RESEARCH ARTICLE

Exploring the active components of Banxia Houpo Decoction and its therapeutic effects on periodontitis based on network pharmacology data mining

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Periodontitis (PD) is a common oral disease characterized by persistent inflammatory responses, which can lead to the destruction of tooth-supporting tissues. The pathogenesis of this disease is complex and involves multiple aspects such as inflammatory reactions and immune imbalance. As a classic traditional Chinese medicine (TCM) prescription, Banxia Houpu Decoction (BHD) features multi-components and multi-targets. The anti-inflammatory and immunomodulatory active components contained in it indicates its potential value in the treatment of PD, which awaits clinical verification. However, its potential active components and underlying mechanisms of action against PD remains unclear currently. This study elucidated the potential mechanisms of (BHD) in the treatment of PD using network pharmacology (NP). The chemical components of the 5 medicinal herbs in this prescription were collected from the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP). Active ingredients with favorable pharmacokinetic properties were screened out according to specific screening criteria, and their candidate targets were predicted *via* the PubChem platform. Meanwhile, with "PD" as the search term, PD-related target genes were collected from multiple disease target databases. After removing duplicate entries, the common targets of the drug and the disease were screened out through Venn diagram analysis platform (VENNY), and the core targets were identified. Enrichment analysis was performed by using the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) to explore the key biological functions of the core targets and the pathways associated with disease phenotypes. Computer simulation technology was used to evaluate the interaction intensity and binding potential between the main active ingredients and core targets. The results showed that a total of 44 active ingredients and 476 potential targets were screened out, and 3,420 PD-related target genes were collected, ultimately yielding 51 common targets of the drug and the disease. The protein-protein interaction (PPI) network contained 286 edges with tight connections between nodes. GO functional enrichment analysis involved biological processes such as angiogenesis and inflammatory response. The potential mechanisms of BHD mainly focused on the pathways related to inflammation and immune regulation. Molecular docking results showed that the binding energies of most core active ingredients in BHD with key target proteins were lower than -5 kcal/mol, suggesting a strong binding potential between them. The binding energies of some ligand-receptor complexes were even lower, indicating more stable binding, which might form stable complex structures through intermolecular forces such as hydrogen bonds. BHD might exert anti-PD effects by targeting the key pathological proteins of PD and regulating multiple cellular pathways associated with disease progression. This study provided a theoretical basis for the subsequent in-depth investigation of its mechanisms of action and clinical application.

Keywords: Banxia Houpu decoction; periodontitis; network pharmacology; active ingredients; targets.

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Introduction

Oral health as an essential component of overall health has been widely proven to be associated with various systemic diseases. Periodontitis (PD) is a very common infectious disease in stomatology and a hidden danger affecting human oral health, which is caused by the continuous stimulation and disorder of the host's immune - inflammatory response by the dental plaque biofilm, resulting in gingival swelling and redness, bleeding, periodontal pocket, and alveolar bone absorption [1]. Globally, the incidence of PD is higher than it was before. It not only affects the masticatory function of the patient but also may cause other systemic illnesses such as cardiovascular disease and diabetes due to its systemic inflammatory process and blood flow [2]. Therefore, it has been a hot spot in stomatology research. In the past, the clinical treatment of PD mainly focused on mechanical removal of local irritants such as dental plaque and oral calcification and treated residual infection with oral antibiotics [3]. However, such treatments also have some limitations including that it is difficult to completely remove harmful bacteria from hidden areas through mechanical treatment and to completely remove all bacteria. In addition, it is hard to help periodontal tissues stop inflammation in the long term [4]. Therefore, it is urgent to develop a safe new regimen of therapy, which has effects of anti-inflammatory, immuno-modulatory, tissue repairing, *etc*.

Traditional Chinese medicine (TCM) prescriptions feature multi-component synergy and multi-target regulation, which provides a potential direction for meeting this demand. Meanwhile, modern pharmacological studies have indicated that the mechanisms of TCM prescriptions are mostly associated with the regulation of inflammatory factors and the activity of immune cells, which lay the preliminary pharmacological foundation for their application in the treatment of PD. Banxia Houpu Decoction (BHD) is a classic prescription for regulating “qi” in TCM and is composed of 5 medicinal herbs. With the in-depth development of modern pharmacological research, scientists have found that this prescription contains a variety of biologically active chemical components [5]. Existing studies have confirmed that these components participate in the regulation of inflammatory factors, the modulation of immune cell activity, the improvement of oxidative stress, and other processes, exhibiting significant potential in anti-inflammatory, antiviral, and the balance regulation of functional body [6]. However, whether BHD can act on the pathological links related to PD through specific active components, as well as its specific action targets and molecular regulatory networks, has not been clearly elucidated, which largely restricts the development and popularization of this prescription in the prevention and treatment of oral diseases. Network pharmacology (NP) is a modern technique that integrates the theories of multiple disciplines such as systems biology, bioinformatics, and pharmacology with its core lying in the adoption of a holistic and systematic research perspective [7]. By utilizing various databases, this technique can comprehensively excavate and integrate the data of pharmaceutical active components, protein targets and disease-related genes, and clearly reveal the complex and multi-level interaction relationships among drug-component-target-disease with the help of biological network construction and analysis algorithms [8]. This research strategy has effectively made up for the deficiencies of the "single drug-single target" research model in traditional pharmacology and provides a systematic and efficient research path for in-depth elucidation of the mechanisms TCM prescriptions.

This study aimed to adopt the data mining method of network pharmacology to systematically screen the active components in BHD, predict its potential action targets, and combine the pathological mechanism of PD to deeply explore the target associations and related molecular pathways between BHD and PD. The results of this study were expected to provide scientific and theoretical supports for the

treatment of PD with BHD, further enrich the application system of multi-target and holistic regulation of TCM in the treatment of oral diseases, and offer valuable ideas and directions for subsequent relevant experimental research and clinical translation.

Materials and methods

Identification of active ingredients of BHD and screening of target genes

Based on the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database and analysis platform (https://tcmsp-e.com/), this study systematically retrieved the chemical constituents of the components in BHD including *Pinellia ternata*, *Cortex magnoliae officinalis*, *Poria cocos*, *Zingiber officinale*, and *Perilla frutescens*. Combined with drug disposition metrics, oral bioavailability (OB) and drug-likeness (DL) thresholds functioned as initial filters for identifying candidate bioactive substances. Subsequently, these active ingredients were analyzed using the PubChem platform (https://pubchem.ncbi.nlm.nih.gov/) followed by a normalization process to standardize the retrieved gene names.

Screening of PD-related gene targets and identification of shared genes between drug and disease

With "periodontitis" as the search term and the species limited to *Homo sapiens*, systematic searches were conducted through six disease target databases including GeneCards (https://www.genecards.org/), DisGeNET (https://www.disgenet.org/), OMIM (https://omim.org/), TTD (http://db.idrblab.org/ttd/), DrugBank (https://go.drugbank.com/), PharmGKB (https://www.pharmgkb.org/) to comprehensively collect gene targets associated with the pathogenesis and progression of PD. The retrieved target entries were compiled and organized. The redundant information was eliminated through duplicate removal. A total of 3,420 PD-related gene targets were finally obtained, which covered all types of currently known gene information closely associated with the pathological processes of PD. Meanwhile, 476 potential targets corresponding to the 44 active ingredients in BHD were systematically organized. By using VENNY online Venn diagram analysis platform (https://bioinfogp.cnb.csic.es/tools/venny/), intersection analysis was performed on the PD-related targets and the potential targets of the active ingredients in BHD. The shared gene set of the two was systematically extracted as the core potential action targets for investigating the intervention of BHD in the pathological process of PD. Through rigorous matching verification and data integration, 51 common potential regulatory targets were finally identified from the intersection analysis, laying a data foundation for further functional network analysis. For those 51 common targets, further topological analysis of the protein-protein interaction (PPI) network was conducted *via* the CytoNCA and MCODE plug-ins of Cytoscape software (https://cytoscape.org/) according to the characteristics of network topological parameters. This study set the node screening criterion as "the degree of connectivity must be more than three times higher than the median degree of connectivity of network nodes" to screen out the core targets that occupied hub positions and had important regulatory functions in the network. Through network analysis and computational verification, a total of 10 core targets including TP53, AKT1, IL-6, VEGF-A, TNF, EGFR, CASP3, JUN, MMP9, PTGS2 were finally screened out for subsequent functional enrichment analysis and molecular docking verification.

Protein-protein interaction (PPI) network and "herb-component-target" regulatory network

The obtained overlapping targets were submitted to the STRING platform (https://string-db.org/), adopting the "*Homo sapiens*" organism setting and a confidence score cutoff of 0.7 for PPI network construction, which was graphically represented *via* Cytoscape software. Network topology analysis was conducted, adopting plugins of CytoNCA (https://apps.cytoscape.org/apps/cytonca) and

MCODE (https://apps.cytoscape.org/apps/mcode). The key nodes with significantly higher connectivity than the median value of the network (e.g., more than 3 times) were selected as core targets. Meanwhile, based on the active ingredients and corresponding targets of the compound, a multi-dimensional regulatory network of "herb-chemical component-target of action" was constructed using Cytoscape to systematically display the potential pharmacological mechanisms and multi-component synergistic action patterns of BHD in treating PD.

Implementation of analyses

The overlapping targets of BHD and PD were first entered online into the KOBAS website (http://kobas.cbi.pku.edu.cn/). The gene list was submitted for analysis. "KEGG Pathway Enrichment" was selected in the "Annotation" section, while "Single List Enrichment Analysis" was chosen in "Select Analysis Type" and the species was selected in "Select Species". In "Input Gene/Protein List," the converted ENTREZ_GENE_ID list was pasted or uploaded. The core targets screened previously were analyzed.

Docking verification process for core active ingredients and key targets

In the docking verification phase, the 3D structure files of the effective compounds of this formula and the core targets were first retrieved from the PubChem and Protein Data Bank databases (https://www.rcsb.org/), respectively, to lay the structural foundation for the subsequent docking experiments. For the obtained protein receptor structures, PyMOL 3.8.5 software (https://pymol.org/) was used for preprocessing operations, including that water molecules that might interfere with the docking results in the protein receptor were accurately removed using the software functions, and small-molecule ligands bound to the protein were also deleted to ensure that the protein active pocket was exposed and to enhance the precision of the virtual screening process. After the structural preprocessing was completed, Discovery Studio Visualizer 3.5 (https://discover.3ds.com/discovery-studio-visualizer) was used to conduct docking experiments. According to the industry-standard criteria [9], in docking studies, if the binding energy of the obtained complex conformation was below -5 kcal/mol, it was regarded that the ligand had a strong binding affinity with the receptor protein and could form a relatively stable molecular complex. PyMOL software was adopted again to draw the binding mode diagrams of the receptor-ligand complexes with better binding effects, and the key information such as the binding sites and modes of action of the two was clearly presented in a visual manner.

Results

Active ingredients of BHD and acquisition of related targets

49 active ingredients were initially obtained. After removal of duplicate ingredients, 44 active ingredients were finally determined (Table 1). Potential targets of the screened active ingredients were predicted. After summarizing all prediction results and removing redundancies, 476 potential targets for the compound were identified.

PD-associated targets and overlapping targets between drug and disease

After conducting a standardized retrieval process in 6 preset disease target databases and performing duplicate gene elimination and data purification on the retrieval results, a total of 3,420 PD-related disease targets were screened out, which covered all types of currently known gene information associated with the pathological process of PD. Meanwhile, systematic sorting and standardized arrangements were carried out for the 476 potential action targets corresponding to the active components of BHD. After conducting an intersection analysis of these targets with the identified 3,420 PD-related targets, a significant overlap of targets between the two was found. Subsequently, the screened PD target genes and

Table 1. Active ingredients of the five components. The data were retrieved from the TCMSP database, verified for standardization, and summarized.

Mol ID	Molecule name	OB (%)	DL
MOL001755	24-Ethylcholest-4-en-3-one	36.08	0.76
MOL002670	Cavidine	35.64	0.81
MOL002714	baicalein	33.52	0.21
MOL002776	Baicalin	40.12	0.75
MOL005030	gondoic acid	30.70	0.20
MOL000519	coniferin	31.11	0.32
MOL006936	10,13-eicosadienoic	39.99	0.20
MOL006937	12,13-epoxy-9-hydroxynonadeca-7,10-dienoic acid	42.15	0.24
MOL006957	(3S,6S)-3-(benzyl)-6-(4-hydroxybenzyl) piperazine-2,5-quinone	46.89	0.27
MOL003578	Cycloartenol	38.69	0.78
MOL006967	beta-D-Ribofuranoside, xanthine-9	44.72	0.21
MOL000273	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-6-methylhept-5-enoic acid	30.93	0.81
MOL000275	trametenolic acid	38.71	0.80
MOL000276	7,9(11)-dehydrodacrymycic acid	35.11	0.81
MOL000279	Cerevisterol	37.96	0.77
MOL000280	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid	31.07	0.82
MOL000282	ergosta-7,22E-dien-3beta-ol	43.51	0.72
MOL000283	Ergosterol peroxide	40.36	0.81
MOL000285	(2R)-2-[(5R,10S,13R,14R,16R,17R)-16-hydroxy-3-keto-4,4,10,13,14-pentamethyl-1,2,5,6,12,15,16,17-octahydrocyclopenta[a]phenanthren-17-yl]-5-isopropyl-hex-5-enoic acid	38.26	0.82
MOL000287	3beta-Hydroxy-24-methylene-8-lanostene-21-oic acid	38.70	0.81
MOL000289	padymic acid	33.63	0.81
MOL000290	Poricoic acid A	30.61	0.76
MOL000291	Poricoic acid B	30.52	0.75
MOL000292	poricoic acid C	38.15	0.75
MOL000296	hederagenin	36.91	0.75
MOL000300	dehydroeburicoic acid	44.17	0.83
MOL005970	Eucalyptol	60.62	0.32
MOL005980	Neohesperidin	57.44	0.27
MOL000358	beta-sitosterol	36.91	0.75
MOL006129	6-methylgingediacetate2	48.73	0.32
MOL000449	Stigmasterol	43.83	0.76
MOL001771	porifrast-5-en-3beta-ol	36.91	0.75
MOL008698	Dihydrocapsaicin	47.07	0.19
MOL000006	luteolin	36.16	0.25
MOL006202	LAX	44.11	0.20
MOL002773	beta-carotene	37.18	0.58
MOL006209	cyanin	47.42	0.76
MOL006210	eugenyl-β-D-glucopyranoside(citrusiinc)	40.52	0.23
MOL000492	(+)-catechin	54.83	0.24
MOL000953	CLR	37.87	0.68
MOL001506	Supraene	33.55	0.42
MOL001749	ZINC03860434	43.59	0.35
MOL001779	Linolenic acid ethyl ester	46.10	0.20
MOL007514	methyl icosaa-11,14-dienoate	39.67	0.23

the target genes corresponding to the active components of BHD were input into the VENNY 2.1.0 database simultaneously. The intersection was obtained, and a Venn diagram was constructed. After precise matching and statistical analysis, 51 overlapping targets were finally obtained, which suggested that these targets might be the potential key action sites of BHD in the treatment of PD.

"TCM-active ingredients-potential target" network

10 core drug components were selected including Eucalyptol, Neohesperidin, (+)-catechin, Dihydrocapsaicin, cyanin, 6-methylgingediacetate2, ZINC03860434, Linolenic

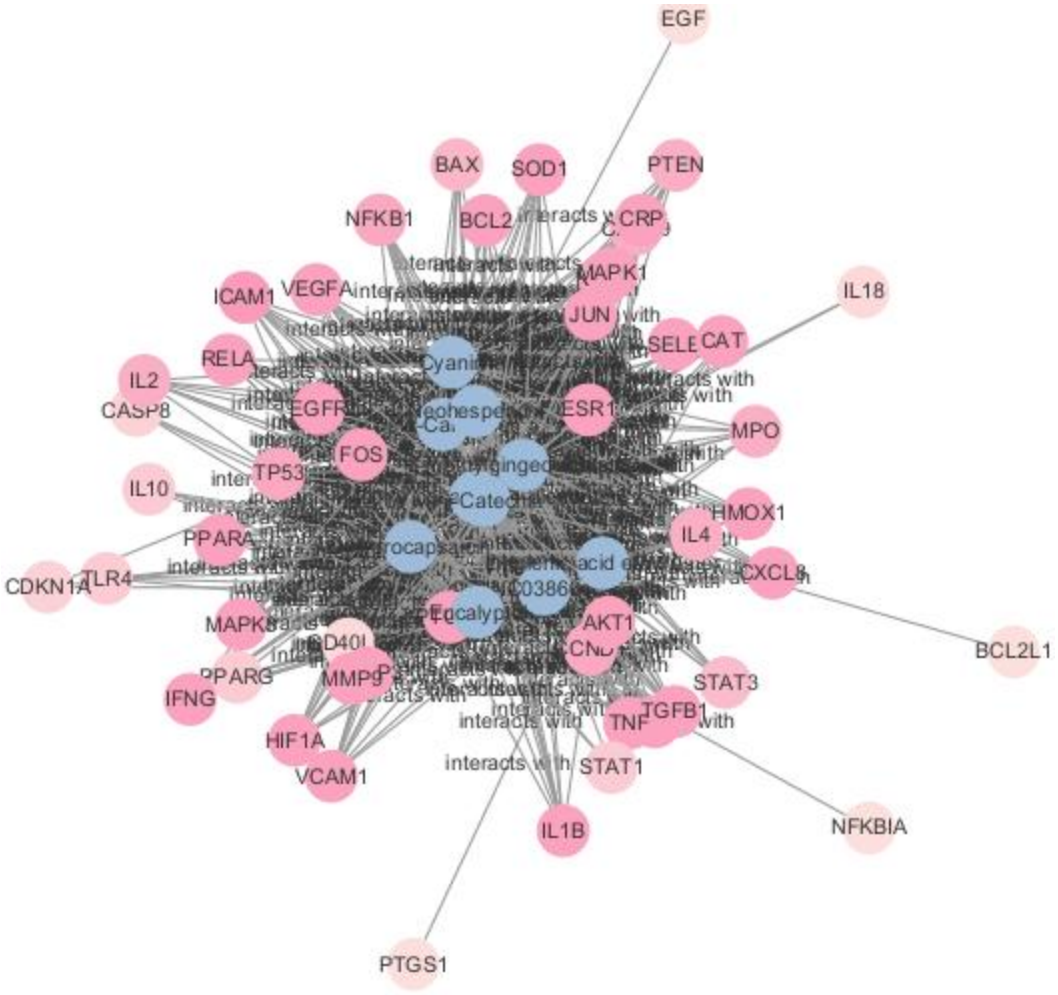

Figure 1. TCM-active ingredients-potential target network.

acid ethyl ester, methyl icosa-11,14-dienoate, and beta-carotene (Figure 1). These components were connected to multiple potential targets in the network and were the important material basis for the action of this formula.

PPI network and evaluation of core targets

The results showed that the constructed network contained a total of 286 edges with relatively close connections between nodes, suggesting that these targets might participate in related physiological and pathological processes through synergistic actions (Figure 2). By using plugins of CytoNCA and MCODE to score and analyze the network nodes, 10 core nodes with higher scores were selected including TP53, AKT1, IL-6, VEGF-A, TNF, EGFR, CASP3, JUN, MMP9, and PTGS2. These core nodes were in key positions in the network and might be the important targets for BHD to regulate PD.

GO and KEGG enrichment analysis

The result mainly covered three major aspects, which included biological processes representing coordinated cellular activities, molecular functions describing molecular-level tasks, and cellular components indicating specialized and distinct subunits. In the BP aspect, the core targets were mainly enriched in processes including angiogenesis, autophagy, cell adhesion, chemokine production, cytokine-mediated pathways, endoplasmic reticulum stress response, epithelial-mesenchymal transition, extracellular matrix organization, inflammatory

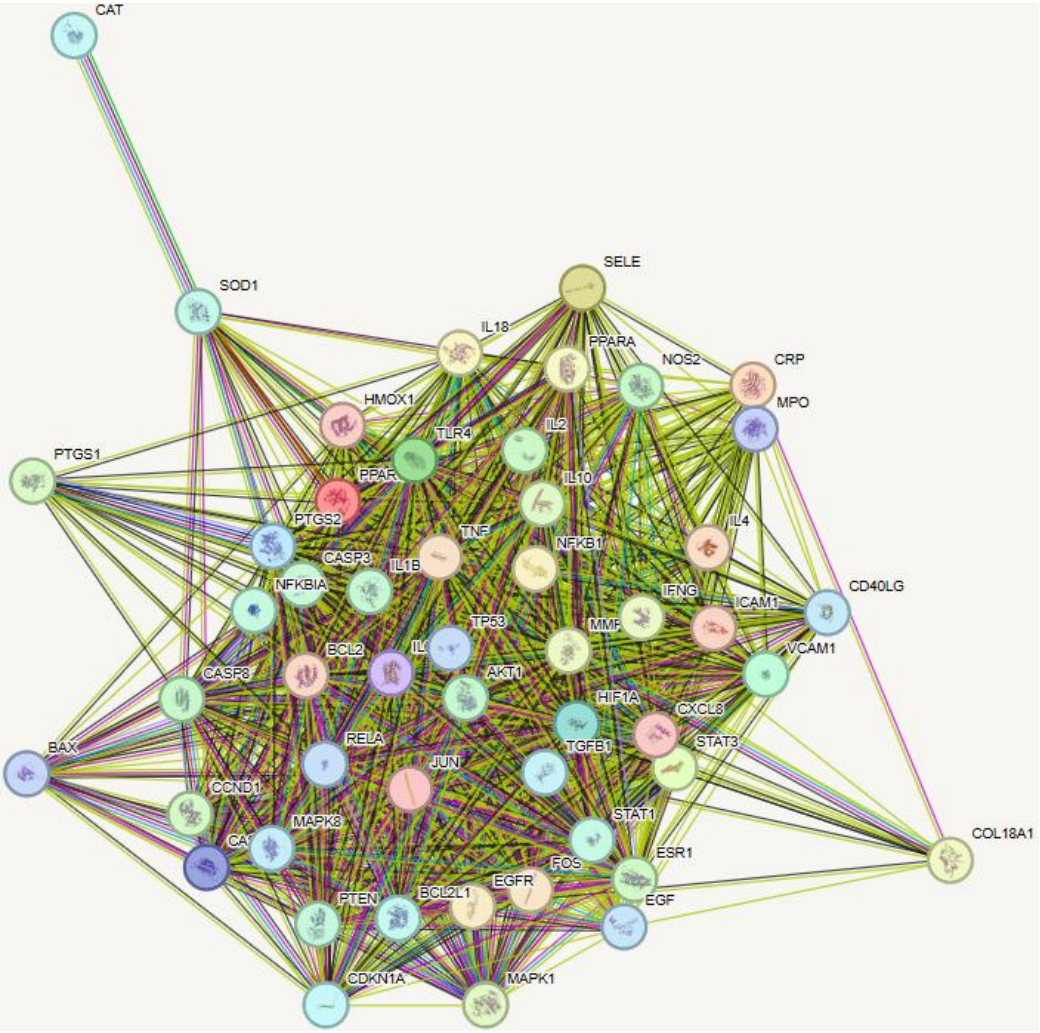

Figure 2. PPI network.

response, and leukocyte migration, suggesting that these targets might exert their effects by participating in the above physiological and pathological processes. In the cellular components' aspect, the more significantly enriched functions included aspartic-type endopeptidase activity, catalytic activity, *etc*., indicating that the core targets might participate in related metabolism or signal transduction by having these molecular functions. In the molecular function aspect, it mainly involved cellular components, cilia, endoplasmic reticulum, lamellipodium, mitochondrial ATP synthase complex, mitochondrial carrier, mitochondrial DNA, mitochondrial matrix, mitochondrial outer membrane, and mitochondrial porin, showing that these targets were mostly located in the above cellular structures and might perform their biological functions in the corresponding locations (Figure 3). TNF, PI3K-Akt, and NF-κB pathways participated in the inflammatory regulation and immune response of PD. MAPK and JAK-STAT pathways were associated with inflammatory signal transduction and cytokine action. The Toll-like receptor pathway could recognize periodontal pathogens and initiate inflammatory responses. The IL-17 pathway was correlated with the persistent development of chronic periodontal inflammation. The Arachidonic acid metabolism pathway was involved in the synthesis of inflammatory mediators and

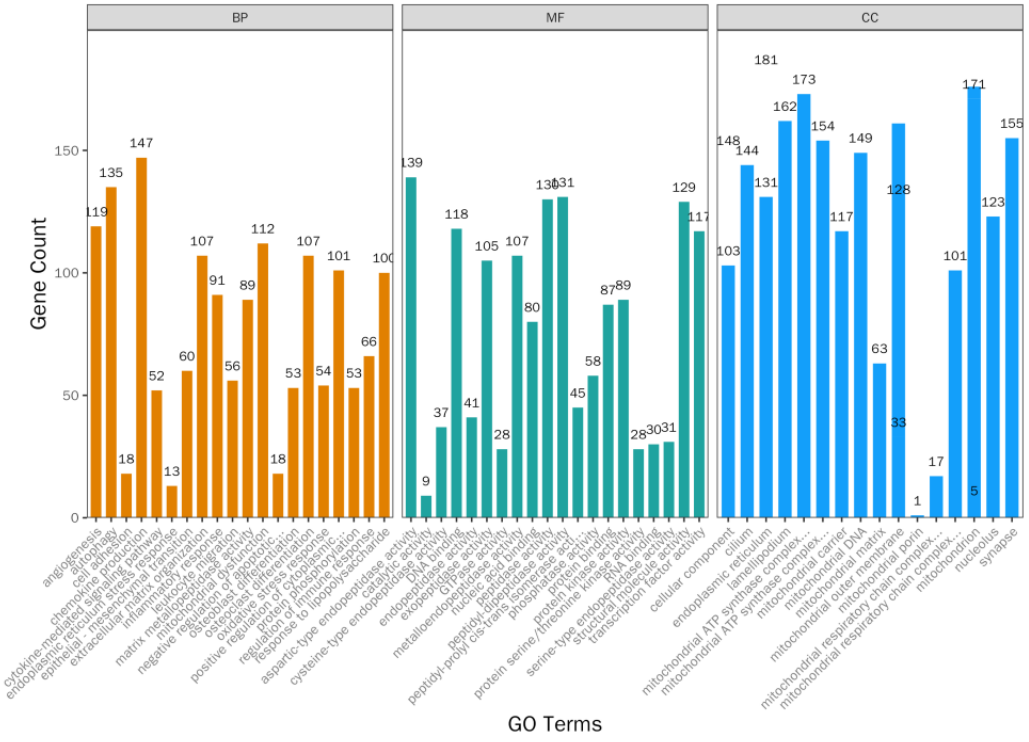

Figure 3. GO enrichment analysis.

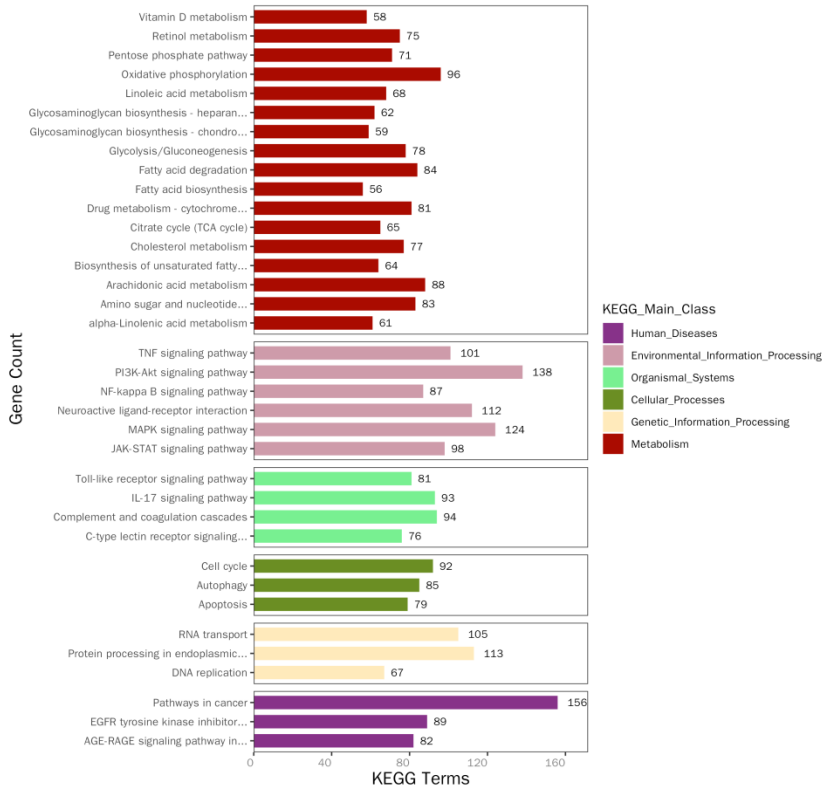

Figure 4. KEGG enrichment analysis.

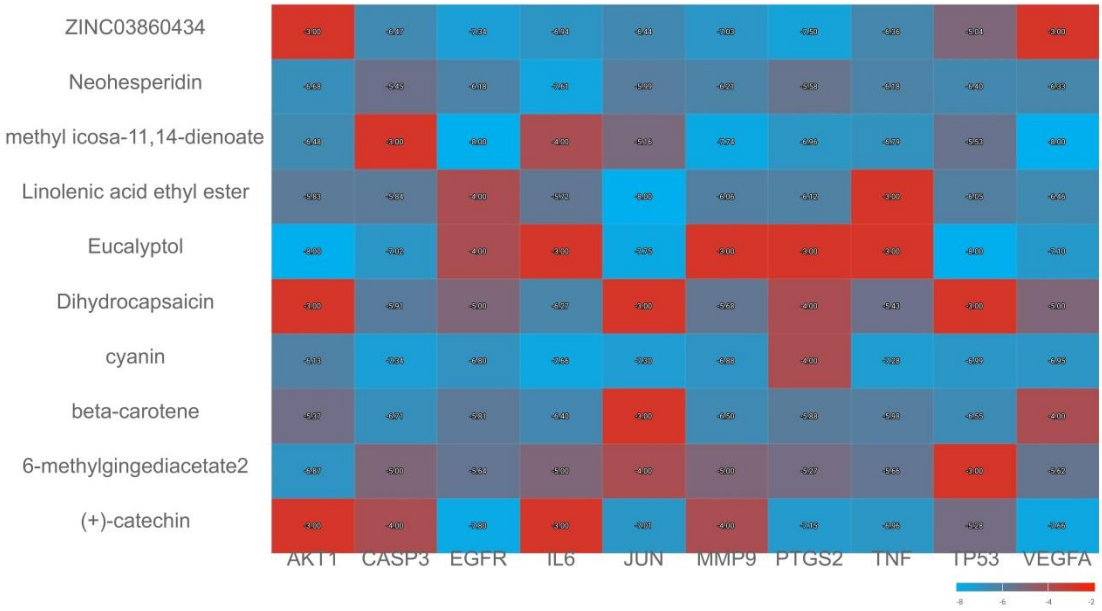

Figure 5. Docking heatmap.

affected local inflammation. The Complement and coagulation cascades pathway contributed to the modulation of periodontal immune defense. The Autophagy pathway affected the response of periodontal cells to damage through cellular autophagy. These pathways were all correlated with the inflammatory progression and tissue damage of PD and might be the key pathways for BHD in intervening PD (Figure 4).

Docking validation of key active ingredients and core targets of BHD

Docking validation was conducted using the identified 10 key active ingredients and the 10 selected core targets. The results showed that the binding energies between most active ingredients and core target proteins were below -5 kcal/mol, suggesting strong binding capabilities between these components and targets and the potential formation of stable complex structures (Figure 5). The binding energies of Eucalyptol with TP53, Eucalyptol with AKT1, and Linolenic acid ethyl ester with JUN were even lower, suggesting stronger interactions between these ingredients and targets. The docking conformation diagrams of some compounds and targets further demonstrated that active ingredients formed specific interactions with the essential amino acid residues of target proteins, forming stable complex structures (Figure 6). For example, in the docking conformation of cyanin and TNF, the compound molecule could fit into the active pocket of the target and form multiple hydrogen bonds with surrounding amino acids, providing a structural basis for their specific binding.

Discussion

The results of this research explored the material bases and potential therapeutic targets of the BHD and provided clues for the biological processes of the PD treatment. 44 active ingredients were finally obtained with the oral bioavailability of *Eucalyptol*, *Neohesperidin*, and (+)-catechin as 60.62%, 57.44%, and 54.83%, respectively, which might indicate the high absorbability of the body. As core components, their advantages were passing pharmacokinetic screening and possessing potential anti-inflammatory and/or immunomodulatory effects. Eucalyptol, as a common volatile oil component, can control inflammatory factors by

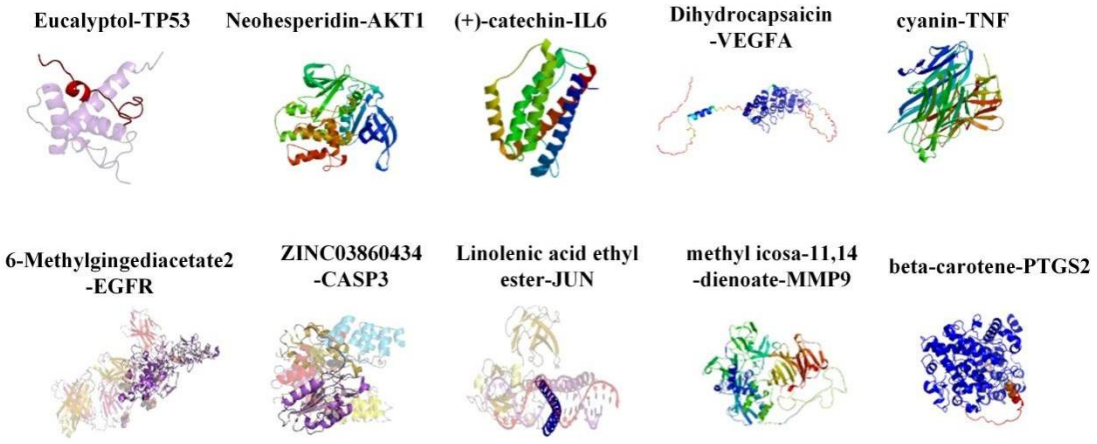

Figure 6. Docking ribbon diagram.

binding with PD-related elements [10]. The efficacy of TCM prescriptions is determined by their components, which is a characteristic of the multi-component effects of TCM prescriptions. All those components interact with each other by working on different physiological areas [11]. A total of 3,420 targets related to PD were screened out in this study. After intersecting with the 476 PD-targeted TCM active ingredients, a total of 51 common targets were screened out, which covered inflammation reduction, tissue damage repair, disturbance of the immune system and suggested that the active ingredients of BHD might affect the disease process of PD. 10 core drug ingredients were identified through this study, while 286 closely related nodes with edges demonstrated synergistic actions [12]. The 10 core nodes of the molecules included TP53, AKT1, IL6, and TNF, which were involved in both physiological and pathologic processes [13]. IL6 and TNF are traditional inflammatory factors that play a role in the initiation of inflammation in PD. The results suggested that BHD might control the amount and level of the inflammatory to prevent the damage to the periodontal tissues caused by inflammation. In PD, the apoptosis process is disrupted, which can lead to further tissue damage. BHD might maintain cell survival through TP53 to maintain normal apoptosis. AKT1 was identified as the main target, which indicated that BHD might affect the life of cells during the repairing of periodontal tissue. These core targets together constituted the important nodes at which the BHD exerted its effects. They worked synergistically to ultimately influence the disease progression of PD [14]. There is constant damage caused by inflammatory response in PD, and abnormal angiogenesis may also have an impact on the nutrition supply and repair. Core targets identified in this research indicated that BHD might slow down the PD process by regulating both physiological and pathological processes. Normal enzyme activity is directly related to metabolism and signaling. The BHD might regulate the metabolic steadiness by controlling the enzymes. The TNF and PI3K-Akt pathways are associated with PD. Once TNF pathway is activated, the inflammatory factors are synthesized and secreted, which in turn exacerbates the inflammatory response. BHD might reduce the inflammation by halting this path. The PI3K-Akt pathway regulates important cell activities for cell survival and growth, which can promote the survival of healthy periodontal cells and tissue repairing. NF-kB pathway is the main pathway of inflammation and immunity [15]. BHD might have some influences on the NF-kB pathway for anti-inflammatory and immunoregulation effects. The results suggested that BHD probably interfered with the pathological process of PD by adjusting multi-pathways cooperatively rather than a single pathway. The results of this study showed that most active ingredients of BHD with the core

targets had binding energies less than -5 kcal/mol. Eucalyptol's binding energy with TP53 and AKT1 was less than that of others, indicating a good binding with TP53 and AKT1 and strong structural biological evidence for the 1st target predictions. Cyanin formed stable complex with TNF through H-bonding. Structurally, cyanin demonstrated an anti-inflammatory effect by binding on TNF target [12]. The results confirmed the dependability of the main active ingredients and targets binding and further confirmed the effect of BHD on PD treatment [16]. The results of network analysis showed that BHD could manage PD through multiple targets and pathways, mainly controlling the inflammatory response and activating immune cells, which was confirmed by the results that certain targets had good binding capacities from core active ingredients. BHD exhibited a synergistic effect through networks, which formed the basis for its application in the treatment of PD and served as a complement to treatment.

This research identified several active ingredients of BHD, which affected the molecular targets related to PD. The key active ingredients of BHD participated in some important physiological and pathological processes of PD, including inflammatory response, cell death, and tissue repair by regulating several inflammation and immunity pathways. Most of the major active ingredients in the BHD could be well bound by the main target proteins with good intermolecular interactions. However, this study had some limitations. Bias and unmeasured confounders should be considered in future studies. Screening for active ingredients based solely on a single database and established pharmacokinetic data might overlook some potentially effective ingredients. Docking was only an external docking and had not been verified through any actual experiments. Future research should incorporate multiple databases and optimize screening criteria to better predict the components and targets of BHD intervention in PD patients. Meanwhile, cell and animal experiments are needed to prove the true efficacy and mechanism of action of these compounds.

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