks the G0/G1 phase of rat BMSCs and promotes their differentiation into osteoblasts [39, 40]. (3) Antioxidant. The mitochondrial dysfunction of chondrocytes and synovial cells produces NO and leads to oxidative damage in cartilage. The active component of dogwood, β-sitosterol, increases the activity of superoxide dismutase and glutathione peroxidase and decreases the activity of catalase. Cinnamaldehyde inhibits the oxidation of chondrocytes by increasing the activity of antioxidant enzymes [25]. Cinnamomum polyphenols, the active component of cassia twig, also has a strong reducibility [41].

Conclusion

The main mechanisms of wenshenxuanbi decoction in treating OA are its anti-inflammatory properties, its ability to regulate cellular proliferation, differentiation, and apoptosis, and its ability to promote the balance between OB and OC and antioxidation.

Acknowledgements

We are grateful to all the co-workers and partners in this study.

Disclosure of conflict of interest

None.

Address correspondence to: Jirong Shen, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing 210029, China. Tel: +86-138-1383-7751; E-mail: joint66118@sina.com

References

[1] McHugh D and Gil J. Senescence and aging: causes, consequences, and therapeutic avenues. J Cell Biol 2018; 217: 65-77.

[2] Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A and Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Ann Rheum Dis 2014; 73: 1659-1664.

[3] Xing D, Wang Q, Chen YL and Lin JH. Exploration on developing the diagnosis and treatment guidelines for osteoarthritis in primary

care of China. Zhonghua Wai Ke Za Zhi 2019; 57: 39-43.
[4] Bennell KL, Nelligan R, Dobson F, Rini C, Keefe F, Kasza J, French S, Bryant C, Dalwood A, Abbott JH and Hinman RS. Effectiveness of an internet-delivered exercise and pain-coping skills training intervention for persons with chronic knee pain: a randomized trial. Ann Intern Med 2017; 166: 453-462.
[5] Yu D, Peat G, Bedson J and Jordan KP. Annual consultation incidence of osteoarthritis estimated from population-based health care data in England. Rheumatology (Oxford) 2015; 54: 2051-2060.
[6] Martel-Pelletier J, Barr AJ, Cicuttini FM, Conaghan PG, Cooper C, Goldring MB, Goldring SR, Jones G, Teichtahl AJ and Pelletier JP. Osteoarthritis. Nat Rev Dis Primers 2016; 2: 16072.
[7] Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, Bridgett L, Williams S, Guillemin F, Hill CL, Laslett LL, Jones G, Cicuttini F, Osborne R, Vos T, Buchbinder R, Woolf A and March L. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014; 73: 1323-1330.
[8] Huan W, Xuezhang T, Haitao D, Meili Z, Lili Y, Dong Z, Siting L and Wen G. Experimental study on effects of cinnamic aldehyde on synovial inflammation in osteoarthritic based on the Micro RNA-146a interference. World Chinese Medicine 2017; 12: 151-156.
[9] Chen SZ MG, Sun YM, Jiang DM, Ma Y and Cao LM. A study of professor Fangshou Zhu's experience. Chinese Journal of Traditional Medical Traumatology & Orthopedics 2019; 27: 3.
[10] Zhang R, Zhu X, Bai H and Ning K. Network pharmacology databases for traditional chinese medicine: review and assessment. Front Pharmacol 2019; 10: 123.
[11] Li S and Zhang B. Traditional Chinese medicine network pharmacology: theory, methodology and application. Chin J Nat Med 2013; 11: 110-120.
[12] Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol 2008; 4: 682-690.
[13] Szklarczyk D, Franceschini A, Wyder S, Forslund K, Heller D, Huerta-Cepas J, Simonovic M, Roth A, Santos A, Tsafou KP, Kuhn M, Bork P, Jensen LJ and von Mering C. STRING v10: protein-protein interaction networks, integrated over the tree of life. Nucleic Acids Res 2015; 43: D447-452.
[14] Zhang B, Wang X and Li S. An Integrative platform of TCM network pharmacology and its application on a herbal formula, Qing-Luo-Yin. Evid Based Complement Alternat Med 2013; 2013: 456747.
[15] Kanehisa M, Furumichi M, Tanabe M, Sato Y and Morishima K. KEGG: new perspectives on genomes, pathways, diseases and drugs. Nucleic Acids Res 2017; 45: D353-D361.
[16] Daheshia M and Yao JQ. The interleukin 1beta pathway in the pathogenesis of osteoarthritis. J Rheumatol 2008; 35: 2306-2312.
[17] Tetlow LC, Adlam DJ and Woolley DE. Matrix metalloproteinase and proinflammatory cytokine production by chondrocytes of human osteoarthritic cartilage: associations with degenerative changes. Arthritis Rheum 2001; 44: 585-594.
[18] Minond D, Lauer-Fields JL, Cudic M, Overall CM, Pei D, Brew K, Visse R, Nagase H and Fields GB. The roles of substrate thermal stability and P2 and P1' subsite identity on matrix metalloproteinase triple-helical peptidase activity and collagen specificity. J Biol Chem 2006; 281: 38302-38313.
[19] Verma P and Dalal K. ADAMTS-4 and ADAMTS-5: key enzymes in osteoarthritis. J Cell Biochem 2011; 112: 3507-3514.
[20] Xia T, Gao R, Zhou G, Liu J, Li J and Shen J. Trans-cinnamaldehyde inhibits IL-1beta-stimulated inflammation in chondrocytes by suppressing NF-kappaB and p38-JNK pathways and exerts chondrocyte protective effects in a rat model of osteoarthritis. Biomed Res Int 2019; 2019: 4039472.
[21] Huang K and Wu LD. Aggrecanase and aggrecan degradation in osteoarthritis: a review. J Int Med Res 2008; 36: 1149-1160.
[22] Sondergaard BC, Henriksen K, Wulf H, Oestergaard S, Schurigt U, Brauer R, Danielsen I, Christiansen C, Qvist P and Karsdal MA. Relative contribution of matrix metalloprotease and cysteine protease activities to cytokine-stimulated articular cartilage degradation. Osteoarthritis Cartilage 2006; 14: 738-748.
[23] Liu WL JY and Huang AX. Research and development progress of beta-sitosterol Farm Products Processing 2019; 01: 6.
[24] Wilt TJ, MacDonald R and Ishani A. beta-sitosterol for the treatment of benign prostatic hyperplasia: a systematic review. BJU Int 1999; 83: 976-983.
[25] Li Y, Wang J, Chen G, Feng S, Wang P, Zhu X and Zhang R. Quercetin promotes the osteogenic differentiation of rat mesenchymal stem cells via mitogen-activated protein kinase signaling. Exp Ther Med 2015; 9: 2072-2080.
[26] Zhou Y, Wu Y, Jiang X, Zhang X, Xia L, Lin K and Xu Y. The effect of quercetin on the osteogenesic differentiation and angiogenic factor expression of bone marrow-derived mesenchymal stem cells. PLoS One 2015; 10: e0129605.
[27] Chen Y, Zhao B, Zhu Y, Zhao H and Ma C. HIF-1-VEGF-Notch mediates angiogenesis in temporomandibular joint osteoarthritis. Am J Transl Res 2019; 11: 2969-2982.

[28] Yudoh K, Nakamura H, Masuko-Hongo K, Kato T and Nishioka K. Catabolic stress induces expression of hypoxia-inducible factor (HIF)-1 alpha in articular chondrocytes: involvement of HIF-1 alpha in the pathogenesis of osteoarthritis. Arthritis Res Ther 2005; 7: R904-914.
[29] Deng Z, Wang Z, Jin J, Wang Y, Bao N, Gao Q and Zhao J. SIRT1 protects osteoblasts against particle-induced inflammatory responses and apoptosis in aseptic prosthesis loosening. Acta Biomater 2017; 49: 541-554.
[30] Khuwijitjaru P, Sayputikasikorn N, Samuhasaneetoo S, Penroj P, Siriwongwilaichat P and Adachi S. Subcritical water extraction of flavoring and phenolic compounds from cinnamon bark (Cinnamomum zeylanicum). J Oleo Sci 2012; 61: 349-355.
[31] Ge Y, Zhou S, Li Y, Wang Z, Chen S, Xia T, Shen J, Teng H and Jiang Q. Estrogen prevents articular cartilage destruction in a mouse model of AMPK deficiency via ERK-mTOR pathway. Ann Transl Med 2019; 7: 336.
[32] Liu-Bryan R and Terkeltaub R. Emerging regulators of the inflammatory process in osteoarthritis. Nat Rev Rheumatol 2015; 11: 35-44.
[33] Xiao YP, Tian FM, Dai MW, Wang WY, Shao LT and Zhang L. Are estrogen-related drugs new alternatives for the management of osteoarthritis? Arthritis Res Ther 2016; 18: 151.
[34] Fu D, Shang X, Ni Z and Shi G. Shikonin inhibits inflammation and chondrocyte apoptosis by regulation of the PI3K/Akt signaling pathway in a rat model of osteoarthritis. Exp Ther Med 2016; 12: 2735-2740.
[35] Sun K, Luo J, Guo J, Yao X, Jing X and Guo F. The PI3K/AKT/mTOR signaling pathway in osteoarthritis: a narrative review. Osteoarthritis Cartilage 2020; 28: 400-409.
[36] Wang C, Zeng L, Zhang T, Liu J and Wang W. Tenuigenin prevents IL-1beta-induced inflammation in human osteoarthritis chondrocytes by suppressing PI3K/AKT/NF-kappaB signaling pathway. Inflammation 2016; 39: 807-812.
[37] Xue JF, Shi ZM, Zou J and Li XL. Inhibition of PI3K/AKT/mTOR signaling pathway promotes autophagy of articular chondrocytes and attenuates inflammatory response in rats with osteoarthritis. Biomed Pharmacother 2017; 89: 1252-1261.
[38] Y YJW. Effects of cinnamic acid on the proliferation and differentiation of rat spontaneous transformed mesenchymal stem cells. Journal of Hubei University of Medicine 2016; 35: 5.
[39] Liao JC, Deng JS, Chiu CS, Hou WC, Huang SS, Shie PH and Huang GJ. Anti-inflammatory activities of cinnamomum cassia constituents in vitro and in vivo. Evid Based Complement Alternat Med 2012; 2012: 429320.
[40] Yang J YL, Gong YX, Gong XR and Lu J. Effect of cinnamic acid on proliferation and differentiation of BMSCs in rats. Modern Journal of Integrated Traditional Chinese and Western Medicine 2014; 23: 3.
[41] Im K, Issac A, Nm J, Ninan E, Maliakel B and Kuttan R. Effects of the polyphenol content on the anti-diabetic activity of Cinnamomum zeylanicum extracts. Food Funct 2014; 5: 2208-2220.