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Network Pharmacology Identifies the Mechanisms of Action of Shaoyao Gancao Decoction in the Treatment of Osteoarthritis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Osteoarthritis (OA) affects the health and wellbeing of the elderly. Shaoyao Gancao decoction (SGD) is used in traditional Chinese medicine (TCM) for the treatment of OA and has two active components, shaoyao (SY) and gancao (GC). This study aimed to undertake a network pharmacology analysis of the mechanism of the effects of SGD in OA.

Material/Methods: The active compounds and candidates of SGD were obtained from the Traditional Chinese Medicine (TCM) Databases@Taiwan, the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database, the STITCH database, the ChEMBL database, and PubChem. The network pharmacology approach involved network construction, target prediction, and module analysis. Significant signaling pathways of the cluster networks for SGD and OA were identified using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

Results: Twenty-three bioactive compounds were identified, corresponding to 226 targets for SGD. Also, 187 genes were closely associated with OA, of which 161 overlapped with the targets of SGD and were considered to be therapeutically relevant. Functional enrichment analysis suggested that SGD exerted its pharmacological effects in OA by modulating multiple pathways, including cell cycle, cell apoptosis, drug metabolism, inflammation, and immune modulation.

Conclusions: A novel approach was developed to systematically identify the mechanisms of the TCM, SGD in OA using network pharmacology analysis.

MeSH Keywords: Health Care Evaluation Mechanisms • Medicine, Chinese Traditional • Osteoarthritis, Knee

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/915821

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Background

Osteoarthritis (OA) is an age-related degenerative disease that is characterized by the degradation of joint cartilage and inflammation of the synovium [1–3]. The typical clinical signs and symptoms of OA are pain, swelling, and stiffness, usually associated with reduced activity and limitation of movement [4]. Chronic OA results in the formation of osteophytes, and deformation and narrowing of the joint space. OA significantly reduces the quality of life for patients and can result in physical disability, which has an increasing socioeconomic and healthcare burden [5,6]. Severe OA commonly results in joint replacement, particularly in elderly individuals [7]. Currently, pharmacological treatments for OA primarily include the use of oral pain medication, including opioid analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injection of corticosteroids, and surgical treatment including osteotomy, arthroplasty, and arthrodesis [8–10]. However, pharmacological treatments for OA are aimed at alleviating the symptoms of the disease rather than treating the underlying causes, and have several side effects, including an increased risk of cardiovascular events and infection [11,12]. Therefore, more effective and safer therapeutic approaches are required for treating patients with OA.

Traditional Chinese medicine (TCM) has been used widely for several decades for the treatment of a range of diseases and has the advantage of being inexpensive and widely available, and because many medicines are derived from natural sources such as herbs, they have fewer side effects [13]. Several TCMs have been used to treat OA and are both effective and safe [14,15]. Therefore, for the treatment of OA, it would be helpful to identify the most effective TCM compounds. Previous studies have shown that Shaoyao Gancao decoction (SGD) is effective in reducing the clinical symptoms of OA by improving joint function and movement. SGD is an effective formula that has been described in the Treatise on Febrile and Miscellaneous Diseases (Shang Han Za Bing Lun) by the third-century Chinese physician Zhang Zhognjing. SGD contains two Chinese herbal medicines, shaoyao (SY) derived from *Radix Paeoniae Alba*, and gancao (GC) derived from *Glycyrrhizae Radix et Rhizoma,* in a 1: 1 ratio [16]. Pharmacological studies have shown that the two compounds in the SGD formulation have a synergistic effect in reducing inflammation, pain, and swelling and improving joint function in patients with OA [17]. However, the underlying pharmacological mechanisms of action of SGD and its components in the treatment of OA remain unclear, and the pharmacodynamic properties of its components and key targets remain to be identified.

Network pharmacology is a new and powerful method that integrates chemo-informatics, bio-informatics, network biology, network analysis and traditional pharmacology [18]. The method of network pharmacology conforms to the systemic or holistic view of TCM theory and is a novel strategy to elucidate the active compounds and potential mechanisms of TCM formulas. Therefore, this study aimed to use network pharmacology to identify the bioactive components and targets of SGD, to search for common targets for SGD in the treatment of OA, to understand the underlying mechanisms of action of the disease targets, and to mine for disease-related genes.

Material and Methods

Construction of a database of the components of Shaoyao Gancao decoction (SGD)

Figure 1 shows a schematic representation of the network pharmacology study of Shaoyao Gancao decoction (SGD) in the treatment of osteoarthritis (OA), including the two active components, shaoyao (SY) and gancao (GC). The data relating to the chemical compounds, SY and GC were derived from the Traditional Chinese Medicine (TCM) Databases@Taiwan (*http://tcm.cmu.edu.tw/*) [19], and the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database (*http://lsp.nwu.edu.cn/tcmsp.php*) [20]. In total, 365 compounds were identified in SGD after removing the duplicate data, including 280 compounds in GC and 85 compounds in SY.

Screening of the active ingredients in SGD

The 365 potential compounds from SY and GC were filtered using two adsorption, distribution, metabolism, and excretion (ADME)-related models, integrating drug-likeness (DL) and oral bioavailability (OB). Drug-likeliness is a qualitative concept used in drug design to determine how drug-like a prospective compound is to describe and optimize pharmacokinetic and pharmaceutical properties [19,21]. Oral bioavailability indicates the drug-like nature of molecules as therapeutic agents and represents the relative amount of orally administered drug that reaches the blood circulation, shown by the convergence of the ADME process [22]. To identify the active components of SGD, the ingredients conforming to the requirements of both OB ≥30% and DL ≥0.18, based on the published literature and the information from the TCMSP database, were identified for further analysis [23]. Also, putative targets of potential compounds in SY and GC were identified from the STITCH, ChEMBL and PubChem databases, and those without target information were excluded.

Target genes related to the identified compounds

To identify the relevant targets of the potential compounds in SY and GC, the STITCH (*http://stitch.embl.de/*) [24], ChEMBL (*http://www.ebi.ac.uk/chembl/*) [25], and PubChem (*http://pubchem.*

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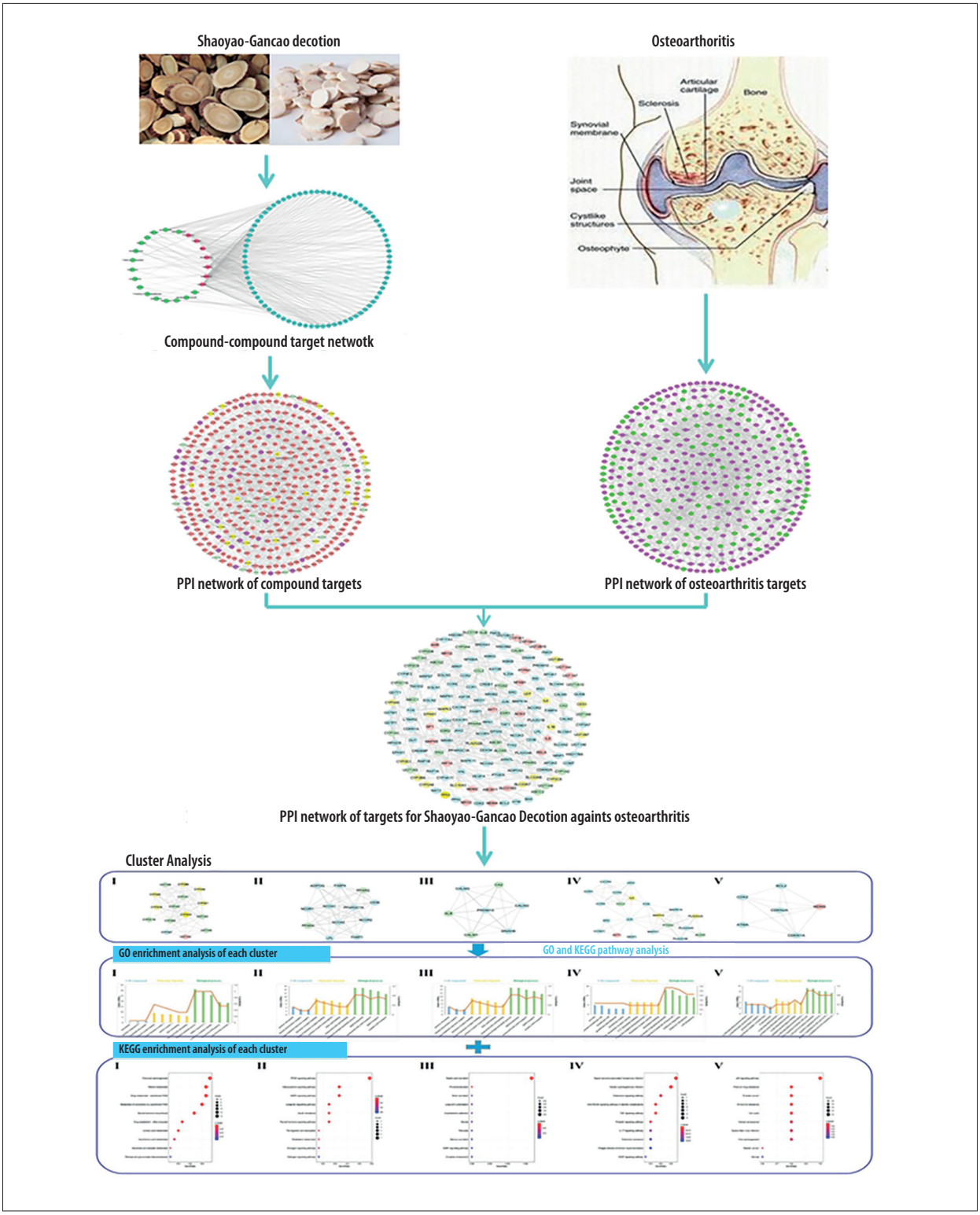

Figure 1. Schematic representation of network pharmacology study of Shaoyao Gancao decoction (SGD) in the treatment of osteoarthritis (OA). SGD – Shaoyao Gancao decoction; OA – osteoarthritis.

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ncbi.nih.gov/) databases were used [26]. A final list of genes associated with compounds, with a confidence score of >0.7, was obtained that suggested a high confidence score according to STITCH. The ChEMBL is a manually curated database for storing standardized bioactivity, molecules, targets, and drug data, which are abstracted regularly from the primary medicinal chemistry literature [27]. The PubChem database is a resource for biological activities of small molecules, including substance information, compound structure, and bioactivity, and the data are experimentally validated. All the active ingredients identified in the present study were entered into the STITCH, ChEMBL and PubChem databases with the *Homo sapiens* species setting. The gene information, including the name, gene ID, and organism, was confirmed using the UniProt protein sequence resource (*https://www.uniprot.org*) [28]. After removing duplicates, the detailed information of targets obtained is described in Supplementary Table 1.

Related targets of osteoarthritis (OA)

Information on OA-associated target genes was collected from the following resources. DrugBank (*https://www.drugbank.ca/*) [29] is a comprehensive online database that provides extensive biochemical and pharmacological information on drugs and their mechanisms of action and targets, and 78 genes related to OA were identified from this database. GeneCards (*http://www.genecards.org/*) is a comprehensive database incorporating information on all annotated and predicted genes [30], which was searched using the keyword "osteoarthritis," which identified 46 genes. The Online Mendelian Inheritance in Man® (OMIM) database (*http://www.omim.org/*) [31] is a comprehensive research resource of human genes and genetic phenotypes, from which 65 genes associated with OA were selected. There were 187 targets linked with OA after deleting redundant targets, and the information regarding these targets is provided in Supplementary Table 2.

Construction of the pharmacological networks

Network construction was established using four main steps. First, a compound-compound target network was established by linking compounds and predicted targets with a degree of >3. Second, a protein-protein interaction (PPI) network of compounds and targets was developed by linking the compound targets and predicted targets of other human proteins. Third, a PPI network of OA targets was constructed by linking the known OA-related targets and predicted targets of other human proteins. Fourth, a PPI network of targets for SGD and OA was developed by intersecting the PPI network of compounds and the PPI network of OA targets. The graphical and diagrammatic visualized networks were constructed using Cytoscape version 3.7.0 (*http://www.cytoscape.org/*) [32], which is a software package for visualizing network analysis.

Cluster analysis

Cluster analysis is a classification method that involves interconnected regions showing the inherent laws in the network [13]. The Molecular Complex Detection (MCODE) plug-in was used to detect densely connected regions and cluster analysis in the PPI network [33]. In this study, we selected significant cluster modules from the constructed PPI network using MCODE. The criteria settings were set as follows: node score cutoff=0.2; K-core=2; and degree of cutoff=2.

Gene Ontology (GO) and pathway enrichment analysis

The Gene Ontology (GO) database (*http://geneontology.org/*), including biological process, cell component, and molecular function terms, was used to identify the possible biological mechanisms using high-throughput genome or transcriptome data [34]. The Kyoto Encyclopedia of Genes and Genomes (KEGG) database (*https://www.kegg.jp/*) is a knowledge database for identifying the systematic functions and biological relevance of candidate targets [35]. In this study, GO functional annotation and KEGG pathway analysis were performed using Bioconductor clusterProfiler, an R package used for enrichment analysis of gene clusters [36].

Results

Screening for the active compounds of Shaoyao Gancao decoction (SGN) involved in osteoarthritis (OA)

From the two active components of Shaoyao Gancao decoction (SGD), shaoyao (SY) and gancao (GC), 365 compounds were obtained from the Traditional Chinese Medicine Systems Pharmacology(TCMSP) database and the traditional Chinese medicine (TCM) Databases@Taiwan, with 280 compounds from GC and 85 from SY. The values of oral bioavailability (OB) and drug-likeness (DL) (OB ≥30% and DL ≥0.18) were used to screen potential active compounds from GC and SY, and a total 23 active compounds met the screening standards. The properties of the compounds are shown in Table 1.

Target screening of SGD in the treatment of osteoarthritis

In the present study, the STITCH, ChEMBL, and PubChem databases were used to screen 226 targets corresponding to the active ingredients in SGD, with 188 targets for SY, 146 targets for GC, and 108 for SY and GC. These gene targets included cellular tumor antigen p53 (TP53), chlorotoxin derivative (CA4), estrogen receptor beta (ESR2), and multidrug resistance protein 1 (ABCB1), which are involved in inflammation [37], cell proliferation [38], and angiogenesis [39]. DrugBank, GeneCards, and the Online Mendelian Inheritance in Man® (OMIM) databases were

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Table 1. The active ingredients of the two components of Shaoyao Gancao decoction (SGD), shaoyao (SY) and gancao (GC).

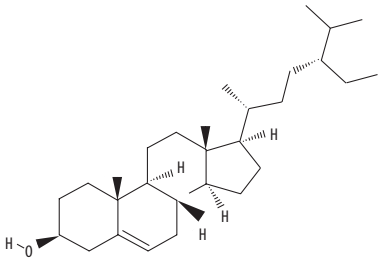
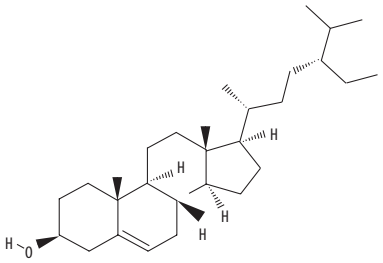
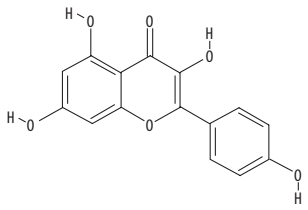
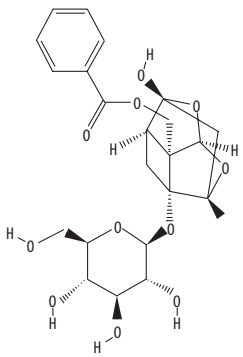
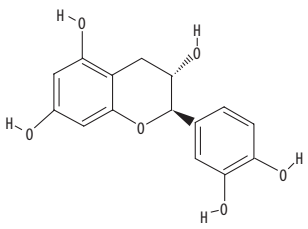
Molecule ID	Molecule name	Structure	OB	DL	Herb
MOL000359	Sitosterol		36.91	0.75	SY
MOL000358	beta-Sitosterol		36.91	0.75	SY
MOL000422	Kaempferol		41.88	0.24	SY
MOL001924	Paeoniflorin		53.87	0.79	SY
MOL000492	(+)-Catechin		54.83	0.24	SY

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Table 1 continued. The active ingredients of the two components of Shaoyao Gancao decoction (SGD), shaoyao (SY) and gancao (GC).

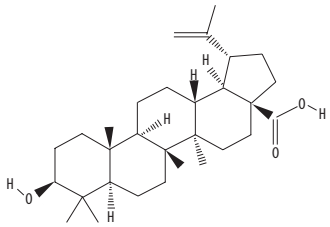
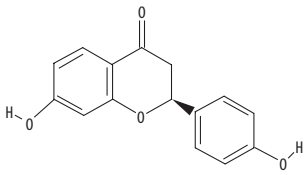
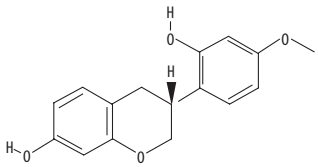
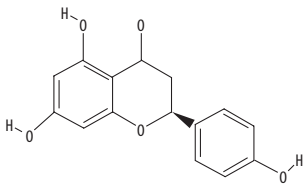
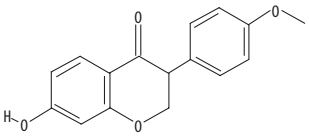
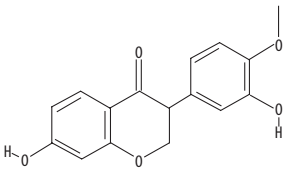
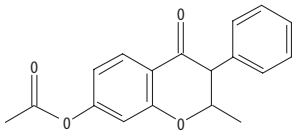
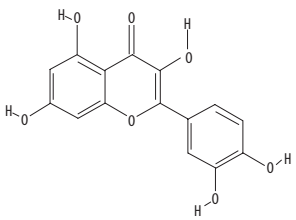
Molecule ID	Molecule name	Structure	OB	DL	Herb
MOL000211	Mairin		55.38	0.78	BS
MOL001792	Liquiritigenin		32.76	0.18	GC
MOL000500	Vestitol		74.66	0.21	GC
MOL004328	Naringenin		59.29	0.21	GC
MOL000392	Formononetin		69.67	0.21	GC
MOL000417	Calycosin		47.75	0.24	GC
MOL004991	7-Acetoxy-2-methylisoflavone		83.71	0.27	GC
MOL000098	Quercetin		46.43	0.28	GC

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Table 1 continued. The active ingredients of the two components of Shaoyao Gancao decoction (SGD), shaoyao (SY) and gancao (GC).

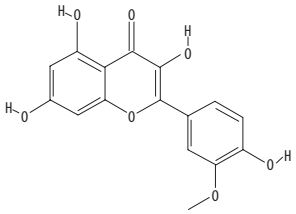
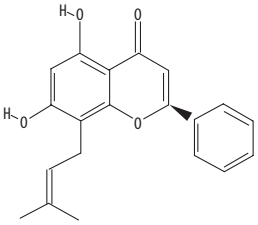
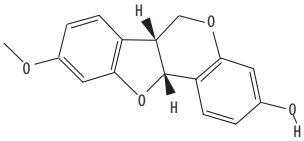
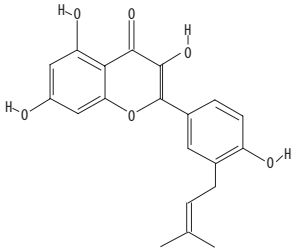
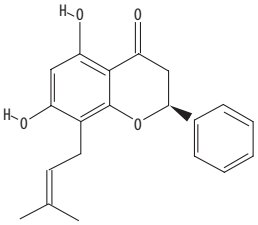
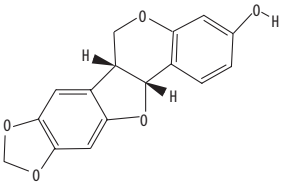
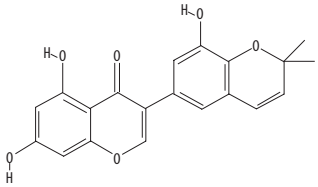
Molecule ID	Molecule name	Structure	OB	DL	Herb
MOL000354	Isorhamnetin		49.6	0.31	GC
MOL004910	Glabranin		52.9	0.31	GC
MOL002565	Medicarpin		49.22	0.34	GC
MOL004949	Isolicoflavonol		45.17	0.42	GC
MOL004908	Glabridin		53.25	0.47	GC
MOL001484	Inermine		75.18	0.54	GC
MOL004827	Semilicoisoflavone B		48.78	0.55	GC

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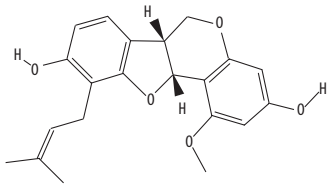
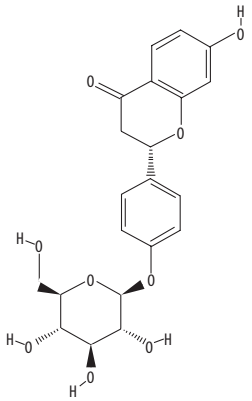
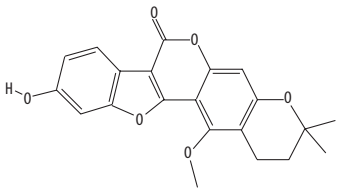
Table 1 continued. The active ingredients of the two components of Shaoyao Gancao decoction (SGD), shaoyao (SY) and gancao (GC).

Molecule ID	Molecule name	Structure	OB	DL	Herb
MOL004959	1-Methoxyphaseollidin		69.98	0.64	GC
MOL004903	Liquiritin		65.69	0.74	GC
MOL004948	Isoglycyrol		44.7	0.84	GC

also used to screen 187 targets associated with OA, removing compounds with duplication targets (Supplementary Table 3). The obtained compounds and targets were used to construct the pharmacology network.

Compound-compound network targets

A compound-compound target network was developed to identify the relationship between the compounds of SGD and their candidate targets (Figure 2). The compound-compound target network consisted of 101 nodes (23 compounds and 78 compound targets) and 338 edges (degree >3). The average degree of 14.69 per compound in such a network was based on the network analysis, demonstrating the multitarget treatment characteristics of SGD. In this network, the values of the degree for quercetin (degree=63) and kaempferol (degree=54) were considerably higher than that of the other components, suggesting that two chemicals probably were served as significant therapeutic compounds in OA.

Protein-protein interaction (PPI) network targets

The PPI networks of compound targets were developed to identify the interactions between SGD-related proteins and other relative proteins with 448 nodes (45 compound targets, 26 OA targets, 19 compound/OA targets, and other relevant proteins) and 1,869 edges (Figure 3) were constructed to determine the interactive effects of compounds modulated by SGD. About 19 intersection targets between compound targets and OA-related targets were identified in this network including, multidrug resistance protein 1 (ABCB1), multidrug resistance-associated protein 1(ABCC1), carbonic anhydrase 2, C-C motif chemokine 2, cytochrome P450 1A1 (CYP1A1), cytochrome P450 1A2 (CYP1A2), cytochrome P450 2C19, cytochrome P450 2C9 (CYP2C9), cytochrome P450 2D6 (CYP2D6), cytochrome P450 3A4 (CYP3A4), estrogen receptor (ER), estrogen receptor beta (ESR2), peroxisome proliferator-activated receptor alpha, peroxisome proliferator-activated receptor gamma, prostaglandin G/H synthase 2 (PTGS2), solute carrier organic anion transporter family member 1B1, TP53, UDP-glucuronosyltransferase 1-3 (UGT1A3), and UDP-glucuronosyltransferase 1–8.

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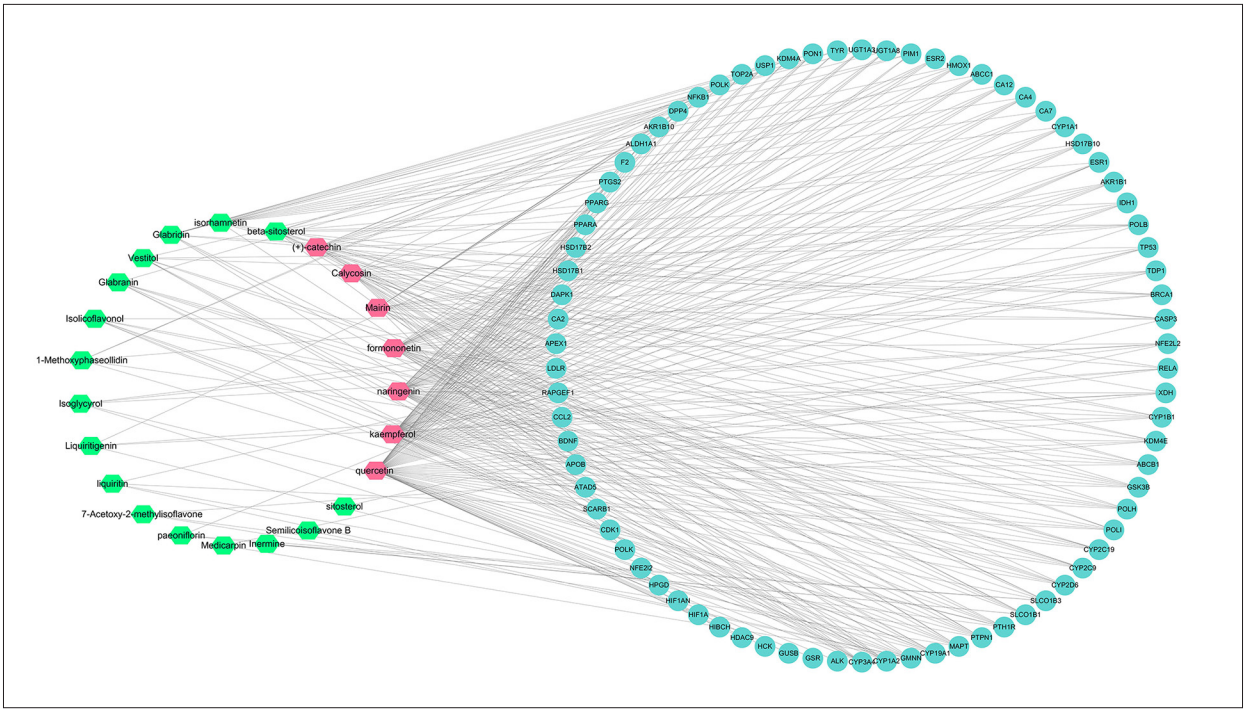

Figure 2. The compound-compound target network of Shaoyao Gancao decoction (SGD) in the treatment of osteoarthritis (OA). Blue represents the compound targets, green represents the compounds of Shaoyao Gancao decoction (SGD), and red hexagons represent the central compounds of SGD.

PPI network of OA targets

The PPI network of OA targets was developed to identify the relationship between the OA-related targets and other proteins, with 394 nodes (123 OA targets and 271 other proteins that interacted with OA targets) and 2,184 edges (Figure 4). Considering the median values for degree (10), betweenness centrality (81.71), and closeness centrality (104.63), 27 highly connected nodes with degree >20, betweenness centrality >81.71, and closeness centrality >104.63 were identified as significant OA-related targets. These targets included collagen alpha-2(V) chain, collagen alpha-1(XII) chain, cytochrome P450 3A5 (CYP3A5), CYP2C9, collagen alpha-1(XI) chain, collagen alpha-1(VI) chain, collagen alpha-1 (III) chain, collagen alpha-1(I) chain, collagen alpha-1(IX) chain, CYP1A2, collagen alpha-1(II) chain, nuclear receptor coactivator 1 (NCOA1), collagen alpha-1(X) chain, nuclear factor NF-kappa-B p105 subunit, UDP-glucuronosyltransferase 1-1 (UGT1A1), vascular endothelial growth factor A, C-C motif chemokine 5, CYP3A4, collagen alpha-2 (I) chain, IL-8, thrombospondin-1, plasminogen activator inhibitor 1, parathyroid hormone, plasminogen, transforming growth factor beta-1 proprotein, IL-6, and transcription factor AP-1 (JUN).

PPI network of targets for SGD in OA

To further identify the functional mechanisms of SGD in OA, the PPI network of targets for SGD in the treatment of OA was established by intersecting the two networks described above (Figure 5). The network was composed of 161 nodes (21 compound targets, 17 OA targets, 27 compound/OA targets, and 96 other proteins) and 546 edges (Figure 5). Based on the median values for degree, betweenness centrality, and closeness centrality, which were 6, 9.93, and 44.68, respectively, nodes with the degree, betweenness centrality, and closeness centrality values that were higher than the corresponding median values (degree >20, betweenness centrality >81.71, and closeness centrality >104.63) were considered as significant targets. The identified nodes included CYP3A4, nuclear receptor corepressor 1, TP53, JUN, CYP2C9, UGT1A1, CYP1A1, CYP1A2, NCOA1, nuclear receptor coactivator 2, UGT1A3, CYP3A5, CYP2D6, peroxisome proliferator-activated receptor gamma coactivator 1-alpha, IL-6, and tyrosine-protein kinase JAK2.

Cluster analysis

The PPI network of targets for SGD in OA was analyzed by using Molecular Complex Detection (MCODE), and five modules were obtained (Figure 6A). The biological processes, molecular functions, and signaling pathways enriched by the targets in the cluster modules were used to clarify the integral regulation of

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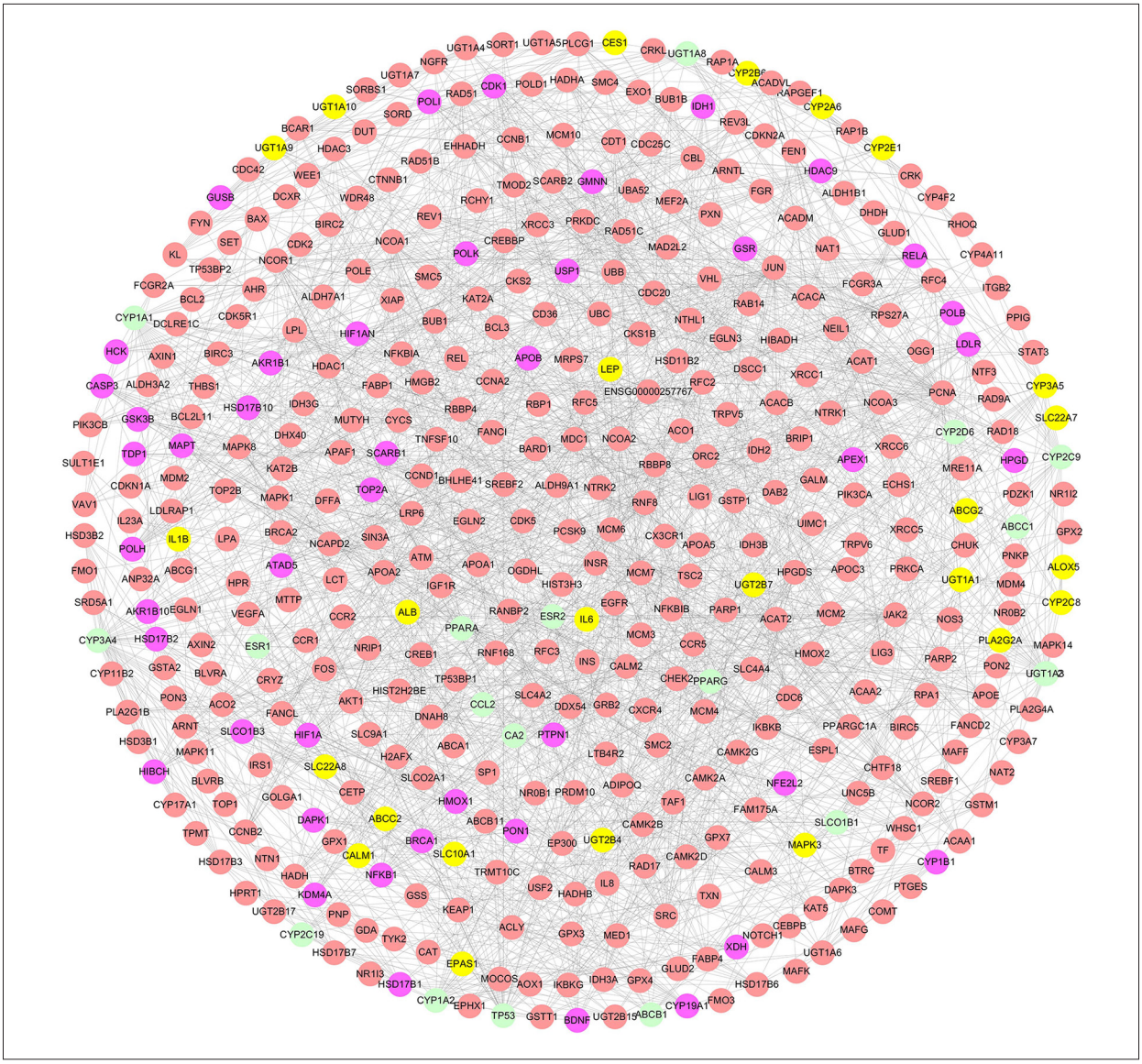

Figure 3. The protein-protein interaction (PPI) network of compound targets of Shaoyao Gancao decoction (SGD) in the treatment of osteoarthritis (OA). Incarnadine (crimson) represent other proteins, purple represent compound targets, yellow represent osteoarthritis (OA) targets, and green represent compound/OA targets).

SGD for the treatment of OA (Figure 6B, 6C). In Gene Ontology (GO) terms, we discovered that (i) fatty acid binding, hormone receptor binding, and microtubules; (ii) regulation of lipid metabolism, hormone receptor binding, and nuclear chromatin; (iii) protein phosphatase activator activity, adenylate cyclase binding, and negative regulation of ryanodine-sensitive calcium-release channel activity; (iv) chemokine receptor activity, C-C chemokine receptor activity, and caveola; and (v) X chromosome, cyclin-dependent protein kinase holoenzyme complex, and cyclin-dependent protein serine, were enriched in clusters, supporting the role of SGD in the treatment of OA. The KEGG enrichment analysis showed that the signaling pathways were enriched in different modules (Figure 6C) [40]. Module 1 was highly associated with drug metabolism, including cytochrome P450; Module 2 was highly associated with the 5'AMP-activated protein kinase (AMPK) signaling pathway; Module 3 was related to gastric acid secretion; Module 4 was associated with the tumor necrosis factor (TNF) signaling pathway and chemokine signaling pathway; Module 5 was associated with the p53 signaling pathway.

Discussion

Osteoarthritis (OA) is a common form of chronic arthritis that is associated with painful symptoms that affect the quality of

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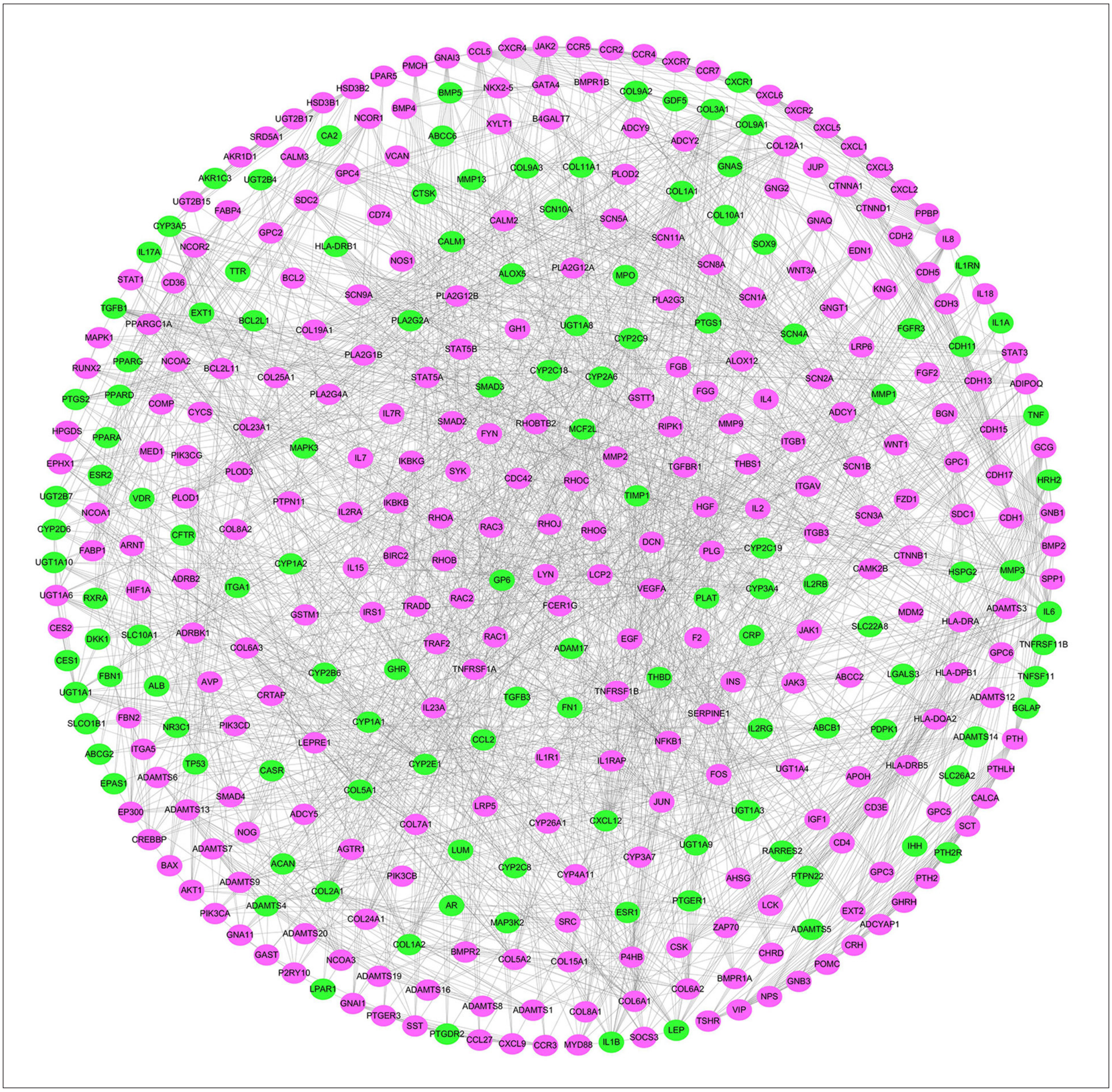

Figure 4. The protein-protein interaction (PPI) network of osteoarthritis (OA) targets. Green ovals represent osteoarthritis (OA) targets and purple ovals represent other human proteins that interacted with OA targets.

life for patients [41,42]. Currently, the therapeutic strategies for OA are mainly symptomatic and do not treat the underlying causes. Herbal traditional Chinese medicines (TCMs) contain several compounds that will have multiple targets, pathways, and modes of action but have been shown to treat the in OA [43]. Although Shaoyao Gancao decoction (SGD) has been used for centuries as an effective TCM for OA, its pharmacological mechanisms of action have been unclear. In this study, a network pharmacology approach was applied to determine the underlying mechanisms of SGD in OA.

After screening SGD for oral bioavailability (OB) (≥30%) and drug-likeness (DL) (≥0.18), 23 bioactive compounds were retrieved, including quercetin (OB=46.43; DL=0.28) and kaempferol (OB=41.88; DL=0.24) as potential bioactive compounds. Quercetin, one of the most abundant bioflavonoids, is known for its anti-oxidative [44], anti-inflammatory [45], antimicrobial [46], and antiviral activities [47] and its active role in promoting apoptosis in arthritic fibroblast-like synoviocytes and in protecting chondrocytes against oxidative stress [48]. Qiu et al. showed that quercetin reduced the symptoms of OA by reducing the level of reactive oxygen species (ROS), reversing mitochondrial dysfunction, and maintaining the integrity of the

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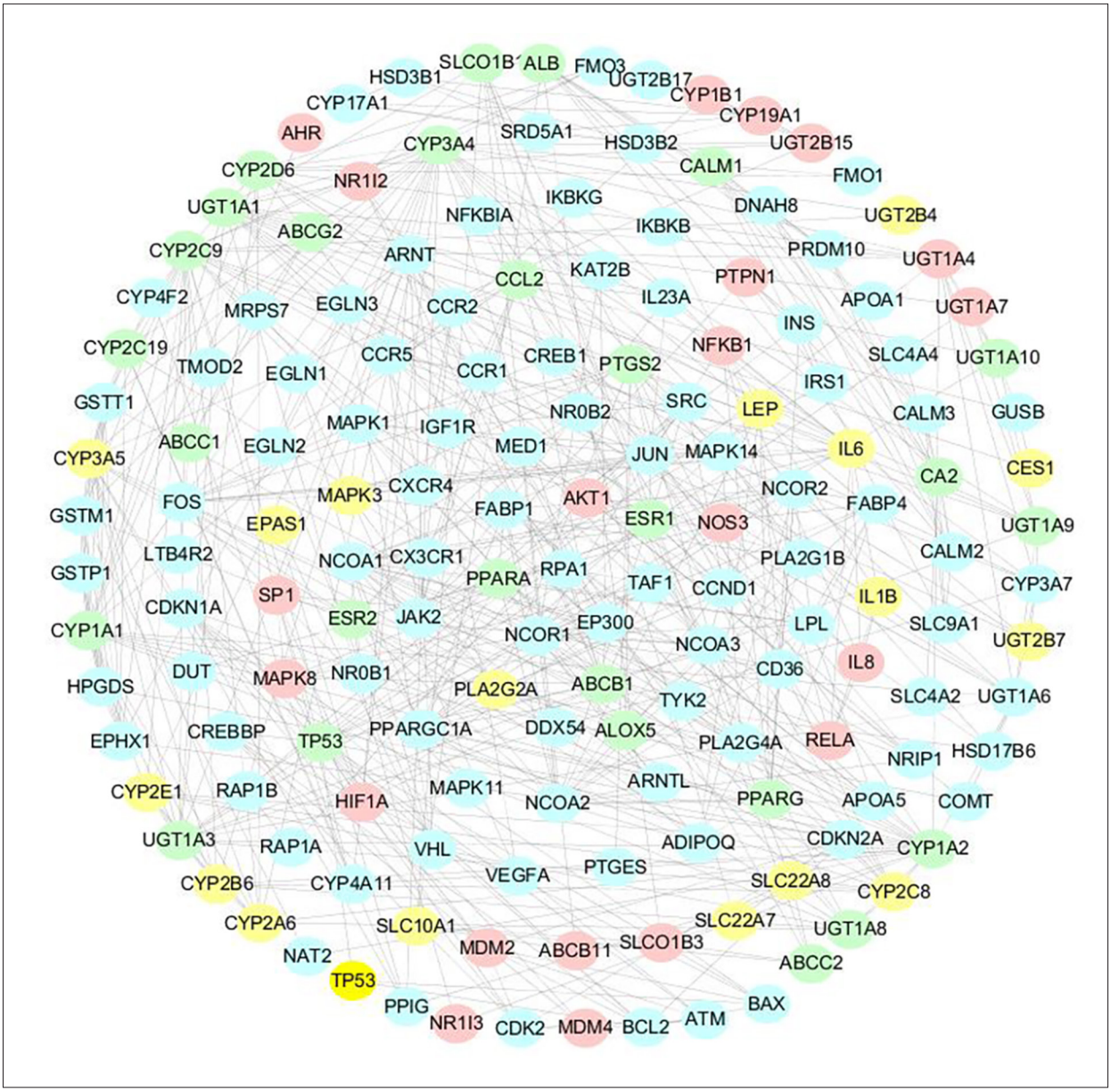

Figure 5. The protein-protein interaction (PPI) network of targets for Shaoyao Gancao decoction (SGD) in osteoarthritis (OA). Yellow ovals represent osteoarthritis (OA) targets, incarnadine (crimson) ovals represent compound targets, green ovals represent compound/OA targets, and blue ovals represent other human proteins that interacted with OA targets or compound targets.

extracellular matrix (ECM) of the joint cartilage [49]. Kaempferol, a dietary element and an important bioflavonoid in vegetables and fruits [50], has a variety of pharmacological effects and acts as an anti-oxidant, anti-inflammatory, anti-apoptotic, anti-estrogenic, and neuroprotective agent [51]. Studies have shown that kaempferol significantly reduced in IL-1β-stimulated pro-inflammatory mediators in rat OA chondrocytes by inhibiting the NF-κB pathway [52]. Paeoniflorin (OB=53.87; DL=0.79) plays an important role in immune regulation [53], and hepatic protection [54]. Several studies have reported that liquiritin (OB=65.69; DL=0.74) has multiple pharmacological effects, as an immunomodulating agent, with anti-inflammatory, anti-allergic, anti-oxidant, and antiviral properties [55].

The PPI network of candidate targets for SGD in the treatment of OA was established based on the component and OA target networks with 161 overlapping genes. Using the median values for the degree of betweenness centrality and closeness of centrality (degree >20, betweenness centrality >81.71, and closeness centrality >104.63), 16 targets were regarded as significant. It was apparent that most of these targets, including CYP3A4, CYP2C9, CYP1A1, CYP1A2, CYP3A5, and CYP2D6

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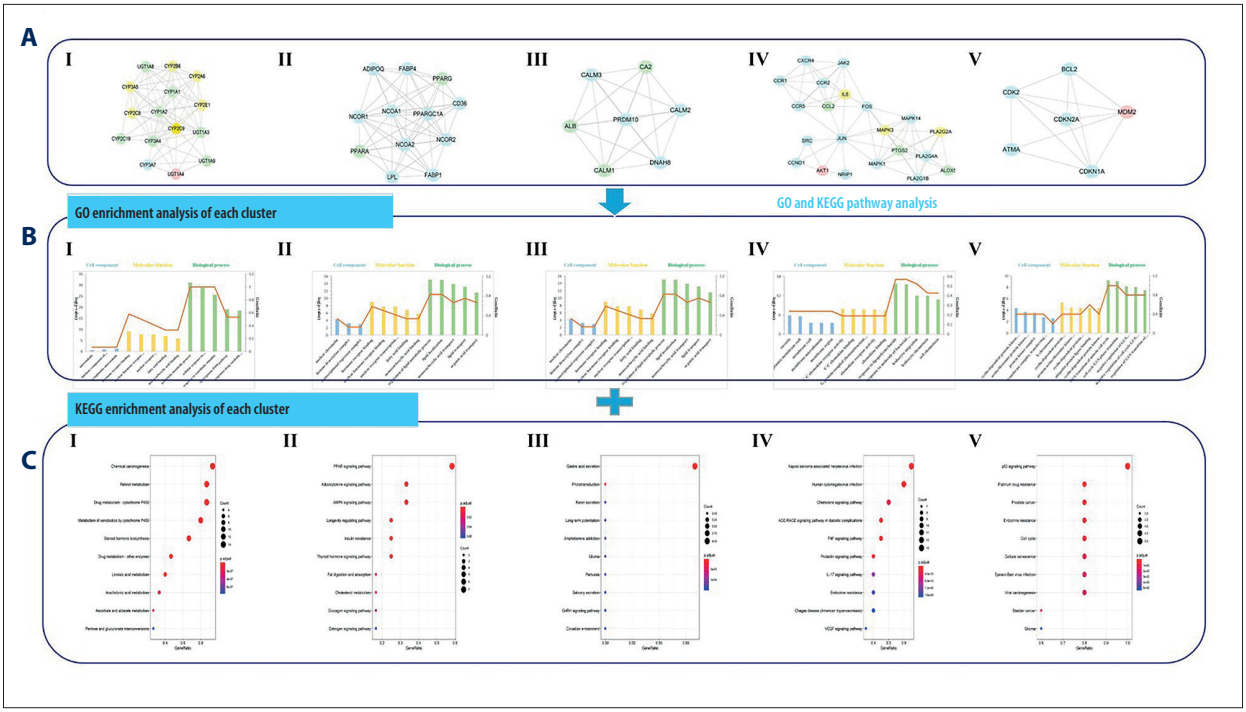

Figure 6. Enrichment analysis of the targets for Shaoyao Gancao decoction (SGD) in osteoarthritis (OA). (**A**) Clusters of the merged protein-protein interaction (PPI) network. Yellow ovals represent osteoarthritis (OA) targets, incarnadine (crimson) ovals represent compound targets, green ovals represent compound/OA targets, and blue ovals represent other human proteins that interacted with OA targets or compound targets. (**B**) The Gene Ontology (GO) pathway enrichment analysis of each cluster. (**C**) The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of each cluster.

in the cytochrome P450 family, were strongly associated with drug metabolism. For instance, CYP2D6 is involved in the metabolism of the dual opioid agonist and norepinephrine-serotonin re-uptake during OA therapy [56]. CYP2C9 is involved in the metabolism of several nonsteroidal anti-inflammatory drugs (NSAIDs), contributing to the wide variability in pharmacokinetics in the metabolism of drugs [56,57]. Some targets, such as TP53 and JAK2, are associated with cell growth. TP53 is associated with OA, and the SIRT1/TP53 signaling pathway modulates the pathogenesis of OA [58]. JAK2 has a role not only in mediating angiotensin-2-induced ARHGEF1 phosphorylation [59], but also cell in the cycle by phosphorylating CNKN1B [60]. Previous studies have shown that the TCM, danshen, reduces cartilage damage in OA by regulating the JAK2/STAT3 and the AKT signaling pathways [61]. Also, JAK2 is a direct target of miR-216a-5p, and long non-coding RNA (lncRNA) DANCR regulates the proliferation, inflammation, and apoptosis of chondrocytes in OA via the miR-216a-5p-JAK2-STAT3 axis [62]. Xiong et al. found that leptin levels significantly increased in the synovial fluid of patients with OA of the temporomandibular joint (TMJ), stimulating IL-6 expression mainly via the JAK2/STAT3, p38 MAPK, and PI3K/Akt pathways [63]. Previous studies have shown that lncRNA gastric cancer-associated transcript 3 affects cell proliferation in OA by the IL-6/STAT3 signaling pathway [64].

Because clustering modules can demonstrate the biological mechanisms of key targets in disease, we classified the PPI network into five clusters (Figure 6A), and performed the Gene Ontology (GO) analysis (Figure 6B) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis (Figure 6C). Based on the GO terms, it may be proposed that the pharmacological effects of SGD in OA occurred by simultaneously activating these biological processes, cell components, and molecular functions. For example, Zhang et al. found that in a mouse model, pharmaceutical inhibition of the fatty acid binding pathway reduced the symptoms of OA induced by a high-fat diet [65]. Also, lipid metabolism is a chemical reaction involving lipids, which are compounds soluble in organic solvents [66]. Park et al. showed that the functional integrity of ABCD2 in modulating lipid metabolism was through the dysregulation of miR-141, and through ACSL4 in OA [67].

From the findings of the present study, based on the KEGG terms, the potential targets for SGD in the treatment of OA were associated with the 5'AMP-activated protein kinase (AMPK) signaling pathway, the tumor necrosis factor (TNF) signaling pathway, and the p53 signaling pathway. In the AMPK signaling pathway, AMPK serves as an intracellular sensor that not only regulates protein synthesis related to inflammation but also modulates the energy balance within chondrocytes [68].

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Previous studies have shown that several bioactive compounds protect against cartilage degeneration in an OA model via the AMPK signaling pathway, including increased mitochondrial biogenesis and reduced mitochondrial dysfunction [69,70]. Zhou et al. showed that AMPK activity in chondrocytes was involved in joint homeostasis and that OA developed by promoting chondrocyte apoptosis and enhancing catabolic activity [71]. As for the TNF signaling pathway, it includes apoptosis, cell survival, inflammation, and immune function [72]. The TNF signaling pathway is important in protecting against the effects of OA, and the correlation between TNF-α levels and the degree of OA has previously been shown [73,74]. Also, the p53 signaling pathway is involved in coordinating cellular responses to different types of stress and in promoting tumor progression. Yan et al. showed that microRNA-34a had a role in chondrocyte apoptosis and proliferation by modulating the SIRT1/p53 signaling pathway in OA [58]. However, we found that pharmacological studies on the mechanisms and targets of the effects of SGD in the treatment of OA were previously limited. Based on the findings from the present study, future studies should be undertaken to assess the relationship between agents used in TCM, including SGD in OA, and their effects in terms of specific targets at the molecular level to validate the results based on data analysis.

Conclusions

This study aimed to undertake a network pharmacology analysis of the mechanism of the effects of the traditional Chinese medicine (TCM), Shaoyao Gancao decoction (SGD), in osteoarthritis (OA). The findings showed that SGD exerted its pharmacological effects in OA by modulating multiple pathways, including the cell cycle, cell apoptosis, drug metabolism, inflammation, and immune modulation. This study also provided a theoretical basis to determine the synergistic effects of TCM in treating diseases and the role of systematic network pharmacology in elucidating the potential mechanisms of action of TCMs. However, as this study was based on data mining and data analysis, further clinical validation studies should be undertaken on the role of SGD in OA.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. The datasets generated and/or analyzed in this study included the Traditional Chinese Medicine Systems Pharmacology (TCMSP) repository, *http://lsp.nwu.edu.cn/tcmsp.php*; TCM@Taiwan, *http://tcm.cmu.edu.tw/*; STITCH, *http://stitch.embl.de/*; PubChem, *http://pubchem.ncbi.nih.gov/*; GeneCard, *http://www.genecards.org/*; ChEMBL, *http://www.ebi.ac.uk/chembl/*; the Kyoto Encyclopedia of Genes and Genomes (KEGG), *https://www.kegg.jp/*; OMIM, *http://www.omim.org/*; DrugBank, *https://www.drugbank.ca/*; Cytoscape, *http://www.cytoscape.org/*; and the Gene Ontology (GO) database, *http://geneontology.org/*.

Abbreviations

ABCB1 – multidrug resistance protein 1; ADME – adsorption, distribution, metabolism, and excretion; BP – biological processes; CC – cellular components; CM – Chinese Medicine; CYP1A1 – cytochrome P450 1A1; CYP1A2 – cytochrome P450 1A2; CYP2C9 – cytochrome P450 2C9; CYP2D6 – cytochrome P450 2D6; CYP3A4 – cytochrome P450 3A4; CYP3A5 – cytochrome P450 3A5; DL – drug-likeness; ESR2 – estrogen receptor beta; GC – Gancao; GO – Gene Ontology; IL – interleukin; KEGG – Kyoto Encyclopedia of Genes and Genomes; lncRNA – long non-coding RNA; MCODE – Molecular Complex Detection; NCOA1 – nuclear receptor coactivator 1; NSAID – nonsteroidal anti-inflammatory drug; OA – osteoarthritis; OB – oral bioavailability; PTGS2 – prostaglandin G/H synthase 2; PPI – protein-protein interaction; SGD – Shaoyao-Gancao decoction; SY – shaoyao; TCM – Traditional Chinese medicine; TCMSP – Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform; TNF – tumor necrosis factor; TP53 – cellular tumor antigen p53; UGT1A1 – UDP-glucuronosyltransferase 1-1; UGT1A3 – UDP-glucuronosyltranserase 1–3.

Conflict of interest

None.

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Supplementary Table 1. GSD-associated target genes.

Gene symbol	Herb	Gene symbol	Herb	Gene symbol	Herb	Gene symbol	Herb
ABCC2	GC	ADAM10	SY	NOS3	SY	AKR1B1	GC, SY
APOB	GC	ADAM17	SY	NPSR1	SY	AKR1B10	GC, SY
ATAD5	GC	ALB	SY	NQO1	SY	AKT1	GC, SY
BAZ2B	GC	ALPI	SY	NR1H2	SY	ALDH1A1	GC, SY
BDNF	GC	ALPL	SY	NR1H3	SY	ALOX15	GC, SY
BRCA1	GC	APOBEC3F	SY	NR1I2	SY	ALOX15B	GC, SY
CALM1	GC	APOBEC3G	SY	NR1I3	SY	ALOX5	GC, SY
CBR1	GC	APOE	SY	PIM2	SY	AMY1A	GC, SY
CBR3	GC	ARSA	SY	PLCG1	SY	APEX1	GC, SY
CBX1	GC	BIRC5	SY	PLCG2	SY	APP	GC, SY
CCL2	GC	BLM	SY	PMP22	SY	AR	GC, SY
GFER	GC	CAT	SY	PRKAA2	SY	ATXN2	GC, SY
GSK3A	GC	CDK1	SY	PRKCB	SY	BACE1	GC, SY
HMOX1	GC	CFTR	SY	PRKCE	SY	BCHE	GC, SY
HSPA5	GC	CHRM1	SY	PTPRS	SY	CA1	GC, SY
LDLR	GC	CISD1	SY	PYGM	SY	CA12	GC, SY
MAPK8	GC	CTDSP1	SY	RACGAP1	SY	CA2	GC, SY
MAPK9	GC	CTSD	SY	RARA	SY	CA4	GC, SY
MAZF	GC	CYCS	SY	RECQL	SY	CA7	GC, SY
MBNL1	GC	CYP2A7	SY	RORC	SY	CASP3	GC, SY
MLLT3	GC	CYP7A1	SY	RPS6KA3	SY	CDK6	GC, SY
MMP9	GC	DHCR24	SY	SAE1	SY	CLK1	GC, SY
NOS2	GC	DNMT1	SY	SOD1	SY	CYP19A1	GC, SY
PDE5A	GC	DRD2	SY	SP1	SY	CYP1A1	GC, SY
PLA2G7	GC	EHMT2	SY	SREBF1	SY	CYP1A2	GC, SY
PPME1	GC	GAA	SY	SREBF2	SY	CYP1B1	GC, SY
RAPGEF1	GC	GLI1	SY	STK16	SY	CYP2C19	GC, SY
RAPGEF3	GC	GLI3	SY	STK33	SY	CYP2C9	GC, SY
SHBG	GC	GLS	SY	SYK	SY	CYP2D6	GC, SY
SLC5A1	GC	GPBAR1	SY	TLR4	SY	CYP3A4	GC, SY
SLC5A2	GC	GPT	SY	UBA2	SY	DAPK1	GC, SY
SLCO2B1	GC	HSD11B2	SY	UBE2I	SY	DPP4	GC, SY
SMAD3	GC	HSF1	SY	UGT1A7	SY	DYRK1A	GC, SY
SMPD1	GC	HSP90AA1	SY	UGT1A9	SY	EGFR	GC, SY
TIM23	GC	HSP90AB1	SY	UGT3A1	SY	ESR1	GC, SY
UGT1A1	GC	ICAM1	SY	XIAP	SY	ESR2	GC, SY
UGT1A10	GC	IL8	SY	ABCB1	GC, SY	ESRRA	GC, SY
UGT2B15	GC	KCNA5	SY	ABCC1	GC, SY	F2	GC, SY
ABCB11	SY	KCNH2	SY	ABCG2	GC, SY	FEN1	GC, SY
ABCG5	SY	KCNMA1	SY	ACHE	GC, SY	FLT3	GC, SY
ABCG8	SY	LMNB1	SY	AHR	GC, SY	GBA	GC, SY

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Gene symbol	Herb
GLO1	GC, SY
GLP1R	GC, SY
GMNN	GC, SY
GSK3B	GC, SY
HDAC9	GC, SY
HIF1A	GC, SY
HPGD	GC, SY
HSD17B1	GC, SY
HSD17B10	GC, SY
HSD17B2	GC, SY
IDH1	GC, SY
KDM4A	GC, SY
KDM4E	GC, SY
LMNA	GC, SY
MAPT	GC, SY
MDM2	GC, SY

Gene symbol	Herb
MDM4	GC, SY
MPG	GC, SY
NEU2	GC, SY
NFE2L2	GC, SY
NFKB1	GC, SY
NFKB2	GC, SY
NOX4	GC, SY
NR1H4	GC, SY
NR3C1	GC, SY
OPRD1	GC, SY
OPRK1	GC, SY
OPRM1	GC, SY
PAFAH1B3	GC, SY
PIM1	GC, SY
PIP4K2A	GC, SY
PNLIP	GC, SY

Gene symbol	Herb
POLB	GC, SY
POLH	GC, SY
POLI	GC, SY
POLK	GC, SY
PON1	GC, SY
PPARA	GC, SY
PPARD	GC, SY
PPARG	GC, SY
PREP	GC, SY
PTGS1	GC, SY
PTGS2	GC, SY
PTH1R	GC, SY
PTPN1	GC, SY
RAPGEF4	GC, SY
RELA	GC, SY
RGS4	GC, SY

Gene symbol	Herb
RXRA	GC, SY
SIAE	GC, SY
SLCO1B1	GC, SY
SLCO1B3	GC, SY
SMN1	GC, SY
TDP1	GC, SY
TOP2A	GC, SY
TP53	GC, SY
TYR	GC, SY
UGT1A3	GC, SY
UGT1A4	GC, SY
UGT1A8	GC, SY
USP1	GC, SY
XDH	GC, SY

Supplementary Table 2. Osteoarthritis-associated target genes.

UniProt ID	Gene symbol	Description	Organism	Source
P43026	GDF5	Growth/differentiation factor 5	*Homo sapiens*	OMIM
P02458	COL2A1	Collagen, type II, alpha-1	*Homo sapiens*	OMIM
P16112	ACAN	Aggrecan	*Homo sapiens*	OMIM
Q9BXN1	ASPN	Asporin	*Homo sapiens*	OMIM
P84022	SMAD3	Mothers against decapentaplegic, drosophila, homolog OF, 3	*Homo sapiens*	OMIM
P0DI81	TRAPPC2	Tracking protein particle complex, subunit 2	*Homo sapiens*	OMIM
Q92765	FRZB	Frizzled-related protein	*Homo sapiens*	OMIM
P20849	COL9A1	Collagen, type IX, alpha-1	*Homo sapiens*	OMIM
Q99814	EPAS1	Endothelial pas domain protein 1	*Homo sapiens*	OMIM
P49747	COMP	Cartilage oligomeric matrix protein	*Homo sapiens*	OMIM
Q9UNA0	ADAMTS5	A disintegrin-like and metalloproteinase with thrombospondin type 1 Motif, 5	*Homo sapiens*	OMIM
O15232	MATN3	Matrilin 3	*Homo sapiens*	OMIM

UniProt ID	Gene symbol	Description	Organism	Source
Q14623	IHH	Indian Hedgehog	*Homo sapiens*	OMIM
Q9NRR1	CYTL1	Cytokine-like protein 1	*Homo sapiens*	OMIM
P49190	PTH2R	Parathyroid hormone 2 receptor	*Homo sapiens*	OMIM
Q92731	ESR2	Estrogen receptor 2	*Homo sapiens*	OMIM
P41159	LEP	Leptin	*Homo sapiens*	OMIM
P0DP23	CALM1	Calmodulin 1	*Homo sapiens*	OMIM
P41180	CASR	Calcium-sensing receptor	*Homo sapiens*	OMIM
P98066	TNFAIP6	Tumor necrosis factor-apha-induced protein 6	*Homo sapiens*	OMIM
Q92743	HTRA1	HTRA serine peptidase 1	*Homo sapiens*	OMIM
P13942	COL11A2	Collagen, type XI, alpha-2	*Homo sapiens*	OMIM
Q9UHF7	TRPS1	Trichorhinophalangeal syndrome, type I	*Homo sapiens*	OMIM
P11473	VDR	Vitamin D receptor	*Homo sapiens*	OMIM
Q92633	LPAR1	Lysophosphatidic acid receptor 1	*Homo sapiens*	OMIM
P30044	PRDX5	Peroxiredoxin 5	*Homo sapiens*	OMIM

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UniProt ID	Gene symbol	Description	Organism	Source
Q9HCJ1	ANKH	ANK, mouse, Homolog OF	*Homo sapiens*	OMIM
Q9Y2L9	LRCH1	Leucine-rich repeats and calponin homology domain-containing 1	*Homo sapiens*	OMIM
P98160	HSPG2	Heparan sulfate proteoglycan of basement membrane	*Homo sapiens*	OMIM
P56199	ITGA1	Integrin, alpha-1	*Homo sapiens*	OMIM
P45452	MMP13	Matrix metalloproteinase 13	*Homo sapiens*	OMIM
P02452	COL1A1	Collagen, type I, alpha-1	*Homo sapiens*	OMIM
P03372	ESR1	Estrogen receptor 1	*Homo sapiens*	OMIM
P13500	CCL2	Chemokine, CC Motif, ligand 2	*Homo sapiens*	OMIM
Q16552	IL17A	Interleukin 17A	*Homo sapiens*	OMIM
P78536	ADAM17	A disintegrin and metalloproteinase domain 17	*Homo sapiens*	OMIM
P51884	LUM	Lumican	*Homo sapiens*	OMIM
P48061	CXCL12	Chemokine, CXC Motif, ligand 12	*Homo sapiens*	OMIM
P43235	CTSK	Cathepsin K	*Homo sapiens*	OMIM
P11712	CYP2C9	Cytochrome P450, subfamily Iic, polypeptide 9	*Homo sapiens*	OMIM
Q99969	RARRES2	Retinoic acid receptor responder 2	*Homo sapiens*	OMIM
Q9NS15	LTBP3	Latent transforming growth factor-beta-binding protein 3	*Homo sapiens*	OMIM
Q9HCN6	GP6	Glycoprotein VI, platelet	*Homo sapiens*	OMIM
P24001	IL32	Interleukin 32	*Homo sapiens*	OMIM
Q92954	PRG4	Proteoglycan 4	*Homo sapiens*	OMIM
O94907	DKK1	DICKKOPF, Xenopus, Homolog OF, 1	*Homo sapiens*	OMIM
Q9H5V8	CDCP1	CUB domain-containing protein 1	*Homo sapiens*	OMIM
Q9Y2U5	MAP3K2	Mitogen-activated protein kinase kinase kinase 2	*Homo sapiens*	OMIM
Q8TCG1	CIP2A	Cell proliferation-regulating inhibitor of protein phosphatase 2A	*Homo sapiens*	OMIM
P14784	IL2RB	Interleukin 2 receptor, beta	*Homo sapiens*	OMIM
P17931	LGALS3	Lectin, galactoside-binding, soluble, 3	*Homo sapiens*	OMIM
Q14050	COL9A3	Collagen, Type IX, alpha-3	*Homo sapiens*	OMIM
P02751	FN1	Fibronectin 1	*Homo sapiens*	OMIM
P30203	CD6	CD6 antigen	*Homo sapiens*	OMIM
Q96S44	TP53	Tumor protein P53	*Homo sapiens*	OMIM
P31785	IL2RG	Interleukin 2 receptor, gamma	*Homo sapiens*	OMIM
P55287	CDH11	Cadherin 11	*Homo sapiens*	OMIM
Q8WVB3	HEXDC	Hexosaminidase (glycosyl hydrolase family 20, catalytic domain)-containing protein	*Homo sapiens*	OMIM
O75711	SCRG1	Stimulator of chondrogenesis 1	*Homo sapiens*	OMIM
P35354	PTGS2	Prostaglandin-endoperoxide synthase 2	*Homo sapiens*	OMIM
Q12794	HYAL1	Hyaluronoglu-cosaminidase 1	*Homo sapiens*	OMIM
Q8IUL8	CILP2	Cartilage intermediate layer protein 2	*Homo sapiens*	OMIM
Q8WVQ1	CANT1	Calcium-activated nucleotidase 1	*Homo sapiens*	OMIM
Q03692	COL10A1	Collagen, Type X, alpha-1	*Homo sapiens*	OMIM
P10600	TGFB3	Transforming growth factor, beta-3	*Homo sapiens*	OMIM
O15530	PDPK1	3-phosphoinositide-dependent protein kinase 1	*Homo sapiens*	Drugbank
P52209	PGD	6-phosphogluconate dehydrogenase, decarboxylating	*Homo sapiens*	Drugbank
Q9Y215	COLQ	Acetylcholinesterase	*Homo sapiens*	Drugbank
P78348	ASIC1	Acid-sensing ion channel 1	*Homo sapiens*	Drugbank
O60218	AKR1B10	Aldo-keto reductase family 1 member B10	*Homo sapiens*	Drugbank
P42330	AKR1C3	Aldo-keto reductase family 1 member C3	*Homo sapiens*	Drugbank
P10275	AR	Androgen receptor	*Homo sapiens*	Drugbank
Q07817	BCL2L1	Apoptosis regulator Bcl-2	*Homo sapiens*	Drugbank

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UniProt ID	Gene symbol	Description	Organism	Source
P09917	ALOX5	Arachidonate 5-lipoxygenase	*Homo sapiens*	Drugbank
Q2M3GO	ABCB5	ATP-binding cassette sub-family B member 5	*Homo sapiens*	Drugbank
Q96J66	ABCC11	ATP-binding cassette sub-family C member 11	*Homo sapiens*	Drugbank
Q9UNQ0	ABCG2	ATP-binding cassette sub-family G member 2	*Homo sapiens*	Drugbank
Q92887	ABCC2	Canalicular multispecific organic anion transporter 1	*Homo sapiens*	Drugbank
O15438	ABCC3	Canalicular multispecific organic anion transporter 2	*Homo sapiens*	Drugbank
P00918	CA2	Carbonic anhydrase 2	*Homo sapiens*	Drugbank
P07451	CA3	Carbonic anhydrase 3	*Homo sapiens*	Drugbank
P06276	BCHE	Cholinesterase	*Homo sapiens*	Drugbank
P08185	SERPINA6	Corticosteroid-binding globulin	*Homo sapiens*	Drugbank
P25024	CXCR1	C-X-C chemokine receptor type 1	*Homo sapiens*	Drugbank
P13569	CFTR	Cystic fibrosis transmembrane conductance regulator	*Homo sapiens*	Drugbank
P04798	CYP1A1	Cytochrome P450 1A1	*Homo sapiens*	Drugbank
P05177	CYP1A2	Cytochrome P450 1A2	*Homo sapiens*	Drugbank
P11509	CYP2A6	Cytochrome P450 2A6	*Homo sapiens*	Drugbank
P20813	CYP2B6	Cytochrome P450 2B6	*Homo sapiens*	Drugbank
P33260	CYP2C18	Cytochrome P450 2C18	*Homo sapiens*	Drugbank
P33261	CYP2C19	Cytochrome P450 2C19	*Homo sapiens*	Drugbank
P10632	CYP2C8	Cytochrome P450 2C8	*Homo sapiens*	Drugbank
P10635	CYP2D6	Cytochrome P450 2D6	*Homo sapiens*	Drugbank
P05182	CYP2E1	Cytochrome P450 2E1	*Homo sapiens*	Drugbank
P08684	CYP3A4	PCytochrome P450 3A4	*Homo sapiens*	Drugbank
P20815	CYP3A5	Cytochrome P450 3A5	*Homo sapiens*	Drugbank
P02693	FABP2	Fatty acid-binding protein, intestinal	*Homo sapiens*	Drugbank
P04150	NR3C1	Glucocorticoid receptor	*Homo sapiens*	Drugbank
P25021	HRH2	Histamine H2 receptor	*Homo sapiens*	Drugbank
Q04760	GLO1	Lactoylglutathione lyase	*Homo sapiens*	Drugbank
P23141	CES1	Liver carboxylesterase 1	*Homo sapiens*	Drugbank
P27361	MAPK3	Mitogen-activated protein kinase 3	*Homo sapiens*	Drugbank
P08183	ABCB1	Multidrug resistance protein 1	*Homo sapiens*	Drugbank
P33527	ABCC1	Multidrug resistance-associated protein 1	*Homo sapiens*	Drugbank
O15439	ABCC4	Multidrug resistance-associated protein 4	*Homo sapiens*	Drugbank
O95255	ABCC6	Multidrug resistance-associated protein 6	*Homo sapiens*	Drugbank
P05164	MPO	Myeloperoxidase	*Homo sapiens*	Drugbank
Q07869	PPARA	Peroxisome proliferator-activated receptor alpha	*Homo sapiens*	Drugbank
Q03181	PPARD	Peroxisome proliferator-activated receptor delta	*Homo sapiens*	Drugbank
P37231	PPARG	Peroxisome proliferator-activated receptor gamma	*Homo sapiens*	Drugbank
P14555	PLA2G2A	Phospholipase A2, membrane associated	*Homo sapiens*	Drugbank
O43526	KCNQ2	Potassium voltage-gated channel subfamily KQT member 2	*Homo sapiens*	Drugbank
O43525	KCNQ3	Potassium voltage-gated channel subfamily KQT member 3	*Homo sapiens*	Drugbank
Q9Y5Y4	PTGDR2	Prostaglandin D2 receptor 2	*Homo sapiens*	Drugbank
P34995	PTGER1	Prostaglandin E2 receptor EP1 subtype	*Homo sapiens*	Drugbank
Q8VDQ1	PTGR2	Prostaglandin reductase 2	*Homo sapiens*	Drugbank
P19793	RXRA	Retinoic acid receptor RXR-alpha	*Homo sapiens*	Drugbank
Q9Y5Y9	SCN10A	Sodium channel protein type 10 subunit alpha	*Homo sapiens*	Drugbank
P35499	SCN4A	Sodium channel protein type 4 subunit alpha	*Homo sapiens*	Drugbank
Q14973	SLC10A1	Sodium/bile acid cotransporter	*Homo sapiens*	Drugbank
P46059	SLC15A1	Solute carrier family 15 member 1	*Homo sapiens*	Drugbank
Q9NSA0	SLC22A11	Solute carrier family 22 member 11	*Homo sapiens*	Drugbank
O15244	SLC22A2	Solute carrier family 22 member 2	*Homo sapiens*	Drugbank

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UniProt ID	Gene symbol	Description	Organism	Source
Q8VC69	SLC22A6	Solute carrier family 22 member 6	*Homo sapiens*	Drugbank
Q9Y694	SLC22A7	Solute carrier family 22 member 7	*Homo sapiens*	Drugbank
Q8TCC7	SLC22A8	Solute carrier family 22 member 8	*Homo sapiens*	Drugbank
P46721	SLCO1A2	Solute carrier organic anion transporter family member 1A2	*Homo sapiens*	Drugbank
Q9Y6L6	SLCO1B1	Solute carrier organic anion transporter family member 1B1	*Homo sapiens*	Drugbank
Q9NYB5	SLCO1C1	Solute carrier organic anion transporter family member 1C1	*Homo sapiens*	Drugbank
O94956	SLCO2B1	Solute carrier organic anion transporter family member 2B1	*Homo sapiens*	Drugbank
P07204	THBD	Thrombomodulin	*Homo sapiens*	Drugbank
P00750	PLAT	Tissue-type plasminogen activator	*Homo sapiens*	Drugbank
P02766	TTR	Transthyretin	*Homo sapiens*	Drugbank
P48775	TDO2	Tryptophan 2,3-dioxygenase	*Homo sapiens*	Drugbank
P22309	UGT1A1	UDP-glucuronosyltransferase 1-1	*Homo sapiens*	Drugbank
Q9HAW8	UGT1A10	UDP-glucuronosyltransferase 1-10	*Homo sapiens*	Drugbank
P35503	UGT1A3	UDP-glucuronosyltransferase 1-3	*Homo sapiens*	Drugbank
Q9HAW9	UGT1A8	UDP-glucuronosyltransferase 1-8	*Homo sapiens*	Drugbank
O60656	UGT1A9	UDP-glucuronosyltransferase 1-9	*Homo sapiens*	Drugbank
P06133	UGT2B4	UDP-glucuronosyltransferase 2B4	*Homo sapiens*	Drugbank
P16662	UGT2B7	UDP-glucuronosyltransferase 2B7	*Homo sapiens*	Drugbank
P02768	ALB	Serum albumin	*Homo sapiens*	Drugbank, Genecards
P23219	PTGS1	Prostaglandin G/H synthase 1	*Homo sapiens*	Drugbank, Genecards
P01584	IL1B	Interleukin 1 Beta	*Homo sapiens*	Genecards

UniProt ID	Gene symbol	Description	Organism	Source
P08123	COL1A2	Collagen Type I Alpha 2 Chain	*Homo sapiens*	Genecards
P08254	MMP3	Matrix Metallopeptidase 3	*Homo sapiens*	Genecards
P01375	TNF	Tumor Necrosis Factor	*Homo sapiens*	Genecards
P08887	IL6	Interleukin 6	*Homo sapiens*	Genecards
P03956	MMP1	Matrix Metallopeptidase 1	*Homo sapiens*	Genecards
P01137	TGFB1	Transforming Growth Factor Beta 1	*Homo sapiens*	Genecards
O75339	CILP	Cartilage Intermediate Layer Protein	*Homo sapiens*	Genecards
Q9NUQ7	UFSP2	UFM1 Specific Peptidase 2	*Homo sapiens*	Genecards
Q14055	COL9A2	Collagen Type IX Alpha 2 Chain	*Homo sapiens*	Genecards
O14788	TNFSF11	TNF Superfamily Member 11	*Homo sapiens*	Genecards
P10145	CXCL8	C-X-C Motif Chemokine Ligand 8	*Homo sapiens*	Genecards
O00300	TNFRSF11B	TNF Receptor Superfamily Member 11b	*Homo sapiens*	Genecards
P01033	TIMP1	TIMP Metallopeptidase Inhibitor 1	*Homo sapiens*	Genecards
O75173	ADAMTS4	ADAM Metallopeptidase With Thrombospondin Type 1 Motif 4	*Homo sapiens*	Genecards
P50443	SLC26A2	Solute Carrier Family 26 Member 2	*Homo sapiens*	Genecards
Q16832	DDR2	Discoidin Domain Receptor Tyrosine Kinase 2	*Homo sapiens*	Genecards
Q9HBA0	TRPV4	Transient Receptor Potential Cation Channel Subfamily V Member 4	*Homo sapiens*	Genecards
P02741	CRP	C-Reactive Protein	*Homo sapiens*	Genecards
P22301	IL10	Interleukin 10	*Homo sapiens*	Genecards
P36222	CHI3L1	Chitinase 3 Like 1	*Homo sapiens*	Genecards
O15068	MCF2L	MCF.2 Cell Line Derived Transforming Sequence Like	*Homo sapiens*	Genecards
P12107	COL11A1	Collagen Type XI Alpha 1 Chain	*Homo sapiens*	Genecards
Q14807	KIF22	Kinesin Family Member 22	*Homo sapiens*	Genecards
P22003	BMP5	Bone Morphogenetic Protein 5	*Homo sapiens*	Genecards

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UniProt ID	Gene symbol	Description	Organism	Source
P48436	SOX9	SRY-Box 9	*Homo sapiens*	Genecards
P18510	IL1RN	Interleukin 1 Receptor Antagonist	*Homo sapiens*	Genecards
P02461	COL3A1	Collagen Type III Alpha 1 Chain	*Homo sapiens*	Genecards
P21941	MATN1	Matrilin 1, Cartilage Matrix Protein	*Homo sapiens*	Genecards
Q8WXS8	ADAMTS14	ADAM Metallopeptidase With Thrombospondin Type 1 Motif 14	*Homo sapiens*	Genecards
P22607	FGFR3	Fibroblast Growth Factor Receptor 3	*Homo sapiens*	Genecards
P51798	CLCN7	Chloride Voltage-Gated Channel 7	*Homo sapiens*	Genecards
P35555	FBN1	Fibrillin 1	*Homo sapiens*	Genecards
P10912	GHR	Growth Hormone Receptor	*Homo sapiens*	Genecards
P02818	BGLAP	Bone Gamma-Carboxyglutamate Protein	*Homo sapiens*	Genecards
P63092	GNAS	GNAS Complex Locus	*Homo sapiens*	Genecards
Q16394	EXT1	Exostosin Glycosyltransferase 1	*Homo sapiens*	Genecards
P01583	IL1A	Interleukin 1 Alpha	*Homo sapiens*	Genecards
Q86Y38	XYLT1	Xylosyltransferase 1	*Homo sapiens*	Genecards
P208908	COL5A1	Collagen Type V Alpha 1 Chain	*Homo sapiens*	Genecards
Q9GIY3	HLA-DRB1	Major Histocompatibility Complex, Class II, DR Beta 1	*Homo sapiens*	Genecards
Q9Y2R2	PTPN22	Protein Tyrosine Phosphatase, Non-Receptor Type 22	*Homo sapiens*	Genecards
O15266	SHOX	Short Stature Homeobox	*Homo sapiens*	Genecards
Q93099	HGD	Homogentisate 1,2-Dioxygenase	*Homo sapiens*	Genecards

Supplementary Table 3. SGD compound targets.

Gene symbol	Herb	Gene symbol	Herb	Gene symbol	Herb	Gene symbol	Herb
ABCC2	GC	MMP9	GC	ADAM17	SY	DNMT1	SY
APOB	GC	NOS2	GC	ALB	SY	DRD2	SY
ATAD5	GC	PDE5A	GC	ALPI	SY	EHMT2	SY
BAZ2B	GC	PLA2G7	GC	ALPL	SY	GAA	SY
BDNF	GC	PPME1	GC	APOBEC3F	SY	GLI1	SY
BRCA1	GC	RAPGEF1	GC	APOBEC3G	SY	GLI3	SY
CALM1	GC	RAPGEF3	GC	APOE	SY	GLS	SY
CBR1	GC	SHBG	GC	ARSA	SY	GPBAR1	SY
CBR3	GC	SLC5A1	GC	BIRC5	SY	GPT	SY
CBX1	GC	SLC5A2	GC	BLM	SY	HSD11B2	SY
CCL2	GC	SLCO2B1	GC	CAT	SY	HSF1	SY
GFER	GC	SMAD3	GC	CDK1	SY	HSP90AA1	SY
GSK3A	GC	SMPD1	GC	CFTR	SY	HSP90AB1	SY
HMOX1	GC	TIM23	GC	CHRM1	SY	ICAM1	SY
HSPA5	GC	UGT1A1	GC	CISD1	SY	IL8	SY
LDLR	GC	UGT1A10	GC	CTDSP1	SY	KCNA5	SY
MAPK8	GC	UGT2B15	GC	CTSD	SY	KCNH2	SY
MAPK9	GC	ABCB11	SY	CYCS	SY	KCNMA1	SY
MAZF	GC	ABCG5	SY	CYP2A7	SY	LMNB1	SY
MBNL1	GC	ABCG8	SY	CYP7A1	SY	NOS3	SY
MLLT3	GC	ADAM10	SY	DHCR24	SY	NPSR1	SY

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Gene symbol	Herb
NQO1	SY
NR1H2	SY
NR1H3	SY
NR1I2	SY
NR1I3	SY
PIM2	SY
PLCG1	SY
PLCG2	SY
PMP22	SY
PRKAA2	SY
PRKCB	SY
PRKCE	SY
PTPRS	SY
PYGM	SY
RACGAP1	SY
RARA	SY
RECQL	SY
RORC	SY
RPS6KA3	SY
SAE1	SY
SOD1	SY
SP1	SY
SREBF1	SY
SREBF2	SY
STK16	SY
STK33	SY
SYK	SY
TLR4	SY
UBA2	SY
UBE2I	SY
UGT1A7	SY
UGT1A9	SY
UGT3A1	SY
XIAP	SY
ABCB1	GC, SY
ABCC1	GC, SY

Gene symbol	Herb
ABCG2	GC, SY
ACHE	GC, SY
AHR	GC, SY
AKR1B1	GC, SY
AKR1B10	GC, SY
AKT1	GC, SY
ALDH1A1	GC, SY
ALOX15	GC, SY
ALOX15B	GC, SY
ALOX5	GC, SY
AMY1A	GC, SY
APEX1	GC, SY
APP	GC, SY
AR	GC, SY
ATXN2	GC, SY
BACE1	GC, SY
BCHE	GC, SY
CA1	GC, SY
CA12	GC, SY
CA2	GC, SY
CA4	GC, SY
CA7	GC, SY
CASP3	GC, SY
CDK6	GC, SY
CLK1	GC, SY
CYP19A1	GC, SY
CYP1A1	GC, SY
CYP1A2	GC, SY
CYP1B1	GC, SY
CYP2C19	GC, SY
CYP2C9	GC, SY
CYP2D6	GC, SY
CYP3A4	GC, SY
DAPK1	GC, SY
DPP4	GC, SY
DYRK1A	GC, SY

Gene symbol	Herb
EGFR	GC, SY
ESR1	GC, SY
ESR2	GC, SY
ESRRA	GC, SY
F2	GC, SY
FEN1	GC, SY
FLT3	GC, SY
GBA	GC, SY
GLO1	GC, SY
GLP1R	GC, SY
GMNN	GC, SY
GSK3B	GC, SY
HDAC9	GC, SY
HIF1A	GC, SY
HPGD	GC, SY
HSD17B1	GC, SY
HSD17B10	GC, SY
HSD17B2	GC, SY
IDH1	GC, SY
KDM4A	GC, SY
KDM4E	GC, SY
LMNA	GC, SY
MAPT	GC, SY
MDM2	GC, SY
MDM4	GC, SY
MPG	GC, SY
NEU2	GC, SY
NFE2L2	GC, SY
NFKB1	GC, SY
NFKB2	GC, SY
NOX4	GC, SY
NR1H4	GC, SY
NR3C1	GC, SY
OPRD1	GC, SY
OPRK1	GC, SY
OPRM1	GC, SY

Gene symbol	Herb
PAFAH1B3	GC, SY
PIM1	GC, SY
PIP4K2A	GC, SY
PNLIP	GC, SY
POLB	GC, SY
POLH	GC, SY
POLI	GC, SY
POLK	GC, SY
PON1	GC, SY
PPARA	GC, SY
PPARD	GC, SY
PPARG	GC, SY
PREP	GC, SY
PTGS1	GC, SY
PTGS2	GC, SY
PTH1R	GC, SY
PTPN1	GC, SY
RAPGEF4	GC, SY
RELA	GC, SY
RGS4	GC, SY
RXRA	GC, SY
SIAE	GC, SY
SLCO1B1	GC, SY
SLCO1B3	GC, SY
SMN1	GC, SY
TDP1	GC, SY
TOP2A	GC, SY
TP53	GC, SY
TYR	GC, SY
UGT1A3	GC, SY
UGT1A4	GC, SY
UGT1A8	GC, SY
USP1	GC, SY
XDH	GC, SY

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