ISSN 2706-6819 Vol.6, Issue 11: 1-10, DOI: 10.25236/IJFM.2024.061101

Network Pharmacology and Molecular Docking Study of the Chinese Miao Medicine LiuYueHuanYang in the Treatment of Osteoarthritis

Xinxin Yang[1,a], Yan Wang[1,2,b], Kaiwei Zhang[1,2,c,*]

[1]Guizhou University of Traditional Chinese Medicine, Guiyang, China
[2]The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guiyang, China
[a]1434940803@qq.com, [b]1217304531@qq.com, [c]zkw1973@aliyun.com
[*]Correspondence author

Abstract: *To examine the potential therapeutic targets of the Chinese Miao medicine formula LiuYue HuanYang (LYHY) in the treatment of osteoarthritis (OA), we analyzed the active compounds of LYHY and the key targets of OA and investigated the interacting pathways using network pharmacological approaches and molecular docking analysis.Network pharmacology was adopted to detect four active components of Hmong medicine LYHY. The key target in the important signal pathway and the main active component in LYHY were linked by molecular docking. In this study, we retrieved the four active ingredients of the Hmong medicine LYHY from the literature, namely kaempferol, arbutin, glucosyringic acid and guajavarin, and predicted the corresponding targets of the active ingredients by Swiss Target Prediction; and screened the targets related to OA by the databases GeneCard (https://www.genecards.org/), Genemap ((https://www.omim.org/search/advanced/geneMap), Drugbank (https://go.drugbank.com/about) and OMIM (https://www.omim.org/) to screen the targets related to OA.The PPI network was then constructed and the results showed that AKT1, EGFR, MMP9, SRC, MMP2, ABCB1 and CYP19A1 were the key targets of LYHY for the treatment of OA.GO enrichment analysis showed that cellular response to lipids, cellular response to reactive oxygen species, and inflammatory response were closely related to the mechanism of June Redux for the treatment of OA; KEGG pathway analysis showed that EGFR tyrosine kinase inhibitor resistance,ErbB signaling pathway,ErbB signaling pathway,VEGF signaling pathway,Rap1 signaling pathway,Estrogen signaling pathway and Ras signaling pathway were associated with the intervention of LYHY in OA.Molecular docking showed that the active components had a good affinity with EGFR and SRC.*

Keywords: *Network pharmacology, LYHY, Osteoarthritis, Molecular docking, EGFR*

1. Introduction

Osteoarthritis (OA) is a chronic degenerative disease of the bones and joints that affects middle-aged and older adults and carries the risk of pain, deformity and disability. Studies have shown that more than 50% of people over the age of 65 have osteoarthritis[1, 2]. Risk factors for developing osteoarthritis include obesity, trauma and ageing[1, 3]. There is more than one pathogenesis of osteoarthritis, including inflammation, joint damage, destruction and remodelling of cartilage and subchondral bone, and the generation of bone redundancy[4], which leads to pain in the affected joints, a decline in the patient's quality of life, sleep disturbance, and a range of psychiatric disorders, as well as a financial burden on the family in terms of treatment.

Currently, there are two views on the treatment of osteoarthritis: one is that osteoarthritis is difficult to cure and its course is irreversible. Osteoarthritis can only be treated with oral non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids, amino acid dextrose or intra-articular injections of lubricating fluids such as hyaluronic acid, combined with oral Chinese medicine, local treatments and traditional Chinese medicine (TCM) physiotherapy to relieve the patient's pain symptoms[5]. None of these can restore cartilage or stop the onset of OA. Another argument is that OA is not incurable and some very promising drugs have been discovered with the advantages of multi-target and multi-efficacy, which allows the drug to be involved in different stages of the disease and play a synergistic role between the different targets[6].

ISSN 2706-6819 Vol.6, Issue 11: 1-10, DOI: 10.25236/IJFM.2024.061101

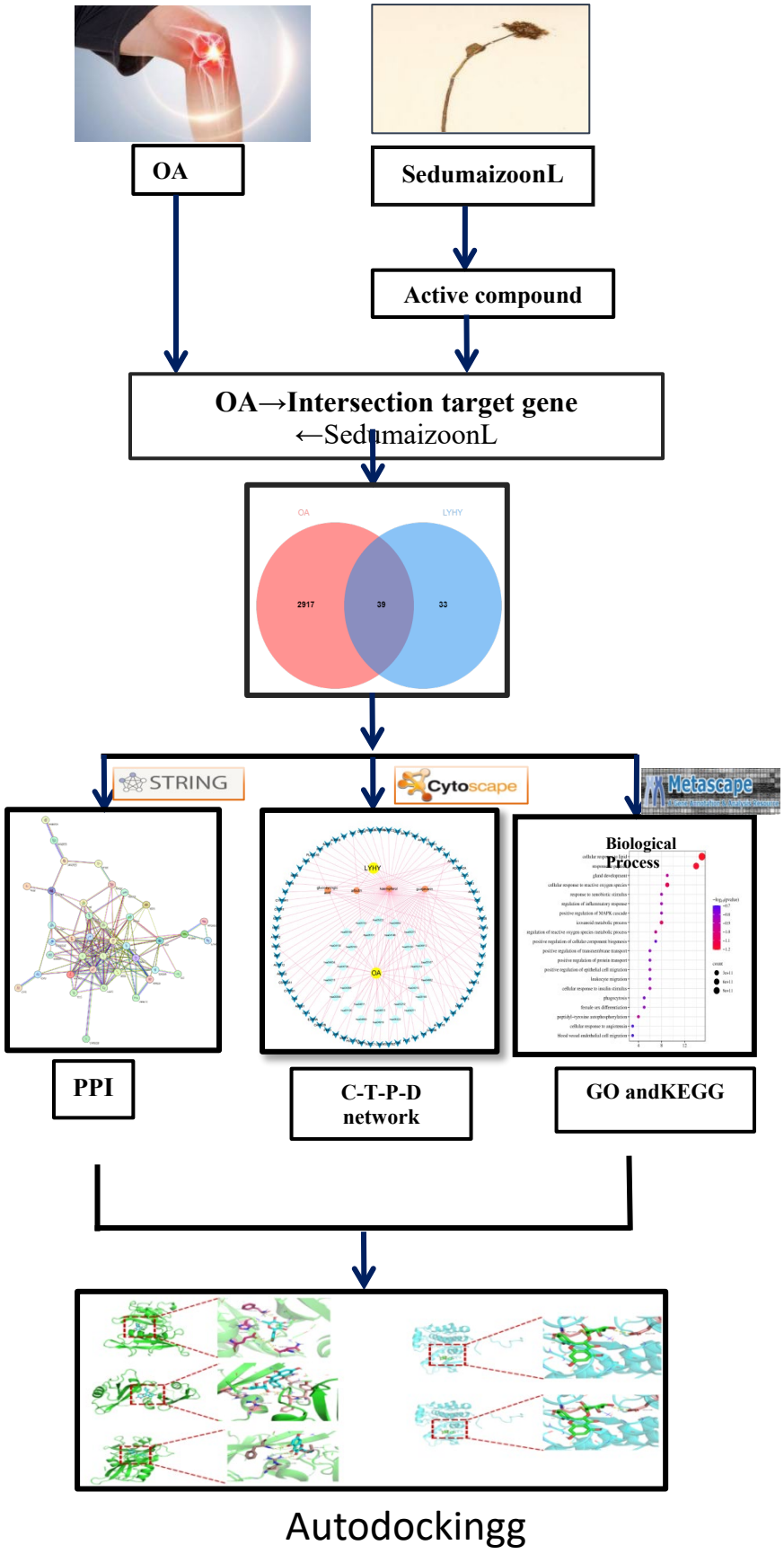

Figure 1: Flow chart of this study based on network pharmacology.

LYHY is a characteristic Miao medicine of Guizhou, derived from the root or whole herb of Sedum

ISSN 2706-6819 Vol.6, Issue 11: 1-10, DOI: 10.25236/IJFM.2024.061101

aizoom L, a plant of the genus Sedum in the family Sedumaceae[7]. It is widely used by Hmong Miao doctors in Guizhou as a medicine for arthritis and joint injuries because of its effectiveness in activating blood circulation and removing blood stasis, reducing swelling and relieving pain. The results of modern pharmacological research show that LYHY can inhibit NO produced by inflammatory cells to achieve its antibacterial and anti-inflammatory effects[7]; in addition, LYHY also lowers blood lipids and improves arterial blood flow, and contains flavonoids, phenolic acids and steroidal terpenoids, which may be the material basis for its anti-OA effects.

We will use a network pharmacology approach to assess the relationship between complex diseases and multi-target drugs by collecting information on the association between LYHY and diseases and using this as a basis for an integrative analysis of the potential mechanisms of multi-target drugs for the treatment of osteoarthritis, which is the main aim of this study, the flow chart is shown in Figure 1.

2. Materials and methods

2.1 Acquisition of the active compounds in LYHY and construction of component-target network.

We obtained the four active compounds of LYHY from previous literature reports and then obtained their SDF structural formulae from the Pub Chem database (https://pubchem.ncbi.nlm.nih.gov/) species[8]. The SDF files were then uploaded to Swiss Target Prediction (http://swiss target prediction.ch/) for target prediction. Targets with Z-scores ≥1 were selected from the prediction results. The predicted targets were then converted into standardised gene symbols using the uniprot data and then using the Uni Prot database (https://www.uniprot.org/).The regulatory network of 'herb-component-target' was then constructed using Cytoscape software.

2.2 OA disease-related target screening

Using osteoarthritis as a keyword, gene targets for the treatment of OA were retrieved from the following databases GeneCard (https://www.genecards.org/), Genemap (https://www.omim.org/search/advanced/geneMap), Drugbank (https://www. omim.org/search/advanced/geneMap) and OMIM (https://www.omim.org/search/advanced/ geneMap). https://go.drugbank.com/about), Drugbank (https://www.omim.org/) and OMIM (https://www.omim.org/); all targets were combined and the duplicate values were deleted for future use. Then, to clarify the interactions between LYHY-related targets and osteoarthritis-related targets, the two sets of data were imported into the online tool jvenn (//jvenn.soulouse.inra.fr/app/index.html) to identify the common targets of the drug and OA and to draw a Venn diagram. A list of potential targets of LYHY for the treatment of OA was then derived from the overlap between drug and disease gene targets.

2.3 Construction of PPI network of common targets of LYHY and OA.

Protein-protein interaction (PPI) networks play an important role in revealing cellular functions and biological processes. PPIs may lead to a better understanding of the molecular mechanisms of SM treatment of OA. To further explore the mechanism of action of LYHY in the treatment of OA, we submitted common targets to the STRING11.0 database (https://string-db.org) to construct a protein-protein interaction (PPI) network model. The PPI network was generated by setting Homo sapiens as a biological species and the minimum interaction threshold of medium confidence was set to > 0.4 and downloaded in TSV format, and then the results were imported into Cytoscape to assess the core targets of LYHY in the treatment of OA using APP Centiscape;

2.4 GO analysis and KEGG pathway enrichment analysis.

Gene Ontology (GO) and Kyoto Encyclopedia of Genomes (KEGG) pathway analyses were performed using the DAVID database (http://david.ncifcrf,gov). Biological process (BP), cellular composition (CC) and molecular function (MF) terms of the acquired targets were analysed by GO enrichment, and important biological pathways were analysed by KEGG pathway enrichment. We selected the top 10 GO annotations and the top 20 KEGG pathways and imported them into the Bioinformatics Atlas website (http://www.bioinformatics.com.cn/) for bubble mapping.

ISSN 2706-6819 Vol.6, Issue 11: 1-10, DOI: 10.25236/IJFM.2024.061101

2.5 Construction the network of C-D-P-T.

The KEGG enrichment results were analysed and the top 20 signalling pathways and the corresponding targets of each pathway were imported into Cytoscape 3.8.2 software in order to map the main component-disease-pathway-target network of LYHY for OA.

2.6 Molecular docking validation

Protein crystal structures were downloaded from the PDB database (https://www.rcsb.org/) using the following search terms. The protein structures were then imported into PyMOL 2.2.0 software (https://pymol.org) for modifications including removal of water molecules, isolation of ligands and addition of hydrogen. Charges were added to the protein molecules using AutoDockTools software (http://autodock.scripps.edu/) and docking grid boxes were placed in the centre of the molecules. Molecular docking was performed using AutoDock Vina 1.1.2 software (http://vina.scripps.edu/). Affinity represents the ability of the ligand to bind to the receptor, with higher absolute affinity values indicating better binding. Finally, the binding of the receptor and protein in molecular docking was analysed using PyMol software (https://www.pymol.org/) and hydrogen bonds were labelled to visualise the docking results.

3. Result

3.1 Active chemical compositions and target prediction of LYHY.

We obtained the 34 components of LYHY from previous literature and 23 SDF structural formulae from the Pub Chem database. Potential targets were predicted using the Swiss Target Prediction database, and after merging and removing duplicates, four potential drug targets with $Z \geq 1$ were listed as core compounds, namely kaempferol, arbutin, glucosyringic acid and guajavarin, and screened for the four compounds corresponding to 91 targets.

To further understand the relationship between the four compounds and the 39 cross-target genes, we constructed a TCM compound-target network Figure 2 containing 76 nodes and 91 edges using Cytoscap 3.8.2 software.The green prismatic nodes represent the four compounds of LYHY, and the yellow V-shape represents the targets corresponding to the compounds. The higher the correlation, the greener the colour, and vice versa, the yellower the colour (Figure 2). The results showed that the greenest node with the highest degree was kampferol, and the top ten node genes were AKT1, EGFR, MMP9, SRC, MMP2, ABCB1 and CYP19A1. The results showed that a single compound could regulate multiple targets, and the active compounds and corresponding genes of LYHY are shown in Fig 2.

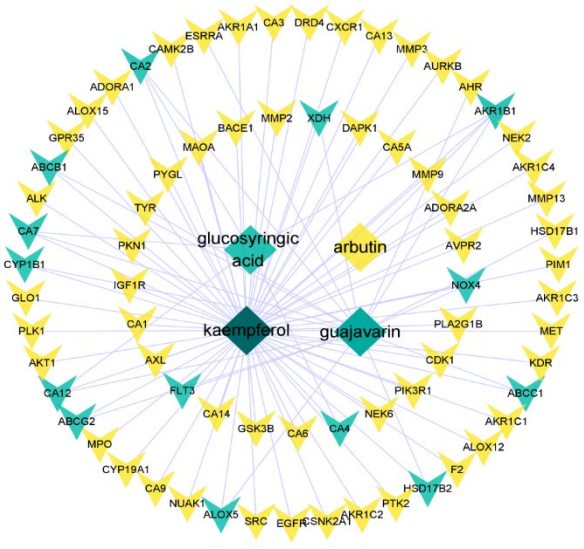

Figure 2: Active intredient -target network of LYHY.

ISSN 2706-6819 Vol.6, Issue 11: 1-10, DOI: 10.25236/IJFM.2024.061101

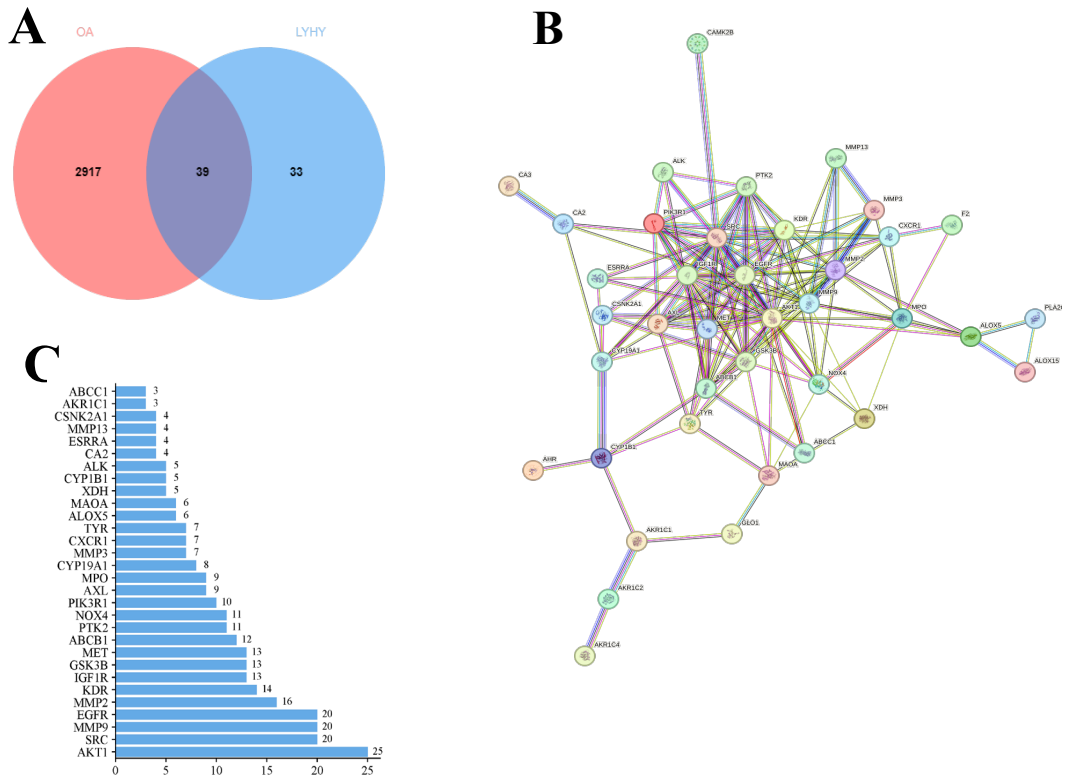

Figure 3: [A] Veen diagram of the targets in OA and LYHY. [B]The PPI newwork of 39 targets according to the STRING database. [C]Top 30 targets ranked by the degree value.

3.2 Prediction of OA targets.

A total of 2611 OA-related targets were obtained from Gene Cards, 30 from Genemap, 366 from OMIM and 125 from Drugbank, and after further removal of duplicates, 2958 OA-related targets were identified for subsequent analyses. Thirty-nine common targets of LYHY and OA were obtained using online Veen software for subsequent studies (see Figure 3A).

3.3 PPI Network Construction and Centiscape Analysis

The PPI network was obtained from the STRING database with 'Homo sapiens' selected in the organism column and the minimum required interaction score set to 0.4 (see Figure 3B). The network contains 39 nodes and 154 edges, where nodes represent protein names and edges represent protein interactions. To obtain the core PPI network, the initial PPI network was imported into Cytoscape 3.8.2 for visualisation (see Fig. 3B), and the PPI network was then centrally analysed and scored using the Centiscape plug-in. For the initial screening in Cytoscape 3.8.2, the selection criteria based on the corresponding medians were as follows BC > 53.435, CC > 0.0116 and DC > 7.89. Only genes meeting these criteria were retained (see Figure 4A). After screening, a new network with 7 nodes and 18 edges was obtained (Fig. 4B) In the core PPI, the larger the node, the higher the degree value. The first seven nodes were AKT1 (degree 25), SRC (degree 20), MMP9 (degree 20), EGFR (degree 20), CYP19A1 (degree 8), MMP2 (degree 16) and ABCB1 (degree 12)(see table 1).

ISSN 2706-6819 Vol.6, Issue 11: 1-10, DOI: 10.25236/IJFM.2024.061101

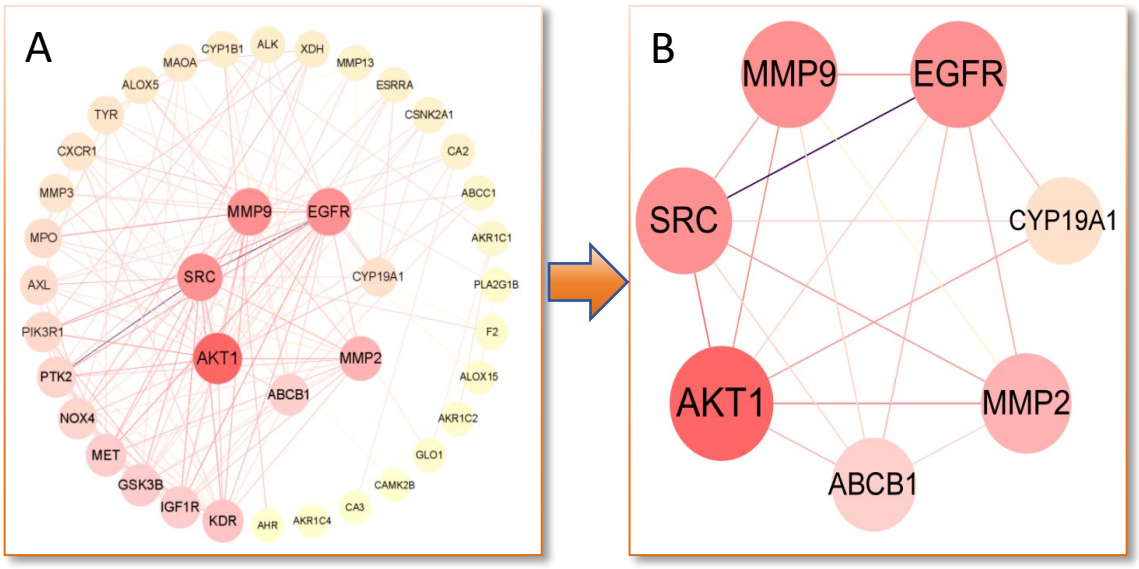

Figure 4: The PPI network of OA and LYHY. [A] the network with total 39 nodes and 154 edges. [B] the core network with 7 nodes and 18 edges.

Table 1: Topological information of key targets.

Target	Degree	Betweenness Centrality	Closeness Centrality
AKT1	25	0.217	0.644
EGFR	20	0.060	0.567
MMP9	20	0.120	0.594
SRC	20	0.119	0.576
MMP2	16	0.041	0.551
ABCB1	12	0.100	0.528
CYP19A1	8	0.067	0.507

3.4 GO analysis and KEGG pathway enrichment analysis.

The cross-targets were entered into David for GO and KEGG enrichment analysis, and the GO enrichment results were reflected in BP, CC and MFF. A total of 2054 enriched GO BPs, 236 enriched CCs, 394 enriched MFs and 93 enriched KEGGs were identified at $P < 0.05$ and $Q < 0.05$. The major biological processes involved in the BPs include protein autophosphorylation, phosphorylation, negative regulation, apoptotic process, positive regulation and negative regulation. Positive regulation of protein kinase B signalling, positive regulation of kinase activity, development of multicellular organisms, transmembrane receptor protein tyrosine kinase signalling pathway peptidyl-tyrosine autophosphorylation. Tyrosine autophosphorylation, cellular response to reactive oxygen species and beta-amide response(see Fig. 5A); Major molecular functions involved CC include receptor complexes, plasma membranes, exosomes, extracellular space, perinuclear cytoplasmic regions, extracellular matrix, matrix membranes, cytosol, extracellular regions and intracellular membranes bound cellular components include protein tyrosine kinase activity, transmembrane receptor protein tyrosine kinase activity, bile acid binding, ATP binding, protein kinase activity, ketone monooxygenase activity, oxidoreductase activity, oxidoreductase activity, ketone monooxygenase activity and ketone monocyte kinase activity. Activity, oxidoreductase activity, kinase activity, androstenedione dehydrogenase activity and androsta-3-alpha and 17-b-one activity. 3-alpha- and 17-beta-diol dehydrogenase activity; 3-alpha- and 17-beta-diol dehydrogenase activity. Diol dehydrogenase activity(see Fig. 5B and 5C); Major KEGG pathways include the EGFR tyrosine kinase inhibitor resistant ErbB pathway, the ErbB pathway, the vascular endothelial growth factor pathway, the Rap1 pathway, the estrogen pathway and the Ras pathway(see Fig. 5D).

ISSN 2706-6819 Vol.6, Issue 11: 1-10, DOI: 10.25236/IJFM.2024.061101

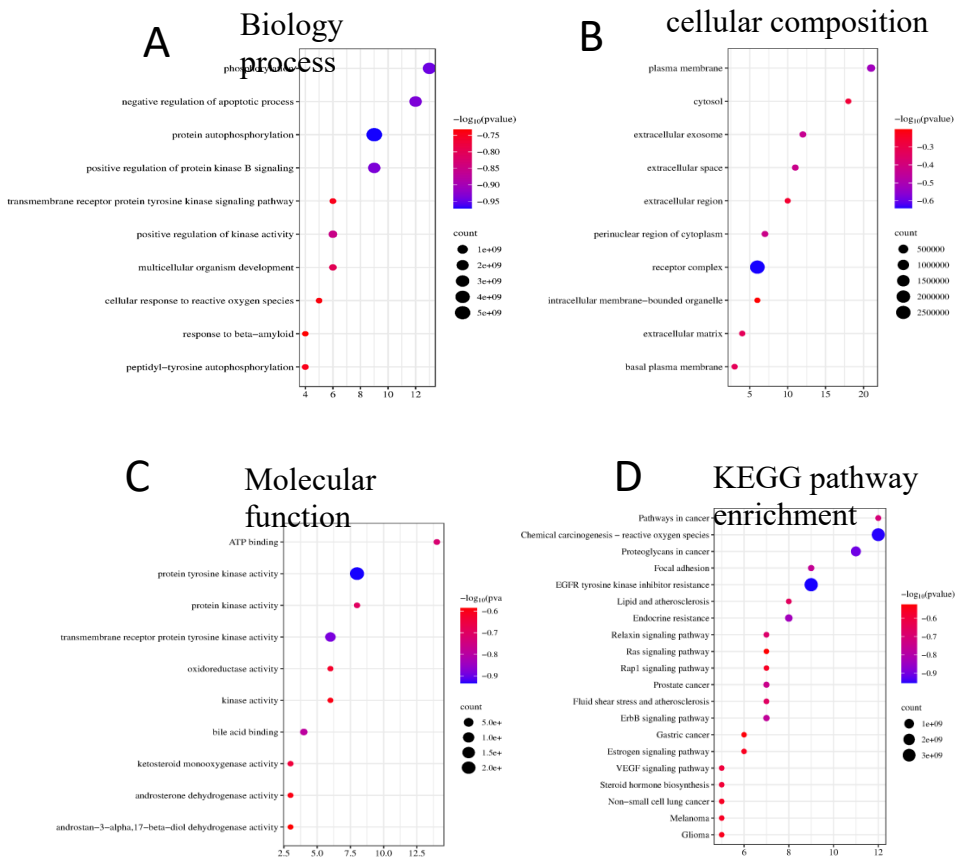

Figure 5: The GO and KEGG enrichment analysis of key targets.Including[A]Biology process, [B] cellular composition ,[C] molecular function, [D]and KEGG pathway analysis.

3.5 C-D-P-T network of LYHY for the treatment of OA.

We used Cytoscape 3.8.2 software to visualise the top 20 KEGG-enriched signalling pathways and their corresponding targets with the four active ingredients of the drug LYHY and their targets(see figure 6).

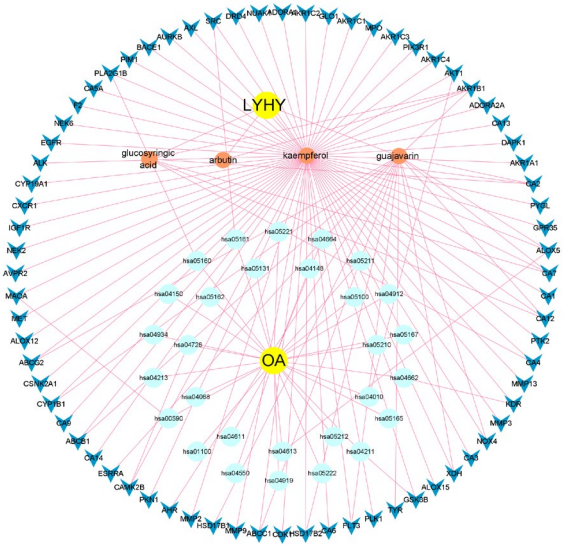

Figure 6: The target-pathways network of OA and LYHY. The two yellow circles represent OA and LYHY respectively, the orange circle represents the active ingredient, the light blue circle represents the KEGG pre-20 pathway, and the dark blue V-shape represents the common target.

ISSN 2706-6819 Vol.6, Issue 11: 1-10, DOI: 10.25236/IJFM.2024.061101

3.6 Molecular Docking Analysis.

Molecular docking strategies are used to study ligand-receptor interactions and predict binding modes and affinities. In this study, candidate target proteins were selected for molecular docking analysis based on their human origin and higher degree value in the PPI core network (Figure 4D). Drug candidates were selected for docking based on higher degree values in the C-D-T network (Figure 3). Thus, the top seven candidate target proteins with the highest degree values, AKT1 (degree 25), SRC (degree 20), MMP9 (degree 20), EGFR (degree 20), CYP19A1 (degree 8), MMP2 (degree 16), and ABCB1 (degree 12), as well as the four compounds were subjected to molecular docking. SRC-arbitin (-6.9 kcal/mol), SRC-guajavarin (-9.5 kcal/mol), SRC-kaempferol (-8.0 kcal/mol), and EGFR-guajavarin (-8.1 kcal/mol) were further analysed on the basis of minimum binding energy, EGFR-kaempferol (-7.7 kcal/mol) binding patterns(see table 2 and figure 7).

Table 2: Affinity of gene binding to LYHY.

number	Ingredient	Target	Affinity value(Kcal/mol)	
1	arbutin	SRC	-6.9	
2	guajavarin	SRC	-9.5	
3	kaempferol	SRC	-8	
4	guajavarin	EGFR	-8.1	
5	kaempferol	EGFR	-7.7	

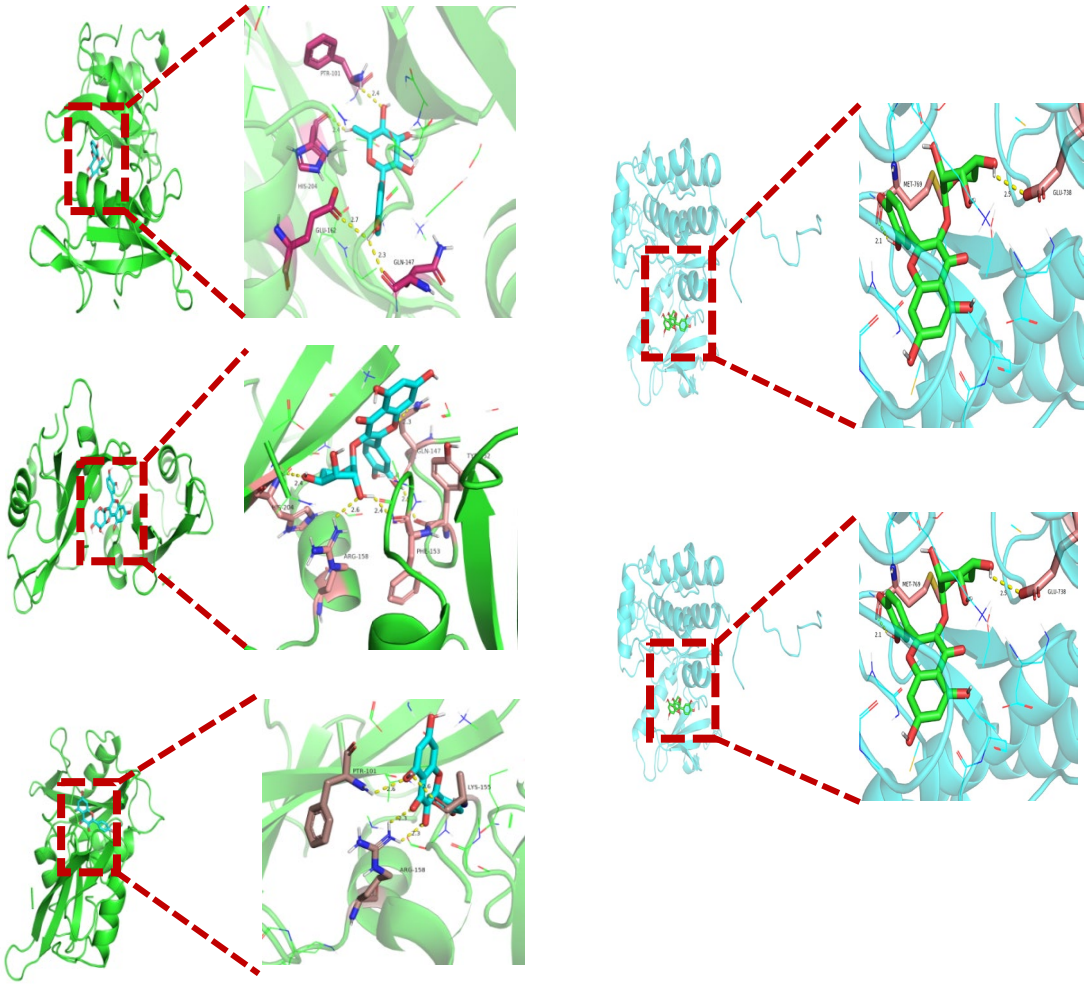

Figure 7: Molecular docking simulation diagram. The LYHY is violet stick models and protein molecules are green and blue cartoon models.The protein molecules at the docking site are represented as other color stick models. The connected hydrogen bonds are indicated by yellow dotted lines.

ISSN 2706-6819 Vol.6, Issue 11: 1-10, DOI: 10.25236/IJFM.2024.061101

4. Discussion

The pro-inflammatory effects of cells have been shown to be an important mechanism in early joint damage in OA[9, 10]. In OA, initiation and progression, are mediated by various bioactive substances, such as pro-inflammatory and inflammatory cytokines, abnormal metabolism of chondrocytes, producing enzymes that lead to matrix degradation, chondrocyte apoptosis, and eventual cartilage destruction[11]. At the same time, chondrocyte apoptosis leads to an imbalance in the synthesis and degradation of collagen and proteoglycan metabolism[12]. As inflammatory mediators spread to other joint structures, they cause changes in synovial tissue, cartilage and subchondral bone, leading to osteosclerosis and increased thickness of synovial and periosteal structures [12]. Eventually, gaps are created in the cartilage surface and free cartilage fragments drive synovial inflammation[13].

While the pathogenesis of late-stage OA is closely linked to changes in the subchondral bone, OA is an age-related degenerative disease in which the effects of cellular senescence are critical to the process[14, 15]. Chondrocyte senescence releases SASPs during ageing , while TGF-β and IL-6 are both SASP factors that contribute to chondrocyte senescence by activating P15, P21 and P27. A recent study showed that activation of the Wnt/β-catenin pathway promotes chondrocyte senescence by down-regulating Sirtuin1 (SIRT) expression while up-regulating acetylated P53 expression[16] . In addition, SASP in bone can act in a paracrine or autocrine manner on surrounding senescent cells as well as neighbouring cells, exacerbating the senescence effect and stimulating cartilage degradation [17].

Therefore, it is reasonable to assume that LYHY may be indicated for OA patients with these co-morbidities.Furthermore, results of network pharmacology and molecular docking revealed that SRC kinase and epidermal growth factor receptor may be the potential targets responsible for the effects of LYHY, which is consistent with previous studies. The present study demonstrated that LYHY is able to regulate the expression of epidermal growth factor receptor genes or proteins. In addition, previous studies have reported that EFGR is a key player in the regulation of a variety of cellular functions such as cell proliferation, survival, adhesion, migration and differentiation[18]. For example, it has been shown that the progression of OA is significantly accelerated after ageing or OA injury in a mouse model of articular cartilage surface defects; and that Mig6 is a negative feedback inhibitor of the epidermal growth factor receptor [19, 20]. Cellular experiments have shown that the epidermal growth factor receptor is anabolic and catabolic, and that the addition of epidermal growth factor receptor ligands to the culture medium inhibits the expression of cartilage matrix genes while promoting proliferation and survival[21]. This evidence supports the apparent ability of the epidermal growth factor receptor to maintain articular cartilage surface homeostasis and ameliorate the consequences of OA. Thus, our findings again suggest that LYHY may be a very promising drug for the treatment of OA. In addition, we found that SRC is a potential functional target of LYHY for the treatment of OA. Intervention with the SRC kinase inhibitor PP2 in a rat model of knee osteoarthritis has been shown to ameliorate articular cartilage destruction, alleviate OA symptoms and delay articular cartilage degeneration in rat knee OA[22]. However, there are no reports on the interaction of LYHY with this target in OA. Therefore, the identification of SRC targets may provide a new explanation for the efficacy of LYHY in OA.

5. Conclusion

Our bioinformatics based research found that LYHY is effective in the treatment of osteoarthritis with multi-component, multi-target and multi-pathway properties. Our results also provide directions for subsequent basic experiments.

Author Contributions

YXX and ZKW designed the study, YXX wrote the manuscript, and derived the datasets. YXX and WY performed statistical analyses, ZKW revised the manuscript, and YXX and WY generated all figures and prepared the supplementary information.

Acknowledgement

This work was supported by the projects of National Natural Science Foundation of China [82160914].Thanks to the support of the institutions involved, this study was made possible.

ISSN 2706-6819 Vol.6, Issue 11: 1-10, DOI: 10.25236/IJFM.2024.061101

References

[1] D. T. Felson, R. C. Lawrence, P. A. Dieppe, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. [J]. Ann Intern Med, 2000, 133(8): 635-46.
[2] G. A. Hawker and L. K. King. The Burden of Osteoarthritis in Older Adults. [J]. Clin Geriatr Med, 2022, 38(2): 181-192.
[3] H. Bliddal. [Definition, pathology and pathogenesis of osteoarthritis]. [J]. Ugeskr Laeger, 2020, 182(42)
[4] M. H. M. Yunus, A. Nordin and H. Kamal. Pathophysiological Perspective of Osteoarthritis. [J]. Medicina (Kaunas), 2020, 56(11)
[5] L. Lippi, M. Ferrillo, A. Turco, et al. Multidisciplinary Rehabilitation after Hyaluronic Acid Injections for Elderly with Knee, Hip, Shoulder, and Temporomandibular Joint Osteoarthritis. [J]. Medicina (Kaunas), 2023, 59(11)
[6] S. Dai, H. Wang, M. Wang, et al. Comparative transcriptomics and network pharmacology analysis to identify the potential mechanism of celastrol against osteoarthritis. [J]. Clin Rheumatol, 2021, 40(10): 4259-4268.
[7] L. Xudan, ZHONG Ke, W. Liqing, et al. Research Progress of Miao Medicine Sedum aizoon L. [J]. Chinese Journal of Ethnomedicine and Ethnopharmacy, 2023, 32(18): 76-80.
[8] H. xicheng, Z. xuefen, W. shanshan, et al. The content of 7 components in the freeze-dried powder of the seedling medicine from different origins was determined in June. [J]. Journal of Chinese Medicinal Materials, 2022, 45(07): 1669-1673.
[9] C. G. Kim, D. G. Lee, J. Oh, et al. Effects of Balneotherapy in Jeju Magma-Seawater on Knee Osteoarthritis Model. [J]. Sci Rep, 2020, 10(1): 6620.
[10] B. Jeremiasse, C. Matta, C. R. Fellows, et al. Alterations in the chondrocyte surfaceome in response to pro-inflammatory cytokines. [J]. BMC Mol Cell Biol, 2020, 21(1): 47.
[11] N. Hu, J. Qiu, B. Xu, et al. The Role of Cartilage Stem/Progenitor Cells in Cartilage Repair in Osteoarthritis. [J]. Curr Stem Cell Res Ther, 2023, 18(7): 892-903.
[12] R. Giorgino, D. Albano, S. Fusco, et al. Knee Osteoarthritis: Epidemiology, Pathogenesis, and Mesenchymal Stem Cells: What Else Is New? An Update. [J]. Int J Mol Sci, 2023, 24(7)
[13] T. Kmiołek and A. Paradowska-Gorycka. miRNAs as Biomarkers and Possible Therapeutic Strategies in Rheumatoid Arthritis. [J]. Cells, 2022, 11(3)
[14] S. A. Mahoney, R. Venkatasubramanian, M. A. Darrah, et al. Intermittent supplementation with fisetin improves arterial function in old mice by decreasing cellular senescence. [J]. Aging Cell, 2024, 23(3): e14060.
[15] F. Neri, N. Basisty, P. Y. Desprez, et al. Quantitative Proteomic Analysis of the Senescence-Associated Secretory Phenotype by Data-Independent Acquisition. [J]. Curr Protoc, 2021, 1(2): e32.
[16] W. Li, Y. Xiong, W. Chen, et al. Wnt/β-catenin signaling may induce senescence of chondrocytes in osteoarthritis. [J]. Exp Ther Med, 2020, 20(3): 2631-2638.
[17] I. W. Yen and H. Y. Li. Dipeptidyl peptidase-4 inhibition targeting vascular senescence as a novel treatment for atherosclerosis. [J]. J Diabetes Investig, 2024, 15(2): 143-144.
[18] C. Li, R. Wei, Y. L. Jones-Hall, et al. Epidermal growth factor receptor (EGFR) pathway genes and interstitial lung disease: an association study. [J]. Sci Rep, 2014, 4(4893).
[19] Y. W. Zhang, B. Staal, K. J. Dykema, et al. Cancer-type regulation of MIG-6 expression by inhibitors of methylation and histone deacetylation. [J]. PLoS One, 2012, 7(6): e38955.
[20] C. A. R. Mojica, W. S. Ybañez, K. C. V. Olarte, et al. Differential Glucocorticoid-Dependent Regulation and Function of the ERRFI1 Gene in Triple-Negative Breast Cancer. [J]. Endocrinology, 2020, 161(7)
[21] K. Peng, X. Tian, Y. Qian, et al. Novel EGFR inhibitors attenuate cardiac hypertrophy induced by angiotensin II. [J]. J Cell Mol Med, 2016, 20(3): 482-94.
[22] R. Li, L. Li, Y. Liu, et al. VE-cadherin regulates migration inhibitory factor synthesis and release. [J]. Inflamm Res, 2019, 68(10): 877-887.