Exploring the mechanism of action of Perilla seeds in the treatment of hypertension based on network pharmacology

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ABSTRACT

Objective: The potential targets and mechanism of action of Perilla seeds in the treatment of hypertension was explored by using network pharmacology. **Methods:** The seed components and related indicators of Perilla frutescens were screened through TCMSP database with OB value ≥ 30% and DL value ≥ 0.18, and the names of target proteins were standardized with the help of the UniProt database. Targets related to hypertension were screened out by GeneCards and OMIM disease databases, and were de-duplicated and sorted out, and then the common targets of drugs and diseases were extracted with the help of Venn diagrams. Imported the relevant files in Cytoscape 3.9.0 software and generated a component-target-disease network diagram about Perilla seeds for the treatment of hypertension. Generated a PPI network diagram using the String database and Cytoscape 3.9.0 software to identify the core targets of Perilla seeds for the treatment of hypertension. Applied the DAVID database for the GO function and KEGG pathway enrichment analysis, and speculated the main signaling pathways interfering with hypertension. AutodockTool 4 software was used to molecularly dock the core targets and components screened. **Conclusion:** Perilla seeds may be used to treat hypertensive disorders through components such as lignans and β-sitosterol, which act on target genes such as AKT1, TNF and IL6, and regulate the PI3K/Akt pathway and AGE-RAGE pathway. The results showed that Perilla seeds can be used to treat hypertension in a variety of ways, such as regulating the PI3K/Akt pathway and the AGE-RAGE pathway.

Keywords: Hypertension, Perilla seeds, mechanism of action, network pharmacolog

1. INTRODUCTION

Hypertension is one of the most common chronic diseases, and the presence of hypertension significantly increases a patient's risk of cardiovascular events. Typical symptoms of hypertension include headache, fatigue or restlessness, and cardiac arrhythmia, but many hypertensive patients may have developed other complications, such as stroke, myocardial infarction, heart failure, chronic kidney disease, blurred vision, loss of consciousness, and amnesia, without any symptoms, which is why hypertension is also known as the “silent killer” [1].

In recent years, the prevalence of hypertension has been steadily increasing worldwide. According to the latest survey, the prevalence of adult hypertension in China is 27.9%, about one out of every two adults is hypertensive, and the prevalence of hypertension in rural areas has exceeded that in urban areas [2]. The age distribution of hypertensive patients is wide, but middle-aged and old-aged are predominant. In recent years, with the aging of the population, the proportion of hypertensive elderly has gradually increased, and the prevalence of hypertension in those aged ≥80 years is about 90% [3]. And the prevalence of hypertension in adults in China is high, the rate of blood pressure measurement is low, and patients' awareness, treatment, and control of hypertension are not satisfactory enough, and the prevention and control efforts should be increased. Clinically, western drugs are usually used to control blood pressure, but western drug therapy has certain limitations and adverse reactions. The results of modern pharmacological research show that traditional Chinese medicine has many functions such as lowering blood pressure, improving endothelial cells, protecting target organs, etc., and it has certain superiority in terms of systematicity, diversity, and safety [4].

Perilla seed oil is a component of perilla seed, perilla seed oil is also a high-quality source of α-linolenic acid, the content of which is 57% ~ 62% or so, is an omega-3 polyunsaturated fatty acid vegetable oil, which enjoys the reputation of

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"deep-sea fish oil on land" [5]. Perilla oil in the maintenance of cardiovascular health, the treatment of hypertension and other aspects of the positive effect has shown a variety of aspects [6]. Lignans, β-sitosterol, arachidonic acid and other components in perilla seeds have also been reported to intervene in hypertension [7-9].

Network pharmacology is a discipline that utilizes modern scientific methods and techniques to study the interactions between drugs and complex networks in living organisms. The use of network pharmacology to study traditional Chinese medicine provides important scientific and technological support for the modernization and internationalization of traditional Chinese medicine and helps to develop a completely new mode of research and development of traditional Chinese medicine, which has significant advantages and characteristics compared with traditional research methods. This research model covering multiple drugs, multiple targets, and multiple diseases is able to work with multiple drug components acting on one or more disease targets to achieve the accuracy and effectiveness of the holistic concept and dialectical approach of TCM [10].

Therefore, this study summarizes the active ingredients and targets of Perilla frutescens in the treatment of hypertension through the analysis of network pharmacology and systems biology, in-depth to the synergistic effect between "drug-component-target-disease" of Perilla frutescens, and obtains a reliable basis for the treatment of hypertension with Perilla frutescens in terms of genes, molecules, proteins, etc. Its mechanism of action is explored, and the results are expected to be useful for the treatment of hypertension with Perilla frutescens. The mechanism of action will be explored to provide scientific support and theoretical basis for clinical application, provide new ideas for follow-up research, and promote the further development of Chinese medicine research and treatment of hypertension.

2. INFORMATION AND METHODS

2.1 Screening of active ingredients and prediction of action targets of Perilla frutescens seeds

The TCMSP database was used to search for the chemical constituents contained in Perilla frutescens, and specific parameters were set to optimize the results. Oral bioavailability (OB) $\geq$ 30% and drug-likeness (DL) $\geq$ 0.18 were screened to pinpoint the relevant chemical constituents. Subsequently, the SMILES codes in the PubChem database were utilized for input into the Swiss Target Prediction platform, and "Homo sapiens" was selected for human target prediction to reveal the active ingredients and their corresponding potential targets in Perilla frutescens. After deleting the mismatched and duplicated targets, the data were organized and saved in an Excel table. Finally, the screened protein targets were standardized and annotated with the help of UniProt database.

2.2 Target screening for hypertensive diseases

GeneCards and OMIM databases were used to search for the keyword "hypertension". All targets related to hypertension were retrieved from these databases, intersected, de-emphasized and summarized.

2.3 Construction of "drug-component-target-disease" interaction network diagrams

Venn diagrams were prepared by using the Venny 2.1 online tool to identify common target gene intersections between drug active components and hypertensive disease-related target genes. Subsequently, the built-in NetworkAnalyzer module of Cytoscape software was utilized to deeply dissect the structural features of the network. By adjusting the parameters, a network map was constructed to visualize the drug-component-target-disease interactions.

2.4 Construction of PPI network diagram of Perilla frutescens and hypertension

In order to construct a protein interaction network (PPI) with Perilla frutescens for hypertension, Firstly, we imported the target genes into the String database and customized the conditions of the analysis: specify the species Homo sapiens (human), set the minimum threshold of 0.7 or above, and exclude all the protein nodes that do not have any interactions. Thus, a more precise protein interaction network was refined. Then the data were exported in TSV format and imported into Cytoscape 3.9.1 software, and the NetworkAnalyzer tool in Cytoscape 3.9.1 was utilized to compute the topological properties of the network, followed by the application of the cytoNCA plug-in to analyze and compute the six key topological property metrics for each node in the network: betweenness centrality (Betweenness Centrality (BC), Closeness Centrality (CC), Degree Centrality (DC), Eigenvector Centrality (EC), Network Centrality, NC) and Local Average Connectivity (LAC), where increasing values of these parameters represent the importance of nodes in the network. It is necessary to ensure that the value of each parameter is higher than the median value of the corresponding parameter in the PPI network in order to construct a new PPI network. The String database assigns a value based on the strength of the interactions among the input target genes, which is referred to as the degree value. The magnitude of the

degree value directly reflects the intensity of the interactions among the target genes, i.e., the larger the degree value, the stronger the interactions among the genes, implying that these genes may play a more critical role in the biological process. Therefore, the greater the likelihood that will be able to treat hypertension through these targets, and vice versa. Therefore, there is greater likelihood of treating hypertension through these targets, and vice versa with perilla seed.

2.5 Enrichment analysis of functions and pathways of perilla-hypertension targets

GO enrichment analysis is the comprehensive characterization of the function of genes and their products in an organism. It is an important means of studying the relationship between gene expression profiles and function, and helps to identify genes that play key roles in specific biological processes, leading to an in-depth understanding of gene regulatory networks. The GO system establishes three separated but complementary ontological domains: biological process (BP), cellular component (CC), and pathway (P). Component (CC) and Molecular Function (MF), which are common properties of all genes and gene products [11]. The Kanehisa Laboratory at Kyoto University, Japan, created the KEGG database in 1995 as an important comprehensive database in the field of bioinformatics. The database contains several sub-databases covering a wide range of fields such as genomics, biochemical reactions, biochemical substances, diseases and drugs, etc. In particular, the pathway information is most commonly used, which provides a rich bioinformatics resource for researchers. One of the key strengths of the KEGG enrichment analysis which helps us to gain a deeper understanding of the functions and interactions of genes in specific biological processes. This analysis can reveal the close connection among genes and thus the specific roles they play in biological processes [12].

The key targets of Perilla frutescens obtained for the treatment of hypertension were copied into an Excel sheet and uploaded into the DAVID database. In the screening conditions, we specifically selected “Homo sapiens” and “official gene symbol”.

2.6 Molecular docking

The mol2 files of the key active ingredients were downloaded from the TCMSP database, and the 3D structural patterns of the core target proteins were downloaded from the Protein Structure Database (RCSB-PDB, https://www.rcsb.org/), saved as “PDB” files, and imported into the PyMOL2.5.2 software for dehydration and ligand separation. Two softwares for dehydration and ligand separation. The core compounds obtained were docked with the target proteins by using AutoDockVina software, and finally the conformations with the highest binding energies in the docking results were selected.

3. RESULTS

3.1 Effective components and predicted targets of perilla seed

According to the final database collation, 14 active ingredients of Perilla frutescens were finally obtained (Table 1). 180 targets of action related to Perilla frutescens ingredients were obtained. Using Excel to merge and reorganize the relevant targets of action of all drugs, deleting non-human sources, unproven, and duplicate items, a total of 109 targets of action related to perilla seeds were finally identified after screening and validation, and these targets provided the basis for subsequent studies.

3.2 Acquisition of disease targets and collection of intersecting targets

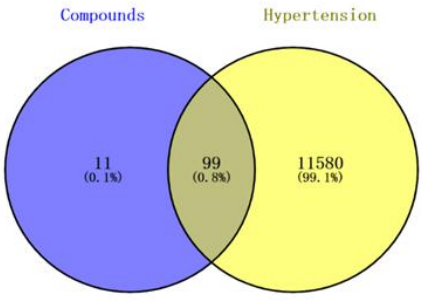

Figure 1. Active ingredient target - Hypertension target Venn diagram

Using “hypertension” as the search term, we searched the Gene Cards and OMIM databases to find the genes closely related to hypertension. Afterwards, all of the retrieved gene targets were systematically combined and organized by using Excel software. After screening and comparison, a total of 11637 targets related to hypertension were finally identified, which provided the data basis for the subsequent study.

Firstly, the potential action targets of Perilla frutescens previously screened were intersected with the gene targets related to hypertension disease to find out the common targets between them. Subsequently, a Wayne diagram (Figure 1) was drawn using the Venny 2.1 tool to visualize the distribution of these common targets. After analysis, a total of 99 common targets among the active ingredients of Perilla frutescens and hypertension diseases were obtained. These common targets provide important clues for further investigating the potential mechanism of action of Perilla frutescens in the treatment of hypertension.

Table 1. The active ingredient of perilla seeds

MolId	Compound Name	DL	OB（%）
MOL012888	citrostadienol	0.78	43.28
MOL012893	E-4-methylbenzylidene (4-phenyltriazol-1-yl) amine	0.18	57.87
MOL000449	Stigmasterol	0.75	43.82
MOL001439	arachidonic acid	0.20	45.57
MOL002773	beta-carotene	0.58	37.18
MOL000358	beta-sitosterol	0.75	36.91
MOL004355	Spinasterol	0.76	42.98
MOL000006	luteolin	0.24	36.16
MOL000953	CLR	0.68	37.87
MOL007449	24—methylidenelophenol	0.75	44.19
MOL005481	2,6,10,14,18-pentamethylicosa; 2,6,10,14,18-pentaene	0.24	33.4
MOL005043	campest-5-en-3beta-ol	0.71	37.58
MOL009681	Obtusifoliol	0.76	42.55
MOL005030	gondoic acid	0.20	30.70

3.3 Analysis of “drug-component-target-disease” interactions network map

In order to visualize the relationship between active ingredients and gene targets of Perilla frutescens, the information of these two components will be integrated and graphically presented with the help of Cytoscape 3.9.0 software. This graphical presentation will help to understand the potential mechanism of action of perilla seed in the treatment of hypertension better, as shown in Figure 2, where multiple components are present in perilla seed, and significant correlations exist between these components and multiple therapeutic targets for hypertensive disorders. The potential effects of perilla seed in the treatment of hypertension are revealed through the combined effects of multiple components on multiple biological targets.

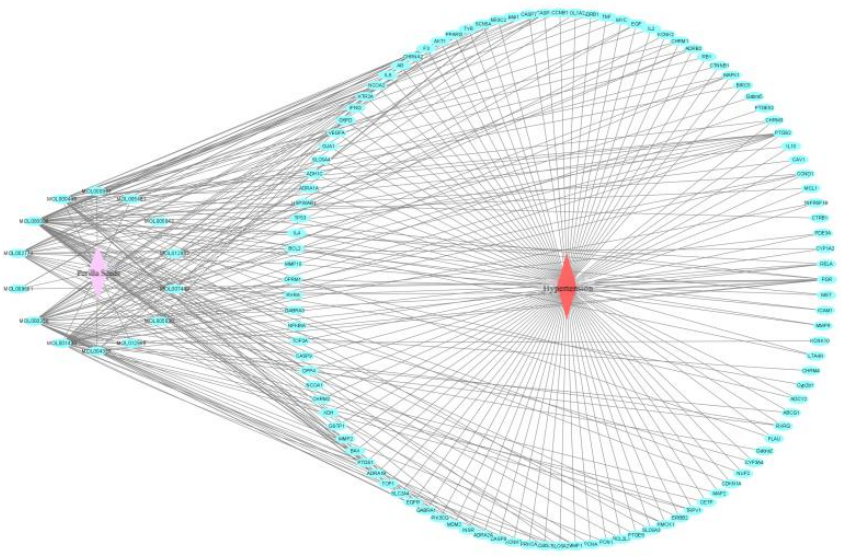

Figure 2. "Component-Target-Disease" Network Construction

3.4 PPI interaction network analysis and core target gene screening

In order to explore the molecular mechanism of the potential association between perilla seed and hypertension, protein interaction (PPI) network analysis was performed for 99 target proteins screened, and protein interaction network diagram was successfully constructed, and visualization diagram (shown in Figure 3) was compiled by using Cytoscape 3.9.0 software to obtain the most prominent target proteins, among which, Degree=68 for RAC-α serine/threonine protein kinase (AKT1), Degree=67 for tumor necrosis factor (TNF), Degree=66 for interleukin-6 (IL6), Degree=63 for cellular tumor antigen p53 (TP53), Degree=61 for prostaglandin G/H synthase 2 (PTGS2), and Degree=61 for epidermal growth factor receptor (EGFR), Degree=56 matrix metalloproteinase-9 (MMP9), Degree=55 cysteine asparaginase-3 (CASP3), Degree=54 Myc proto-oncogene protein (MYC), and Degree=54 peroxisome proliferator-activated receptor gamma (PPARG) have large node degree values in which they played a key role, these proteins are likely to be the core targets of peroxisomes in the treatment of hypertension, and the above results suggest that they may play an important regulatory role in the treatment of hypertension.

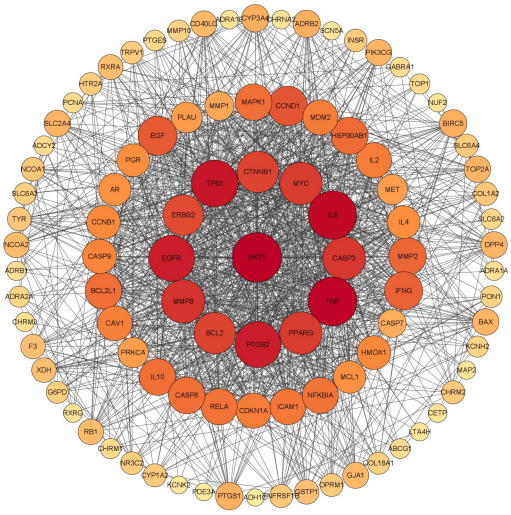

Figure 3. PPI protein interaction network

3.5 Perilla-hypertension GO enrichment analysis and KEGG pathway enrichment analysis

In order to deeply investigate the function and regulatory mechanism of the target genes of Perilla frutescens-hypertension intersection, these genes were submitted to the DAVID database and performed GO and KEGG enrichment analyses, with the significance threshold set at $P<0.05$. After the analysis, GO enrichment analyses successfully identified 516 bioprocesses (BPs) that were closely related to these genes, which mainly included positive regulation of MAPK cascade, positive regulation of apoptotic process, positive regulation of gene expression, positive regulation of cell proliferation, negative regulation of apoptotic process, response to xenobiotic stimulus, and other functions, as detailed in Figure 4A.

GO enrichment analysis yielded 64 cellular compositions (CCs), which contained nucleoplasm, presynaptic membrane, cell surface, plasma membrane, membrane raft, macromolecular complex with receptor, and other functions, as detailed in Figure 4B.

GO enrichment analysis yielded 96 molecular functions (MFs), mainly including enzyme binding, protein heterodimerization, ubiquitin protein ligase, protein homodimerization activity, identical protein binding, and protein binding, as detailed in Figure 4C.

After KEGG analysis, 159 signaling pathways were obtained, mainly including chemical carcinogenesis-receptor activation, Pi3K-Akt signaling pathway, bladder cancer, lipid and atherosclerosis, Lipid and atherosclerosis Prostate cancer Pathways in cancer, etc., suggesting that the treatment of hypertension by Perilla frutescens may work through multiple pathways and routes, as shown in Figure 4D.

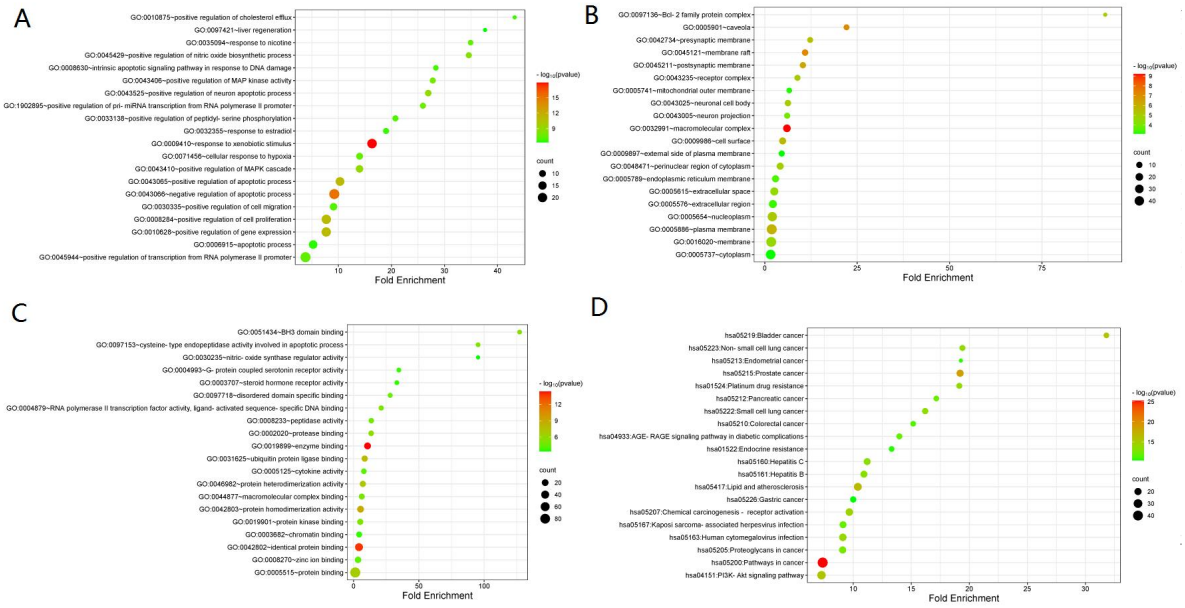

Figure 4. A. GO enrichment analysis of target genes of interest BP bubble map; B. GO enrichment analysis CC bubble plot of target genes of interest; C. MF bubble plot for GO enrichment analysis of target genes of interest; D. KEGG signaling pathway enrichment analysis bubble diagram of target genes.

3.6 Molecular docking results

According to the screening, we obtained the core target proteins AKT1, TNF, IL6, TP53, PTGS2, EGFR, and the core active ingredients lignans, β-sitosterol and arachidonic acid, the docking results showed that the degree of binding of AKT1 target proteins with each active ingredient was good. For details, the results were obtained form Figure 5 and table 2.

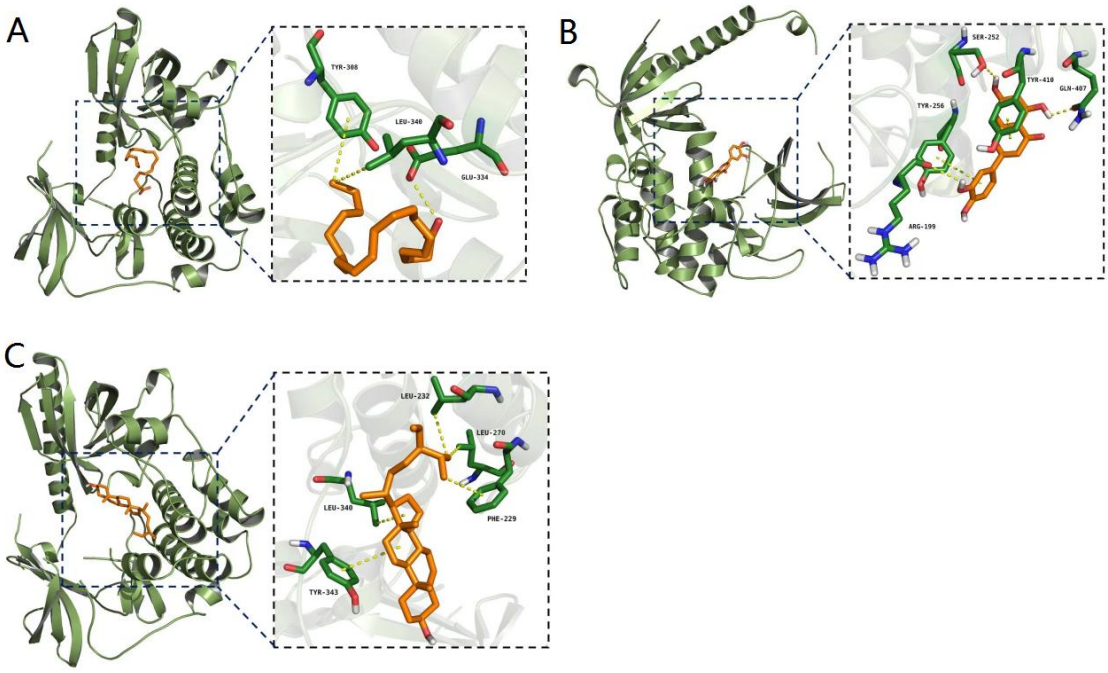

Figure 5. A. AKT1 and arachidonic acid; B. AKT1 and luteolin; C. AKT1 and beta-sitosterol.

Table 2. Molecular docking binding energy data

chemical compound	target point	Binding energy（Kcal/mol）
arachidonic acid	AKT1	-4.7
luteolin	AKT1	-7.0
beta-sitosterol	AKT1	-7.2

4. RESULTS

Hypertension is a common condition that can lead to the development of cardiovascular diseases such as stroke and heart disease. These diseases not only cause serious damage to the health of individuals, but also put a huge burden on the health and healthcare system of the whole society [13].

14 active components of Perilla frutescens were identified through network pharmacological research methods, of which 99 targets were related to Perilla frutescens for the treatment of hypertensive disorders, among which the important active components may be lignans, β-sitosterol, arachidonic acid, and so on. Among them, lignans have good effect on renal hypertension, it inhibits the contraction of renal arteries and dilates already contracted renal arteries by lowering the intracellular calcium ion concentration, reduces blood pressure and improves renal function, and is a potential drug used in the combined treatment of renal hypertension [14]. β-Sitosterol (BSS) induces cell cycle block, enhances apoptosis, and controls invasion and transformation, and helps in the maintenance of blood pressure stabilization, β-sitosterol (BSS) also has a modulatory effect on hypertension in rats, which is through the regulation of some important physiological processes, thus helping to maintain the stability of liver and kidney function in rats [8]. Arachidonic acid plays an important role in the regulation of smooth muscle function and proliferation, cell membrane fluidity, free radical generation, nitric oxide formation, inflammation and immune response, thus participating in the regulation of blood pressure pathogenesis [9].

In the PPI protein interaction network map, it was hypothesized that the treatment of hypertension by Perilla frutescens may act through target genes such as AKT1, TNF, IL6, TP53, PTGS2, EGFR, MMP9, etc. AKT1 is involved in the regulation of cellular proliferation and transformation, and plays an important role in cell signaling pathways, influencing the development of a variety of physiological and pathological processes in living organisms. For example,

the lack of AKT1 may cause systemic hypertension in mice [15]. TNF reverses changes in RAS components and slows down hypertension caused by angiotensin II [16].IL6 disrupts the regulation of Cyp2c produced by cyclooxygenase, which contributes to the modulation of hypertension after protection of the kidneys [17]. Meanwhile, TNF and IL-6 are inflammatory factors, of which TNF-α has a certain role in regulating immunity by intervening in the process of inflammatory response, and also constricting blood vessels through the secretion of endothelin-1 and thus contributes to hypertension [18]. miR-31a-5p inhibits apoptotic process of pulmonary artery smooth muscle cells by specifically targeting the TP53 gene, which is involved in the regulation of hypertension [19]. Epidermal growth factor (EGFR) plays a role in the regulation of pulmonary hypertension [20]. Increased extracellular superoxide and MMP9 attenuate the COMP stability of BMPR2 and may be involved in the development of pulmonary hypertension [21]. In summary, all of the above target genes can intervene in the treatment of hypertension.

After KEGG pathway enrichment analysis, we found that the potential therapeutic targets of Perilla frutescens for hypertension mainly focused on PI3K/Akt signaling pathway and AGE-RAGE pathway. Among them, activation of the PI3K/Akt signaling pathway can trigger the expression of downstream nitric oxide synthase (eNOS), which in turn promotes NO synthesis, which is essential for maintaining the stability of vascular endothelial function [22], and another key target, AKT-1, plays an important role in regulating apoptosis and proliferation, as well as preventing thickening of the inner wall of the pulmonary vasculature, which is mainly achieved by activating the PI3K /Akt signaling pathway [23]. In the AGE-RAGE pathway, the interaction between AGE and RAGE significantly affects the proliferative activity of vascular smooth muscle cells, the accumulation of extracellular matrix and inhibition of apoptosis thus leading to vascular hypertrophy to participate in the regulation of inflammation and cardiovascular disease development Activation of the AGE-RAGE signaling pathway triggers inflammation, endothelial dysfunction and oxidative stress, ultimately leading to vascular sclerosis, which in turn triggers elevated blood pressure [24,25].

In summary, perilla seeds exhibit potential therapeutic value in the treatment of hypertension, and the mechanism may involve anti-inflammatory, anti-oxidative stress and amelioration of vascular endothelial dysfunction effects. In the present study, with the help of a network pharmacology approach, the potential mechanism of action of Perilla frutescens in the treatment of hypertension was revealed in depth, further confirming the possibility that it exerts its therapeutic effects in the treatment of hypertension through multiple targets and multiple pathways. This finding provides a solid theoretical basis and technical support for the application of perilla seed in the clinical treatment of hypertension, and provides new ideas and directions for future related research. However, the expression levels of other related target proteins predicted in this study need to be further verified, which is important for the in-depth investigation of the pharmacological material basis and pharmacological effects of Perilla frutescens in the treatment of hypertension.

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