MEDS Chinese Medicine (2021)
ISSN 2616-1753 Volume 3 Issue 2
DOI: 10.23977/medcm.2021.030209
Clausius Scientific Press, Canada

To explore the mechanism of Epimedium in the treatment of osteoporosis based on network pharmacology

Lei Zhang, Feng Yang*

Shaanxi University of Chinese Medicine

*Corresponding author: 2720375803@qq.com

Keywords: network pharmacology, Epimedium, Osteoporosis, Core target signaling pathway

Abstract: Objective To screen the target and signal pathway of Epimedium active components in the treatment of osteoporosis by using network pharmacology, and to provide more promising evidence for the treatment of osteoporosis. Methods TCMSP analysis platform was used to screen the information of active constituents and active constituents of traditional Chinese medicine.Uniprot database and Excel were used to find the gene names of the active components.The disease-related targets were collected from Genecards database and OMim DRUGBANK database, and the overlapping values between the three databases were deleted. The intersection of Chinese medicine target genes and disease target genes was obtained by Venny software, and the obtained common genes of Chinese medicine and disease were input into Cytoscape software to obtain the disease-Chinese medicine and target regulatory network. Then, String software and Cytoscape software were used to construct the protein interaction network for the common target of TCM and disease. Common target genes were enriched by GO and KEGG function analysis, and the common target pathway was constructed by Cytoscape software.Results Twenty-three active components and 72 common target genes of Epimedium for the treatment of osteoporosis were screened. Concluded that the mechanism may be related to the AGE of diabetes complications -RAGE signaling pathways (AGE-RAGEsignalingpathwayindiabetic complications) way of TNF signaling pathways (TNFsignalingpathway) cancer (Pathwaysincancer) signaling pathway HIF - 1 signalingpathway (HIF - 1) etc, and Bai Jie - 6 gene (IL - 6) RAC - alpha serine/threonine protein...Vascular endothelial growth factor (AKT1)...Tumor necrosis factor (TNF) cell tumor antigen p53(TP53) may play a key role.Conclusion Based on network pharmacology, the mechanism of action of Epimedium in the treatment of osteoporosis was discussed, which provided an effective basis for the treatment of the disease.

1. Introduction

Osteoporosisop (Osteoporosisop) is characterized by bone loss, which is characterized by a decrease in bone mass per unit volume and a decrease in the ratio of mineral salt to bone matrix, leading to a systemic bone disease that greatly increases the probability of fracture.In today's society, aging is serious and osteoporosis has a great side effect on people's life [1].Present on the OP

treatment [2-3] as well as western medicine with western medicine therapy for osteoporosis caused by fracture were treated with surgery or technique, but there are many problems, such as the adverse reactions of western medicine and treatment is expensive, so urgently need to find a can not only improve disorder can relieve pain and reduce the economic burden of patients of new drugs.Traditional Chinese medicine has opened up a new way for us to treat diseases. For example, some medicines, such as Gushu Bu, Epimedium, Cistanchola, Eucommia ulmoides and Radix Achyranthae, have the functions of tonifying kidney and warming Yang, renewing tendon and bone, promoting blood circulation and removing blood stasis, and have their own unique curative effect in treating osteoporosis.Epimedium passes through the meridians of the liver and kidney. The Compendium of Materia Medica says that Epimedium is beneficial to qi, strengthening muscles and bones, tonifying the waist and knees, and strengthening the heart. Flavonoids, polysaccharides, lignins, phenolic glycosides, alkaloids and other active components of Epimedium belong to the main chemical components of Epimedium, which can inhibit cell destruction, promote bone cells, promote bone formation, promote bone marrow hematopoiesis, and have a certain effect on leukemia [4-7].Studies have shown that Epimedium can induce osteoclast apoptosis and inhibit osteogenic resorption, and the effect gradually increases with the increase of concentration [8].Through network pharmacology, further analysis of Epimedium and further study of the mechanism of Epimedium in the treatment of osteoporosis were carried out, so as to provide a good method for better treatment of OP, improving the incidence of OP and people's quality of life.

2. Materials and methods

2.1 Data

The platforms used in this study include the Pharmacological Analysis Platform of Traditional Chinese Medicine System (TCMSP) OMIM database Drugbank database GeneCard database Venny software Cytoscape software Metascape software String software

2.2 Methods

2.2.1 Prediction of active components and targets in Epimedium and conversion of target gene names

This research system in Chinese medicine pharmacological analysis platform TraditionalChineseMedicineSystemsPharmacologyDatabaseandAnalysisPlatform, TCMSP) in the screening of the active components of epimedium.Oral bioavailability (OB) > 30% and druglikeness (DL) > 0.18 were selected as conditions [9], and the screening results were shown in Table 2.TCMSP database was used to predict the target of active ingredients.Uniprot database was used to convert the effective target information into gene names. Because the individual target information did not match the gene names in Uniprot, the actual gene names were less.

2.2.2 Acquisition of known disease target genes

The keyword osteoporosis was searched and input into OMIM, DRUGbank and Genebank databases. The known disease target genes were screened and the duplicates were deleted to obtain the required disease genes.

2.2.3 Obtain the intersection of TCM and diseases

Excel software was used to intersect Chinese medicine target genes and disease target genes to obtain the common target genes of Chinese medicine and disease. Venny software was used to obtain the Venn diagram of the common target genes of Chinese medicine and disease(as shown in Figure.1).

2.2.4 Construction of TCM - disease regulatory network map and construction of target gene protein interaction network of Epimedium in the treatment of OP

The target genes of Chinese medicine, the common target genes of Chinese medicine and disease and the target genes of disease were ploted by Cytoscape, and the regulatory network diagram of Chinese medicine and disease was obtained (as shown in Figure 2). The node types included nodes of the common target genes of Chinese medicine, disease and Chinese medicine and disease.String software was used to set the screening condition as human, and the minimum interaction score was set as 0.4. The obtained target genes were input, and the results were input into Cytoscape for processing (as shown in Figure 3).

2.2.5 GOKEGG enrichment analysis and pathway analysis

The common target genes were input and analyzed by Metascape, MicroSignal and Cytoscape software, and the GO function enrichment analysis (as shown in Figure 4), KEGG enrichment analysis (as shown in Figure 5) and target pathway network (as shown in Figure 6) were obtained.

3. Results

3.1 The active components and target information of Epimedium were screened by TCMSP database

According to 0B>30% and DL>0.18, 23 active components and 511 target information of Epimedium were obtained.

Table 1: Screening results of effective components of Epimedium in TCMSP

MOLID	化合物英文名	化合物中文名	OB	DL
MOL001510	24-epicampesterol	24-表氨酯	37.58	0.71
MOL001645	Linoleyl acetate	乙酸亚油酯	42.1	0.2
MOL001771	poriferast-5-en-3beta-ol	poriferast-5-en-3beta-ol	36.91	0.75
MOL001792	DFV	DFV	32.76	0.18
MOL003044	Chryseriol	色粉	35.85	0.27
MOL003542	8-Isopentenyl-kaempferol	8-异戊烯基山emp酚	38.04	0.39
MOL000359	sitosterol	谷甾醇	36.91	0.75
MOL000422	kaempferol	山萘酚	41.88	0.24
MOL004367	olivil	橄榄石	62.23	0.41
MOL004373	Anhydroicaritin	脱水角蛋白	45.41	0.44
MOL004380	C-Homoerythrinan	C-高赤霉素	39.14	0.49
MOL004382	Yinyanghuo A	Yinyanghuo A	56.96	0.77
MOL004384	Yinyanghuo C	Yinyanghuo C	45.67	0.5
MOL004386	Yinyanghuo E	Yinyanghuo E	51.63	0.55
MOL004388	6-hydroxy-11,12-dimethoxy-2,2-dimethyl-1	6-羟基-11,12-二甲氧基-2,2-二甲基-1	60.64	0.66
MOL004391	8-(3-methylbut-2-enyl)-2-phenyl-chromone	8-（3-甲基丁-2-烯基）-2-苯基色酮	48.54	0.25
MOL004394	Anhydroicaritin-3-O-alpha-L-rhamnoside	脱水甘油30-α-L鼠李糖苷	41.58	0.61
MOL004396	1,2-bis(4-hydroxy-3-methoxyphenyl)propan-1	1,2-双（4-羟基-3-甲氧基苯基）丙烷-1	52.31	0.22
MOL004425	Icariin	伊卡林	41.58	0.61
MOL004427	Icariside A7	伊卡甙A7	31.91	0.86
MOL000006	luteolin	木犀草素	36.16	0.25
MOL000622	Magnograndiolide	甘露聚糖	63.71	0.19
MOL000098	quercetin	槲皮素	46.43	0.28

3.2 TCM - disease target genes

The TCM target genes and disease target genes were screened by OMIM, DRUGBANK and Genebank disease database, and a total of 1365 effective disease target genes were finally obtained. The analysis was carried out by Venny software, and 72 TCM and disease common target genes were

analyzed.

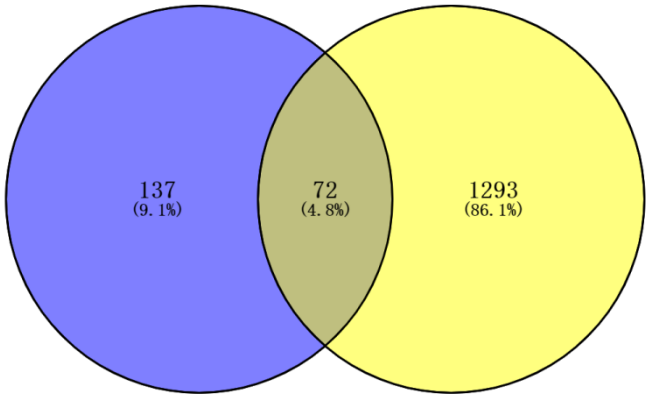

Figure 1: Intersection of TCM target genes and disease target genes

3.3 Construction of TCM - disease regulation network

As shown in the figure, osteoporosis is represented by a blue arrow, Epimedium green by a regular octagonal color, Epimedium purple by a rhomboid by an active component, and Epimedium red by a circular common gene target.The results showed that there were 23 active components and 72 target genes, which may have a great influence on the occurrence of osteoporosis.

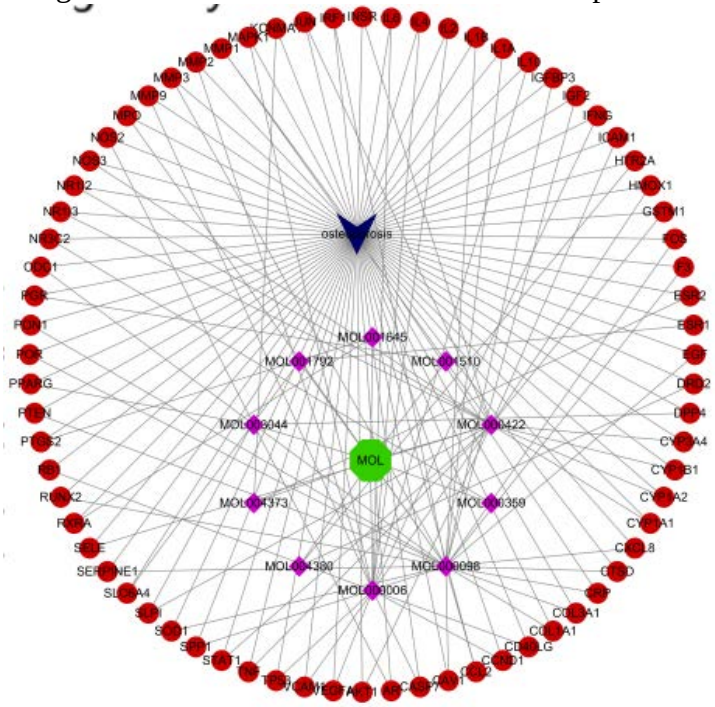

Figure 2: Regulatory network of TCM disease targets

3.4 Epimedium therapy OP target gene protein interaction network

According to the study, the core target gene of Epimedium in the treatment of OP, IL-6 gene (IL-6), vascular endothelial growth factor...(VEGFA) cell tumor antigen p53(TP53) rac-α serine/threonine protein...(AKT1) Tumor necrosis factor (TNF).

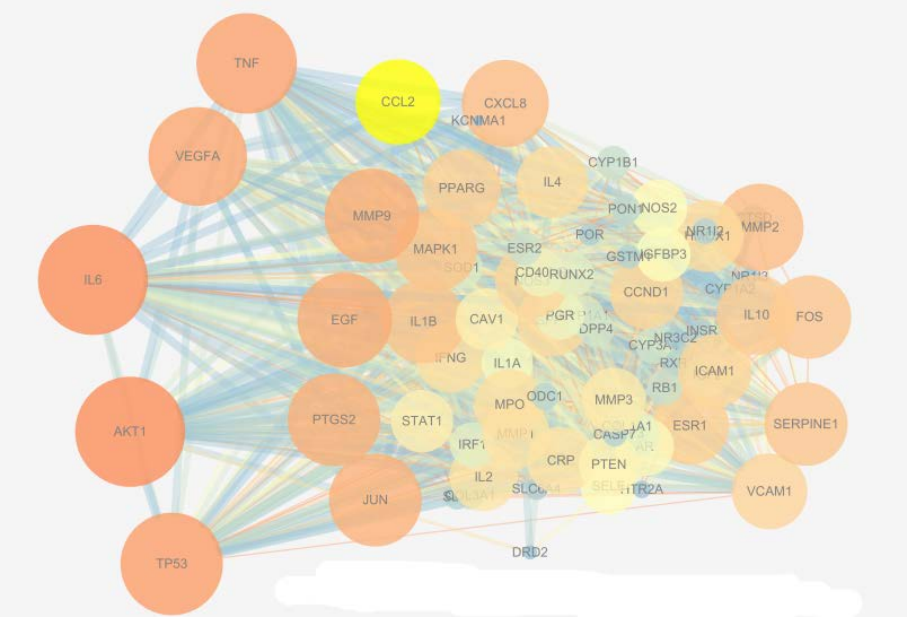

Figure 3: Target protein interaction network of Epimedium in the treatment of OP

3.5 GO functional enrichment analysis

As shown in Figure 4, the function of GO, the core target of Epimefuli in the treatment of OP, is mainly mediated by the cytokine-mediated signalling pathway. Cell response to organic cyclics (cellularresponsetoorganiccycliccompound) negative regulation of cell proliferation (negativeregulationofcellproliferation) positive regulation of cell death (positiveregulationofcelldeath) membrane rafts (membraneraft) RNA polymerase II transcription factor complex (RNApolymeraseIItranscriptionFactorcomplex) extracellular matrix (extracellularmatrix) activity of steroid hormone receptor (steroidhormonereceptoractivity) activity of cytokines (cytokineactivity). Transcription factor binding (transcriptionfactorbinding), etc.

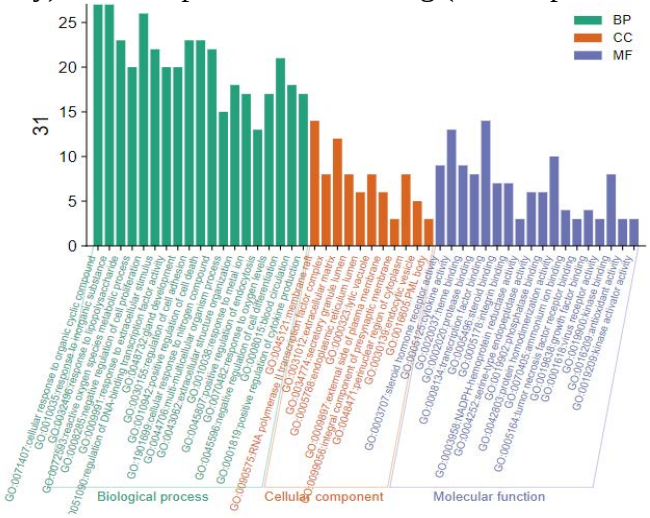

Figure 4: Histogram of GO functional enrichment analysis

3.6 KEGG functional enrichment analysis

The results of pathway enrichment analysis of the core target gene KEGG of Epimedium in the treatment of osteoporosis are shown in Figure 5.Features mainly include the AGE of diabetes complications - RAGE signaling pathways (AGE - RAGEsignalingpathwayindiabeticcomplications) way of TNF signaling pathways (TNFsignalingpathway) cancer (Pathwaysincancer) signaling pathway HIF - 1 signalingpathway (HIF - 1) bubble chart graph on the left side of the letter to KEGG name, use the proportion of genes as the abscissa,The number of enriched genes is represented by the size of the circle. The brighter the color, the greater the P value, the higher the degree of enrichment and the smaller the corresponding P value.

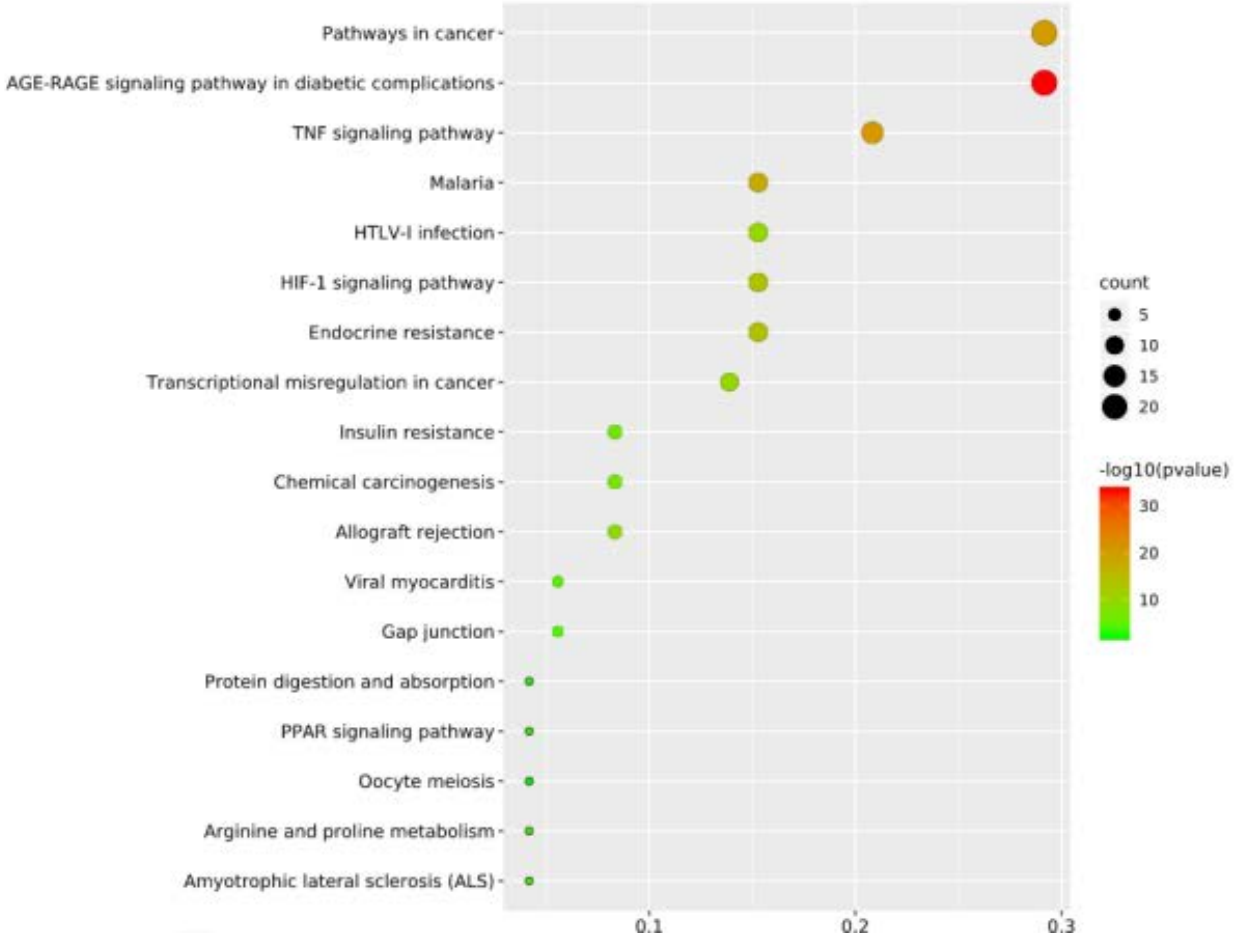

Figure 5: Bubble diagram of KEGG function analysis

As shown in Figure 6, the signal-pathway target network diagram drawn by the Ctyoscape software, in which the arrow nodes represent the potential target for the treatment of OP, and the triangle nodes represent the signal pathways. As shown in the figure, a KEGG pathway is enriched in multiple target genes, and multiple pathways surround one target gene simultaneously.

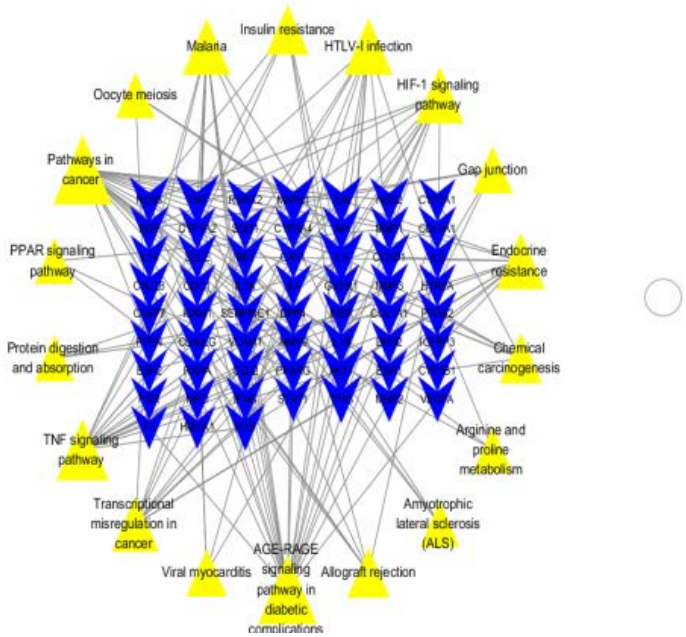

Figure 6: Target - pathway diagram

4. Discuss

With the progress of research, more and more people have known that Epimedium has a good effect in the treatment of osteoporosis, and studies have shown that icariin inhibits osteoclast induction and bone resorption.Gao Mengying et al. [11] found that they could not only block osteoclasts but also block bone resorption of osteoclasts.The treatment of OP by Epimedium is accomplished through multiple target genes and multiple pathways.IL-6 rAC-α serine/threonine protein...Vascular endothelial growth factor (AKT1)...Tumor necrosis factor (TNF) cell tumor antigen p53(TP53) is the core target gene of Epimedium epimedii in the treatment of OP.IL - 6 is an important part of the bone absorption, the role is to promote their own synthesis, inhibiting apoptosis broken drum, promote the osteoblast apoptosis, and is a form through autocrine and paracrine effect then in osteoporosis, AKT1 is osteoblasts can control the osteoblast and osteoclast differentiation in the unique signal transduction of intermediates, and the osteoblast and osteoclast value-added differentiation and so on, can participate in the regulation of bone metabolism [12, 13].Studies have shown that VEGFA plays a positive role in the treatment of osteonecrosis of the jaw in patients with osteoporosis or bone-related cancer complications [14].Studies have shown that TNF can slow down the process of bone erosion and prevent bone loss to some extent [15].Studies have shown that TP53 is a core target in the treatment of osteoporosis [16], and these genes regulate OP by mediating bone resorption and bone formation.Multiple KEGG signaling pathways such as TNF signaling pathway, AGE-RAGE signaling pathway in diabetes complications, cancer pathway and HIF-1 signaling pathway may be effective for OP.[17] Chen Peng et al. Effects of TNF on osteoclast markers (CTSKTrapNF-κBκBα), suggesting that TNF-α can induce osteoclast formation in postmenopausal osteoporosis [J].Studies have found that water extract of mulberry leaves can inhibit tibial and femoral related proteins and reduce damage to prevent and treat diabetic osteoporosis [18]. Studies have shown that [19] RANKL/RANK function to the development of epithelial cell proliferation and cell survival and alveolar is crucial, the regulating function of RANKL is one of the key factors of the mammary gland hyperplasia induced by progesterone, drugs containing it monoclonal antibody denosumab can promote tumor occurrence and metastasis, was used to treat osteoporosis related to

disease, also can treat primary breast cancer.The results showed that the HIF-1α pathway was activated in developing osteoblasts, which greatly increased the ability of VEGF-mediated bone angiogenesis, increased bone formation, promoted osteoclast formation and enhanced osteoclast activity [20-22]. Experimental results showed that inhibition of HIF-1 signaling pathway plays an important role in the pathological process of postmenopausal osteoporosis in mice, and can improve osteoporosis [23].

What has been discussed above, we through the network pharmacology of variety of traditional Chinese medicine compound through the composition selection, use of relational database and the software of target genes and pathways, carries on the analysis research, we have a better understanding of drug mechanism, the treatment of related diseases can be more handy, application of modern research to study of drugs, more adapt to the modern research model, the new drug industry also has a positive role in promoting.

References

[1] Paintin J, Cooper C, Dennison E. [J]. BR J Hosp Med (Lond), 2018, 79 (5): 253-258 XIA Weibo, ZHANG Zhenlin, LIN Hua, et al.

[2] Wang Y, Wang Y, Wang Y, et al. The effect of osteohydrophobic pine on the pathogenesis of osteohydrophobic pine [J]. Chinese Journal of Osteoporosis, 2019, 25 (3): 281-309.

[3] Zhang Shifang, He Qiushuo, Wang Yizhou, Liu Limin, Wang Lei.Journal of Shaanxi University of Traditional Chinese Medicine, 2010, 33(06): 145-147. (In Chinese)

[4] GUO Baolin, PEI Likuan, XIAO Peigen.Taxonomic significance of flavonoids from Epimedium [J]. Acta Botanica Sinica, 2008(06): 874-885.

[5] HUANG T. Study on extraction and purification of Epimedium from Tangshenkang capsule [J]. Tianjin Pharmacy, 2017, 29(06): 25-28. (In Chinese with English abstract)

[6] Wang Jianzhong, Gao Hongyan, Wang Kunzheng, Zhou Rongxing, Li Xiaodong, Guo Jun, Lv Huicheng.Effects of Epimedium on the expression of OPG/RANKL mRNA in osteonecrosis of femoral head [J]. Journal of Southern Medical University, 2011, 31(10): 1714-1717.

[7] Chen Keming, Ge Baofeng, Ma Huiping, Liu Xingyan, Bai Menghai, Ma Liping, Lv Mingbo. Effects of icariin on osteogenic differentiation of bone marrow stromal stem cells cultured in vitro [J]. Chinese Journal of Osteoporosis, 2008(09): 642-645+632.

[8] Gao Xiaoming, Shi Jianping.Effects of Epimedium extract on bone mineral density and weight in ovariectomized rats [J]. Journal of Inner Mongolia Medical University, 2013, 35(06): 442-445.

[9] Liang Xuezhen, Xu Bo, Li Gang, Gai Shuaishuai, Yan Bozhao, Li Jiacheng, Xia Congmin.Study on the mechanism of Bushenhuoxue capsule against osteoporosis based on network pharmacology and bioinformation [J]. Chinese Journal of Osteoporosis, 2018, 24(06): 755-761.

[10] Mingbo Lv, Xingyan Liu, Baofeng Ge, Keming Chen, Menghai Bai.Effects of icariin on bone marrow induced osteoclasts and bone resorption in mice [J]. Chinese Journal of Osteoporosis, 2007(05): 315-319.

[11] Gao Mengying, Huang Huijuan, Xie Shuhong.Effects of olivin on osteoclast proliferation [J]. Chinese Journal of Osteoporosis, 2017, 23(07): 896-899.

[12] Zhou Y N. Expression of PI3K, AKT1, AKT2 and NF-κB in bone tissue of type 2 diabetic osteoporosis rats [D]. Hebei Medical University, 2012.

[13] Mukherjee A, Rotwein P. Comparison of osteoblast differentiation and mediated osteoclast development in AKT1-mediated osteoblast signaling. Mol Cell Biol. 2012; 32 (2): 490 - 500. Doi: 10.1128 / MCB. 06361-11

[14] Lee Kh, Kim H, Kim CH, et al. Identified genetic variants for brady-induced osteonecrosis in the jaw: A case study. J Genet Med. 2019; Published 2019 Nov 20. DOI: 10.1186/s12967-019-2129-3

[15] Dubrovsky AM, Lim MJ, Lane Ne. Osteoporosis in Rheumatic Diseases: Anti- Rheumatic Diseases and the Skeletons. Calcif Tissue Int. 2018; 102 (5): 607 - 618. Doi: 10.1007 / s00223-018-0401-9

[16] Xie W, Ji L, Zhao T, Gao P. Identification of transcriptional factors and key genes in primary osteoporosis by DNA microarray. Med Sci Monit. 2015; 21: 1333-1344. Published 2015 May 9. DOI:10.12659/MSM.894111

[17] Chen Peng, Li Yang, Hu Weiwen, Li Jian, He Runze.TNF-α promotes RANKL-induced osteoclast formation in postmenopausal osteoporosis by activating NF-κB [J].Genomics and Applied Biology, 2019, 38(02): 960-965.

[18] Liu Chenyue. Study on the effect mechanism of mulberry leaves on DOP rats based on AGEs/RAGE/NOX4 /NF-κB and TRPV6 / CABP-28K /VDR pathway [D]: Beijing University of Chinese Medicine, 2018, 1-20. (In Chinese with English abstract)

[19] LV Kiesel, Annemarie Kohl. The Role of RANKL pathway in breast cancer [J]. J Cancer Res, 2016, 86 (1): 87-91.
[20] INDO Y, TAKESHITA S, ISHII KA, et al.Metabolic regulation of osteoclast differentiation and function.J Bone Miner Res, 2013, 28 (11): 2392-2399.
[21] Wang Mingliang, Yan Xiaolong, Tian Sisheng.A network pharmacological study of Erxian decoction in the prevention and treatment of osteoporosis [J]. Chinese Journal of Osteoporosis, 2020, 26(04): 570-577.
[22] Miyauchi Y, Sato Y, Kobayashi T, et al. Osteoclast induction by estrogen deficiency in postmenopausal osteoporosis.Proc Natl ACAD Sci U Sa, 2013, 110 (41): 16588-16573.
[23] Wang Y, Wang Y, Wang Y, et al. The HIF-1 signaling pathway is associated with postmenopausal osteoporosis [J]. Journal of Sichuan University (Medical Science), 2017, 48(06): 862-868.