Type of Article: Original Research

Title: Exploring the Mechanism of Action of the Traditional Chinese Medicine Formula Compound *Qingwei San* in the Treatment of Periodontitis Based on Network-Pharmacology and Molecular Docking Enhanced by Machine Learning

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ABSTRACT

Introduction: Periodontitis is a common chronic inflammatory disease that can lead to tooth loss. Conventional treatments face limitations due to microbial resistance and side effects. *Qingwei San*, a traditional Chinese medicine formula, is widely used for oral inflammation, but its mechanisms remain unclear.

Methods: Active components of *Qingwei San* were retrieved from the TCMSP database and filtered according to pharmacokinetic criteria, while disease-related targets were obtained from multiple genetic databases. Intersecting targets were identified and incorporated into a drug-component-target-disease network constructed in Cytoscape, with protein-protein interactions analyzed through the STRING database. Gene Ontology and KEGG enrichment analyses were conducted to determine biological functions and signaling pathways. A Random Forest (RF) model was applied to evaluate the relative importance of intersecting genes. High-importance genes were cross-referenced with PPI hubs to identify core targets for molecular docking.

Results: The study identified 46 active compounds and 600 associated targets, with 114 overlapping genes linked to periodontitis. Network and topological analyses revealed 24 core targets, with TNF, IL6, IL1B, and TP53 being the most significant. The RF model achieved an AUC of 0.967, identifying ten core targets (TNF, IL1B, IL6, TP53, CXCL8, MMP9, CASP3, MAPK3, PTGS2, and JUN) consistent with network findings. Enrichment analyses highlighted pathways including lipid metabolism and atherosclerosis, AGE-RAGE signaling, and TNF signaling. Molecular docking demonstrated strong binding affinities, particularly between quercetin and IL6/TNF, as well as kaempferol and IL1B.

Conclusion: *Qingwei San* alleviates periodontitis through multiple bioactive compounds, notably quercetin, kaempferol, and paeoniflorin, which target core genes and regulate key

inflammatory pathways. These findings provide a theoretical foundation for its clinical use and warrant further experimental validation.

Keywords: *Compound Qingwei San*; Periodontitis; Network Pharmacology; Molecular Docking Simulation, machine learning

1. Introduction

Periodontitis is an inflammatory and destructive disease affecting the periodontal supporting tissues, including the gums, periodontal ligament, alveolar bone, and cementum.[1] It affects approximately 20%–50% of the global population. In the early stages, the primary clinical manifestations of periodontitis include gingival redness, swelling, and bleeding. As the disease progresses, the gaps between the teeth widen, leading to tooth mobility, gingival recession, and, ultimately, tooth loss if not treated promptly.[2] One of the crucial initiating factors of periodontitis is the presence of microbial dental plaque and its byproducts.[3] Therefore, the core method for treating periodontitis currently involves non-surgical periodontal therapy aimed at effectively removing these microorganisms and preventing their reattachment.[4,5] These treatment measures help reduce harmful plaque on the gums and tooth surfaces, preventing the development of periodontal pockets that cause inflammation. By utilizing these methods, the oral health of periodontitis patients can be effectively improved, inflammation can be reduced, and long-term oral health can be maintained. However, various factors limit the effectiveness of non-surgical periodontal therapy. Although the local application of antibiotics such as metronidazole, amoxicillin, and penicillin may enhance clinical efficacy, the gradual development of resistance in local oral microbial communities to antibacterial drugs can disrupt the normal oral microbiota. Moreover, long-term repeated antibiotic treatments can exacerbate liver and kidney metabolism, affect the patient's digestive system, and cause numerous adverse effects.[6] Therefore, natural antimicrobial agents derived from herbal components in traditional Chinese medicine have gradually become a focus of research.

Qingwei San was first documented during the Jin Dynasty by Li Dongyuan in his seminal work *Pi Wei Lun* (Treatise on the Spleen and Stomach). This classical formula is recognized for its marked efficacy, wide therapeutic applications, and favorable safety profile. It consists of five medicinal ingredients: *Cimicifugae Rhizoma* (Sheng Ma), *Coptidis Rhizoma* (Huang

Lian), *Angelicae Sinensis Radix* (Dang Gui), *Rehmanniae Radix* (Sheng Di Huang), and *Moutan Cortex* (Mu Dan Pi).[7] The principal component, *Coptidis Rhizoma*, effectively clears pathogenic heat from the stomach. *Rehmanniae Radix* and *Moutan Cortex* function as supportive agents, nourishing yin, dissipating heat, and cooling the blood. *Angelicae Sinensis Radix* cools the blood and reduces swelling, while *Cimicifugae Rhizoma* promotes the upward dispersal of heat. In combination with *Coptidis Rhizoma*, these herbs synergistically clear stomach heat, extinguish ascending fire, and alleviate internal heat stasis. Collectively, the five medicinal components act in concert to achieve the overarching therapeutic aim of clearing heat and cooling the blood.[8] In contemporary clinical practice, *Qingwei San* is widely employed in the treatment of stomach heat-related disorders, including oral ulcers, periodontitis, and upper gastrointestinal bleeding.[9]

Network pharmacology is an emerging discipline that integrates systems biology, polypharmacology, and computational biology, leveraging technologies such as artificial intelligence and big data analysis. At its core, it examines the molecular mechanisms underlying drug-disease interactions from a holistic, systems-level, and biological network perspective. By constructing "drug-target-disease" networks, it provides a framework for elucidating the complex interrelationships among these entities. Furthermore, the field employs molecular docking techniques to investigate receptor properties and the interaction modes between receptor and ligand molecules, facilitating the prediction and evaluation of ligand-receptor binding and the strength of these interactions. This approach offers innovative means of exploring the intricate mechanisms of drug action.[10] Network pharmacology facilitates an in-depth investigation of traditional Chinese medicine (TCM) and its compound formulas, particularly at the molecular level, in alignment with the core holistic philosophy of TCM.[11] In this study, network pharmacology and molecular docking techniques are employed to investigate the mechanisms by which the TCM formula *Qingwei San* treats periodontitis,

106 thereby providing a theoretical basis for its clinical application and for future research on its
107 therapeutic potential.
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2. Materials and Methods

Identification of Components and Targets of the Qingwei San Compound

The Traditional Chinese Medicine Systems Pharmacology Database (TCMSP, http://tcmspw.com/tcmsp.php) was used to retrieve the components of the five herbs in *Qingwei San*: *Angelicae Sinensis Radix* (Dang Gui), *Coptidis Rhizoma* (Huang Lian), *Cimicifugae Rhizoma* (Sheng Ma), *Moutan Cortex* (Mu Dan Pi), and *Rehmanniae Radix* (Di Huang). Active components were screened based on pharmacokinetic properties, specifically oral bioavailability ≥30% and drug-likeness ≥0.18. The corresponding protein targets were then identified and annotated uniformly using the UniProt Protein Database (https://www.uniprot.org/). Finally, drug-target ID conversion and data organization were performed.

Acquisition of Periodontitis-Related Targets

Using the keyword "periodontitis", searches were conducted in the GeneCards (https://www.genecards.org/), OMIM (https://www.omim.org/), PharmGKB (https://www.pharmgkb.org/), DrugBank (https://www.drugbank.ca/), and TTD (http://db.idrblab.net/ttd/) databases to identify and screen periodontitis-related target genes. The collected genes were then merged and deduplicated. Visualization was performed using the R package "venn" to generate a Venn diagram.

Obtaining the Intersection of Drug Targets and Disease-Related Genes

Target genes corresponding to the active components were extracted and standardized. The standardized target genes of the drug-related protein components were then intersected with periodontitis-associated target genes to identify the common targets. Visualization of the intersecting genes was performed using the R package "venn", which generated a Venn diagram.

Construction of the Traditional Chinese Medicine Compound Regulation Network

The information was organized and summarized to generate two files of intersecting target genes. The first file lists the component names, their IDs, and the relationships between them. The second file contains node attributes and the corresponding components, serving as preparation files for import. The intersecting target genes were then used as bridges to construct the regulatory network. The "Drug-Active Component-Target-Disease" network was built using Cytoscape v3.10.0 software, and key target genes were identified.

Building and Characterizing the Protein–Protein Interaction (PPI) Network

The intersecting target genes of *Qingwei San* and periodontitis were imported into the STRING platform (http://string-db.org/) with the species set to human. The minimum required interaction score was set to 0.9, and free nodes were removed. A PPI network was then constructed, revealing the interaction relationships between *Qingwei San* target proteins and periodontitis target proteins. The resulting PPI network was imported into Cytoscape v3.10.0. Topological analysis was conducted using the CytoNCA plugin, employing metrics such as betweenness, degree centrality, and closeness centrality to identify core target nodes.

GO Function Enrichment and KEGG Pathway Enrichment

Key target genes were subjected to ID conversion using R packages available on the Bioconductor website. Subsequently, Gene Ontology (GO) functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed to identify the signaling pathways of relevant active factors.[12-14] The threshold was set at $P < 0.05$ to screen for the main molecular biological processes and related signaling pathways involved in *Qingwei* San's treatment of periodontitis. Visualization was performed using bar plots and bubble charts generated in R.

Integration of Machine Learning for Target Prioritization and Validation

To enhance predictive accuracy and refine target selection, a machine learning–based RF approach was applied following network pharmacology and enrichment analyses. Each target gene was annotated with three categories of feature parameters: (1) molecular descriptor features of the corresponding active components, molecular weight, logP, polarity, and hydrogen-bond characteristics, calculated using the "rcdk" and "ChemmineR" packages in R; (2) GO and KEGG enrichment scores represented by −log10 (P value) for major biological processes and signaling pathways; and (3) PPI network topology metrics, including degree, betweenness, and closeness centrality, extracted using "igraph" package in R. All features were standardized and used as inputs for a Random Forest (RF) model implemented with the randomForest package in R. The RF model was trained to distinguish higher-priority targets from background genes, and the Mean Decrease Gini index was used to quantify the relative importance of each gene. Genes with the highest importance scores were identified as potential key targets of Qingwei San in treating periodontitis. Model performance was further evaluated through Receiver Operating Characteristic (ROC) curve analysis and Area Under the Curve (AUC) calculation using "pROC", with k-fold cross-validation ensuring robustness and reliability.

Molecular Docking

The 2D structures of small-molecule ligands were retrieved from the PubChem platform (https://pubchem.ncbi.nlm.nih.gov/). The 2D structures were converted into 3D structures using ChemOffice software, and the resulting files were exported in their energy-minimized forms. The 3D structures of the protein receptors were retrieved from the PDB database (http://www.rcsb.org/). Water molecules and small-molecule ligands were removed from the protein structures using PyMOL software to prepare the receptor files. Subsequently, the ligand and receptor files were converted into PDBQT format using AutoDockTools 1.5.7, and the active binding sites were identified. Molecular docking was performed using AutoDock Vina

182 software, which provided the corresponding binding free energies along with a visual analysis
183 of the docking results.

3. Results

Identification of Traditional Chinese Medicine Components and Targets in Qingwei San

A total of two chemical components from *Angelica*, 11 from *Moutan Cortex*, two from *Rehmannia*, 14 from *Coptis*, and 17 from *Cimicifuga* were screened. After organizing the active components, annotating the corresponding targets, and performing ID conversion, 600 drug targets derived from these medicines were obtained. Table 1 presents the top ten significant targets, mainly derived from *Coptis*, *Moutan Cortex*, and *Cimicifuga*.

Screening of Periodontitis Targets and Identification of Common Drug–Disease Genes

Targets were searched and screened in the GeneCards, OMIM, PharmGKB, DrugBank, and TTD databases. After merging the collected targets and removing duplicates, a total of 3,268 related targets were obtained. Visualization was performed using the "venn" R package to generate a Venn diagram (Figure S1). The canonical drug protein active ingredient target genes (a total of 182) and target genes associated with periodontitis were statistically summarized to identify their intersection, resulting in a total of 114 intersecting target genes. A Venn diagram was plotted to illustrate these findings (Figure S1).

Construction of the Traditional Chinese Medicine Compound Regulation Network

The data were organized and summarized, yielding 255 entries that included the names of the components, their IDs, and the relationships between them, as well as 137 entries detailing node attributes and the components to which they belong. Through network analysis, nodes with higher degree were identified as key active components and targets within the network. These key components included 22 major active compounds such as quercetin, kaempferol, β-sitosterol, and paeoniflorin, along with 114 targets including PTGS2, PTGS1, HSP90AA1, NCOA2, TP53, and TNF. The results demonstrate the multi-component and multi-target characteristics of *Qingwei San*, as depicted in Figure 1A.

Construction and Analysis of the PPI Network

The 114 intersection genes were imported into the STRING platform for PPI analysis. Interactions were filtered using a minimum required interaction score of 0.9, and isolated nodes were removed. The result is an integrated interaction map between the target proteins of *Qingwei San* and those associated with periodontitis (Figure S2). Nodes were filtered using the median value of these attributes as the threshold, ultimately identifying 24 core target genes. Among these, TNF, IL6, IL1B, and TP53 exhibited the highest degree values (Figure 1B).

GO Functional and KEGG Pathway Enrichment analysis

GO enrichment analysis ($P<0.05$) revealed 2018 entries for key target biological process (BP), 40 entries for cellular component (CC), and 145 entries for molecular function (MF). The top 10 results of the BP, CC, and MF enrichment analyses for key targets were plotted (Figure 2A). The results indicate that the biological processes involved in *Qingwei San's* treatment of periodontitis are primarily enriched in responses to molecules of bacterial origin, responses to external stimuli, and responses to lipopolysaccharides. The molecular functions are mainly enriched in DNA-binding transcription factor binding and RNA polymerase II-specific DNA-binding transcription, while the cellular components are predominantly enriched in membrane rafts and membrane microdomains.

Core targets were subsequently subjected to KEGG pathway enrichment analysis ($P<0.05$), yielding 164 related pathways, including lipid metabolism and atherosclerosis, AGE-RAGE signaling, and TNF signaling pathways. The top 30 pathways were visualized using bar charts (Figure 2B). The results suggest that *Qingwei San's* mechanism for treating periodontitis primarily involves lipid metabolism and atherosclerosis, AGE-RAGE signaling, and TNF signaling pathways. Notably, TNF was identified as a key target gene in sections 2.4 and 2.6, and the TNF signaling pathway was mapped, as shown in Figure S3.

Machine Learning Assisted Identification of Core Targets

Feature importance, assessed by the Mean Decrease Gini metric, yielded a ranked list of influential genes with corresponding AUC values: TNF (0.942), IL1B (0.922), IL6 (0.913), TP53 (0.877), CXCL8 (0.833), MMP9 (0.801), MAPK3 (0.780), CASP3 (0.757), PTGS2 (0.733), and JUN (0.714) (Figure 3A–E). The RF model demonstrated robust predictive performance, achieving an average AUC of 0.967 under fivefold cross-validation (Figure 3F). Overlap analysis between RF-derived top features and PPI hub genes identified four core targets: TNF, IL1B, IL6, and TP53.

Molecular Docking Results

The small molecule ligands of the four core target genes with the highest degree values identified in section 2.6 were selected for molecular docking. These ligands were docked individually with the main protein receptors retrieved from the PDB. Using AutoDockTools 1.5.7 software, the ligands were converted to PDBQT format, and the active pockets were identified. Molecular docking was performed using Vina software, resulting in a table of binding energies (Table S1) and visualized analyses of two pairs of docking results with the most significant binding affinities. The molecular docking results indicate that the components of *Qingwei San* exhibit strong binding affinities with all target proteins. Notably, quercetin demonstrated robust binding with IL6 and TNF, while kaempferol showed strong binding with IL1B, suggesting that these may be key components and targets (Figure 5).

4. Discussion

TCM enhances the body's overall condition by adjusting its systemic state, thereby improving local periodontal health. Long-term clinical practice has confirmed the efficacy of TCM in treating periodontitis.[15] In this study, we screened 22 major active components of *Qingwei San, along with* 114 target active component targets and 24 core target genes. By constructing a "drug-active ingredient-target gene" network, we revealed that the mechanism of *Qingwei San* in treating periodontitis does not rely on a single component or target but rather operates through the synergistic action of multiple components and the comprehensive regulation of various targets. This indicates that *Qingwei San*, with its complex pharmacological properties, can simultaneously influence multiple biological pathways, providing a comprehensive treatment for periodontitis. This multi-level mode of action not only enhances its therapeutic effect but also improves oral health from various aspects, reduces inflammation, and facilitates tissue repair. In addition to traditional network pharmacology and enrichment analyses, this study incorporated a machine learning–based RF model to refine the identification of key therapeutic targets. By integrating molecular descriptors, pathway enrichment scores, and network topology metrics, the RF algorithm provided a data-driven prioritization of genes most strongly associated with periodontitis.

The potential action targets for treating periodontitis were enriched in 2018 GO entries and 164 KEGG pathways, including those related to inflammation, the immune system, the cardiovascular system, and microstructure, such as DNA-binding transcription factor binding, RNA polymerase II-specific DNA-binding transcription, rafts and membrane microdomains, lipid metabolism, atherosclerosis pathways, the AGE-RAGE pathway, and the TNF signaling pathway. By constructing the core PPI network and filtering based on betweenness, degree, and closeness using the median value of these attributes as the threshold, we ultimately identified 24 core target genes, with TNF, IL6, IL1B, and TP53 exhibiting the highest degree

values. This further demonstrates that the multiple components of *Qingwei San* may intervene in periodontitis through multi-target interactions. This integrative mechanism suggests potential therapeutic advantages over traditional monotherapies in addressing the complex pathophysiology of periodontitis.

The key components identified through Vina molecular docking analysis are quercetin, kaempferol, and paeoniflorin. Quercetin is a naturally occurring flavanol abundant in fruits and vegetables, known for its promising bioactive properties, including immunoprotective, anti-inflammatory, and antiviral effects.[16-18] Studies have shown that quercetin can disrupt cell membrane integrity, inhibit nucleic acid synthesis, suppress biofilm formation, induce mitochondrial dysfunction, and inhibit the expression of virulence factors, thereby achieving anti-inflammatory effects.[19,20] Compared to antibiotics, these natural compounds tend to have fewer side effects and reduce the risk of microbial resistance. Kaempferol, a natural flavonoid found in various plants, exhibits anti-cancer, anti-inflammatory, and antibacterial properties.[21] It exhibits broad pharmacological effects, such as inhibiting the release of IL-6, IL-1, IL-18, and TNF-α, increasing the mRNA and protein expression of Nrf2-regulated genes, and inhibiting molecules like toll-like receptor 4, thereby achieving anti-inflammatory effects. Paeoniflorin, a monoterpene glycoside isolated from the roots of the Ranunculaceae family plant, Paeonia, possesses bioactivities including immunomodulation, antidepressant effects, and neuroprotection.[22,23] By regulating multiple signaling pathways, *Qingwei San* effectively inhibits the activity of inflammatory cells, impeding the release and expression of key inflammatory factors such as IL-1, IL-6, and TNF-α, thereby reducing local inflammatory responses. Additionally, *Qingwei San* upregulates the expression levels of transforming growth factor-beta, further enhancing its anti-inflammatory and immunomodulatory effects.[24]

Through these mechanisms, *Qingwei San* significantly alleviates tissue damage caused by inflammatory diseases and promotes the repair and regeneration of damaged tissues.[25] This

multi-dimensional regulatory effect underscores *Qingwei San's* broad therapeutic potential in treating inflammatory diseases. Future research should include in vitro assays and in vivo animal studies to validate the predicted targets and pathways, as well as quantitative analyses of active compound concentrations and pharmacokinetic profiling to clarify bioavailability and dose–response relationships.

This study also has several limitations. First, the findings depend on public databases and computational prediction algorithms, which may introduce bias due to incomplete or inconsistent annotations. Second, the machine-learning–based target prioritization remains theoretical and was not validated through experimental approaches. Third, the actual pharmacokinetic properties, biological activities, and potential synergistic interactions of the active components were not evaluated experimentally, limiting direct translational interpretation.

Conclusion

This study demonstrates that *Qingwei San* addresses periodontitis through multi-component, multi-target, and multi-pathway mechanisms. Key compounds such as quercetin, kaempferol, and paeoniflorin interact with core targets (TNF, IL6, IL1B, TP53) and regulate pathways including TNF, AGE-RAGE, and lipid and atherosclerosis. These findings offer a theoretical basis for its clinical application and underscore the need for further experimental validation.

Acknowledgments：None.

Funding statement：This research was funded by the following programs: Liaoning Provincial Department of Education (No. LJ222410164024, No. LJ222410164030); Liaoning Province Science and Technology Joint Plan (Technology Research and Development Program Project. No. 2024JH2/102600237); Shenyang Medical College Horizontal Research Project (No. SYKT2025002, No. SYKT2025005, No. SYKT2025007).

Authors contributions: Z.L., X.M., and Z.Z. Writing, reviewing, and editing; Z.Z., Z.L., and Y.A. Investigation and Formal analysis; X.L. and X.Q. Conceptualization, review, and supervision; X.L. Funding acquisition. All authors reviewed the manuscript.

Ethics approval and consent to participate: Not applicable, this study does not involve new human or animal studies.

Competing interests：The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement: All data generated or analysed during this study are included in this published article. The KEGG pathway database is copyrighted by Kanehisa Laboratories (Permission No. 251945).

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423 Table 1. Top ten drug targets derived from various medicines

Drug	MolId	MolName	Symbol
Coptis	MOL000098	quercetin	TNF
Coptis	MOL000098	quercetin	IL6
Coptis	MOL000098	quercetin	TP53
Coptis	MOL000098	quercetin	IL1B
Moutan Cortex	MOL000422	kaempferol	TNF
Moutan Cortex	MOL000098	quercetin	TNF
Moutan Cortex	MOL000098	quercetin	IL6
Moutan Cortex	MOL000098	quercetin	TP53
Moutan Cortex	MOL000098	quercetin	IL1B
Cimicifuga	MOL001924	paeoniflorin	TNF

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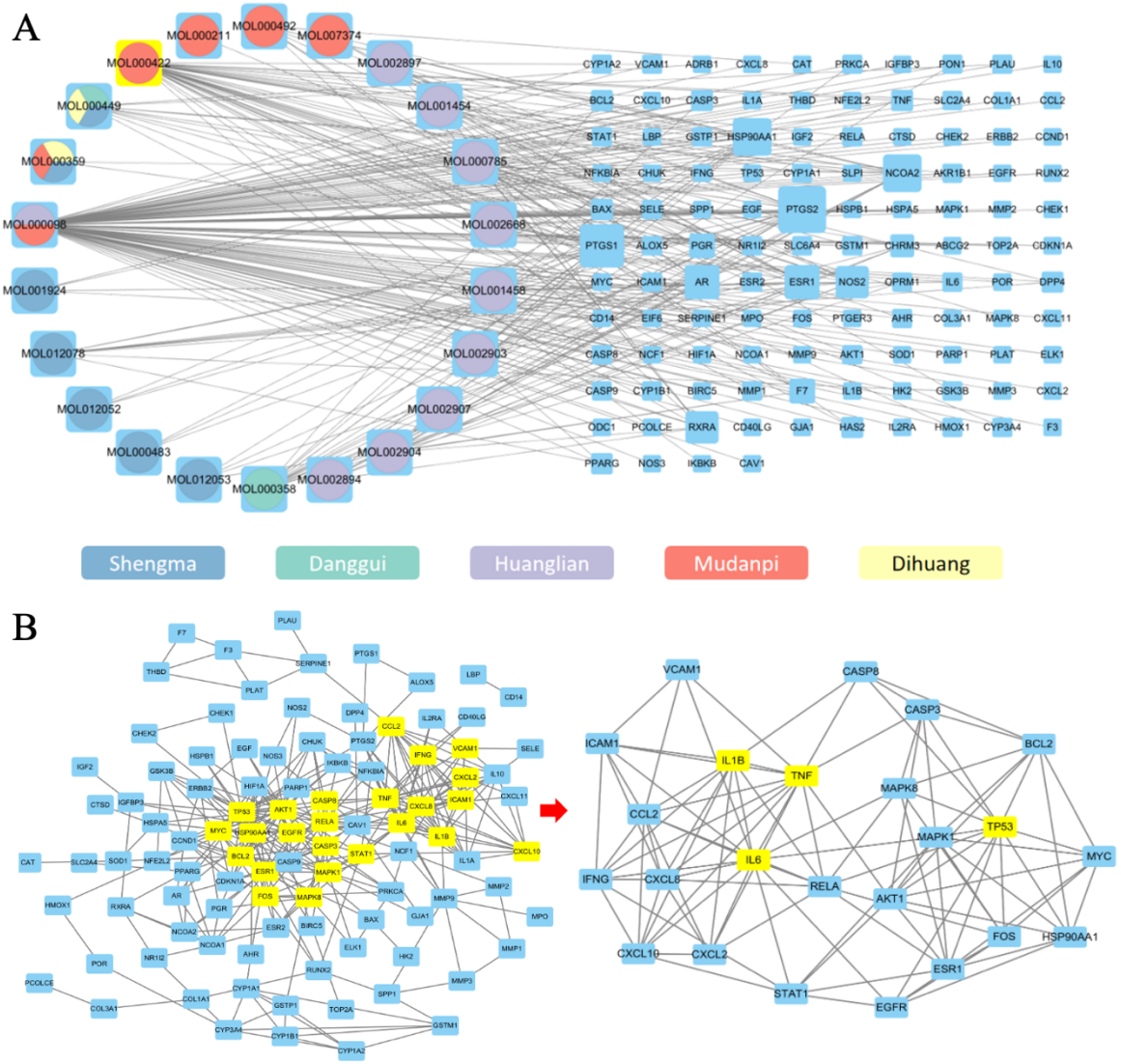
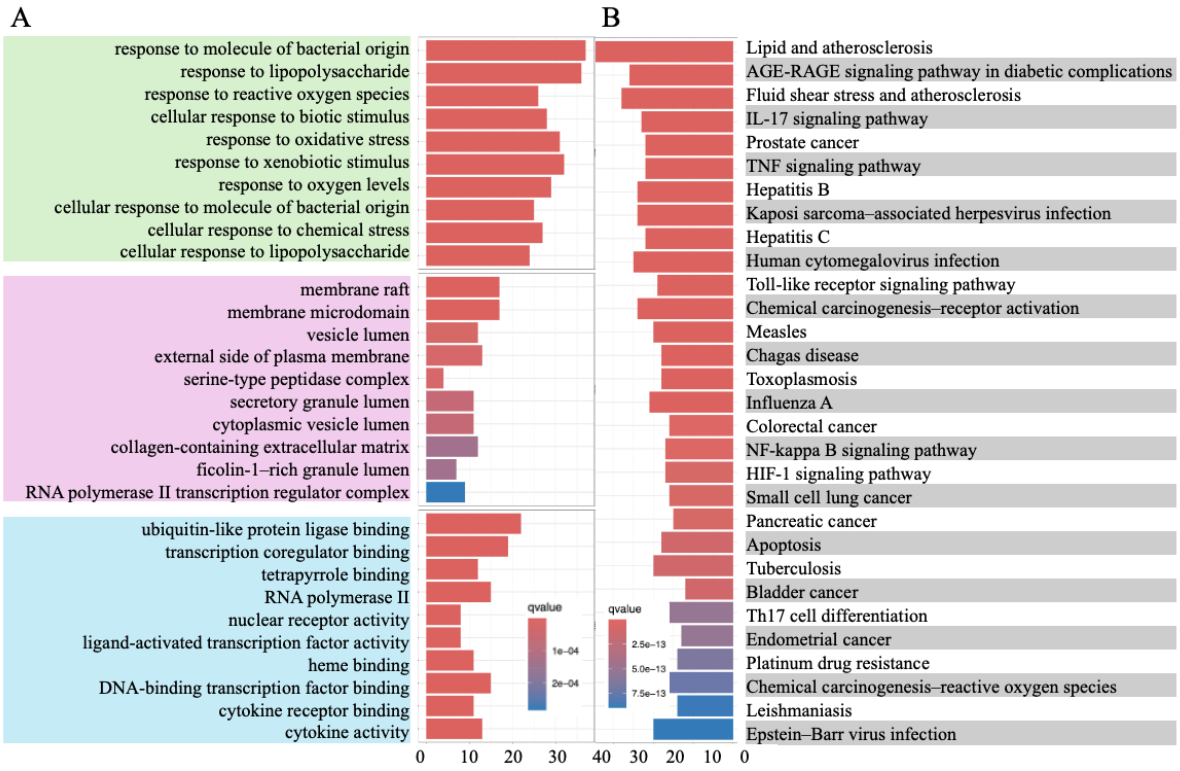
Figure. 1 Construction of the compound–target–pathway interaction and PPI networks



A: compound–target–pathway interaction; B: PPI networks

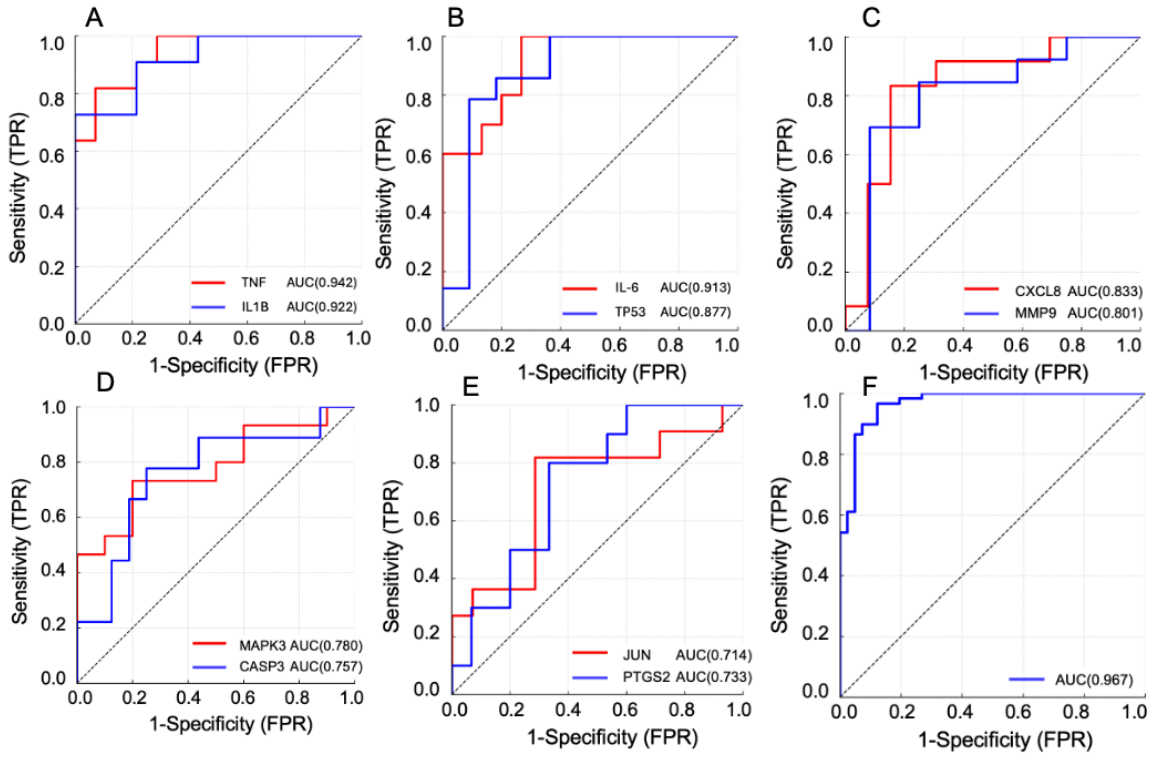
Figure 2. GO Functional and KEGG pathway enrichment analysis



A: GO functional enrichment; B: KEGG pathway analysis.

Contents with green, pink, and light blue backgrounds represent biological process, cellular component, and molecular function, respectively.

436 Figure 3. AUC of core targets identified by machine learning



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438 A–E: AUCs for TNF, IL1B, IL6, TP53, CXCL8, MMP9, CASP3, MAPK3, PTGS2, and JUN.

439 F: AUC for overall estimate

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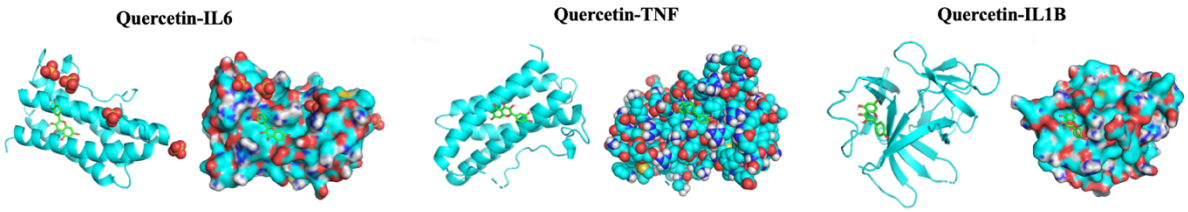
441 Figure 4. 3D visualization of molecular docking for querectin



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