Research Paper

Application of Bioinformatics Technology to Analyse the Mechanism of Guizhi Fuling Capsule in Treating Chronic Pelvic Inflammation

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Zhou *et al.*: Role of Guizhi Fuling Capsule on Chronic Pelvic Inflammation

In this study, we explored the mechanism of Guizhi Fuling capsules for treating chronic pelvic inflammatory disease. The anti-inflammatory effect of Guizhi Fuling capsule is significant, and its active ingredients can also be used as materials, but its mechanism of action is still unclear. Drug components and chronic pelvic inflammatory disease targets of Guizhi Fuling capsules were obtained using traditional Chinese medicine systems pharmacology, PubChem, SwissTarget prediction and GeneCards databases. We obtained intersection targets through network construction using the Search Tool for the Retrieval of Interacting Genes database, and the key drug components and core targets were screened using Cytoscape software. The targets were subjected to gene ontology and Kyoto encyclopedia of genes and genomes enrichment analysis using the web-based gene set analysis. Molecular docking, conducted using AutoDock software identified 69 active ingredients in Cinnamon twig and Poria capsule and 2917 genes related to chronic pelvic inflammatory disease. We found 61 drug disease intersection targets, and 33 key targets based on maximal clique centrality score and degree screening parameters. The biological process enrichment analysis includes response to alkaloids, muscle cell proliferation, etc. where the main cellular components are dopaminergic synapse which includes dopamine binding 3',5' cyclic adenosine monophosphate and immunological synapse. The binding energies of catechin, paeoniflorin and mairin with tumor necrosis factor, interleukin-6 and peroxisome proliferator-activated receptor gamma were >-5 kcal/mol^{-1}. Guizhi Fuling capsule can be used to treat chronic pelvic inflammatory disease due to the multiple active ingredients and targets acting on multiple pathways.

Key words: Network pharmacology, molecular docking, Guizhi Fuling capsule, chronic pelvic inflammatory disease

Chronic pelvic inflammatory disease is a disease that occurs in the female uterus, fallopian tubes, ovaries, surrounding the connective tissues and pelvic peritoneum. It is mainly caused by the delay in treating acute pelvic inflammatory disease or incomplete treatment[1]. Its main clinical manifestations are lumbosacral and abdominal pain, pelvic effusion, adnexal mass and menstrual abnormalities. If the disease is prolonged and persistent, it is prone to complications such as dysmenorrhea and ectopic pregnancy. In severe cases, it will lead to infertility, seriously affecting the health of patients[2]. In clinics, Western medicine involves antibacterial and anti-inflammatory treatment for chronic pelvic inflammatory disease. However, the curative effect is not ideal because of the particularity of pelvic anatomical structure. Antibiotics are prone to drug resistance and long-term application reduces their efficacy, resulting in secondary infection, which is difficult to achieve optimal efficacies[3]. Traditional Chinese medicine is used widely in clinical disease treatment and its effect on chronic pelvic inflammatory disease treatment is significant[4]. The study found that traditional Chinese medicine enema combined with conventional Western medicine treatment for chronic pelvic inflammatory disease has a significant effect[5], which also suggests that the traditional Chinese medicine enema method can balance the patient's blood flow, reduce inflammation and oxidative stress response. The study also found the significance of the curative effect of umbilical moxibustion combined with traditional Chinese medicine enema in cold dampness stagnation-type

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chronic pelvic inflammatory disease treatment[6]. Another study pointed out that the use of traditional Chinese medicine preparations for chronic pelvic inflammatory disease treatment can significantly enhance the treatment efficiency[7], relieve the signs and symptoms of the patients, improve the quality of life, suggesting that anti-inflammatory mixture can be a correct choice for the treatment of pelvic inflammatory disease. Guizhi Fuling capsule contains *Cinnamomi ramulus*, *Poria cocos* (Schw.) Wolf, Cortex Moutan, Persicae Semen (the dried mature seed of *Prunus persica*), and Paeoniae Radix Alba (the dried root of *Paeonia lactiflora* Pall.), which has a good clinical effect in chronic pelvic inflammatory disease treatment[8] and it has also been explored in the preparation of materials. For example, cinnamon extract can be applied for the synthesis and characterization of nano-Copper Oxide (CuO) (applied to antibacterial) [9]. In addition, the solid particles formed in the process of water decoction of Paeoniae Radix Alba can promote the intestinal absorption of total glucosides of Paeoniae Radix Alba, thus enhancing the efficacy[10].

However, due to its complex prescription and unclear pharmacodynamic mechanism, its clinical promotion is seriously limited. However, due to its complex prescription and unclear pharmacodynamic mechanism, the clinical promotion of Guizhi Fuling capsule and the research on the mechanism of new drugs are severely limited. Based on the complexity of capsules and the synergistic mechanism between components, a single evaluation index is not easy to elucidate the mechanism of action comprehensively and effectively. Therefore, this study intends to use network pharmacology of traditional Chinese medicine for analysing the active components and related targets of the Guizhi Fuling capsule and to explore the effective mechanism of the Guizhi Fuling capsule in chronic pelvic inflammatory disease treatment.

MATERIALS AND METHODS

Effective active ingredients and target acquisition of Guizhi Fuling capsule:

Cinnamomi ramulus, *Wolfiporia cocos*, Cortex Moutan, Persicae Semen and Paeoniae Radix Alba are the effective active ingredients in Guizhi Fuling capsule. The Traditional Chinese Medicine Systems Pharmacology (TCMSP)[11] database was applied to screen the active ingredients of the above six traditional Chinese medicines, with drug Oral Bioavailability (OB) ≥30 % and Drug-Likeness (DL) ≥0.18 as the standard[12]. Through the "Related targets" option in the TCMSP and the PubChem databases, 3-Dimensional (3D) structural formula of the compounds from the ingredients was collected. Then to attain the corresponding target of the active ingredient from the drug, target prediction was carried out using the SwissTargetPrediction. We finally obtained drug action targets, by integrating and deleting the duplicate targets in Microsoft Excel.

Chronic pelvic inflammatory disease target collection:

Targets related to chronic pelvic inflammatory disease was obtained by searching "chronic pelvic inflammatory disease" through the GeneCards database. A relevance score >8 times the median value was considered as the screening criteria. A Venn diagram of drug and disease targets was constructed to obtain the intersection targets.

Guizhi Fuling capsule and chronic pelvic inflammatory disease target and network construction:

After sorting out the data of Guizhi Fuling capsule which regulates chronic pelvic inflammatory disease and effect of active ingredients, a drug-active ingredient-target network was constructed using the software Cytoscape. We calculated centrality value and node degree value to screen the core active ingredients.

Protein-Protein Interaction (PPI) network:

Intersection targets of Guizhi Fuling capsule and chronic pelvic inflammatory disease were imported into the Search Tool for the Retrieval of Interacting Genes (STRING) database to integrate the information about PPI interaction. To build a PPI network, the protein parameter was set to multiple proteins, the species was set as *Homo sapiens*, and the minimum interaction score required was 0.7. We hid the discrete targets and constructed the PPI network. The PPI file was downloaded and imported into Cytoscape software for topological parameter analysis. The analysis results included the Maximal Clique Centrality (MCC) score and degree for core target screening.

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis:

We performed GO enrichment and KEGG signaling pathway analysis on Guizhi Fuling capsule and chronic pelvic inflammatory disease targets using the Web-based gene set analysis toolkit (WebGestalt) data platform. We considered $p<0.05$ as the standard to obtain different biological processes, cell components, molecular functions and signaling pathway information[13].

Molecular docking:

3D structure of the core active ingredient was screened (as a ligand molecule) and the 3D structure of the core targets were obtained from the Protein Data Bank (PDB) (as the receptor protein) and molecular docking was obtained using TCMSP database. We applied AutoDock software for molecular docking and formatted the results with Open Babel software. Finally, we optimized the model with PyMOL software to increase visibility.

RESULTS AND DISCUSSION

Through the TCMSP database, screening active components and targets of Guizhi Fuling capsule were identified where we found 69 active ingredients of Cinnamon Twig and Poria capsule. Among them, 7 active ingredients belong to *Cinnamomi ramulus*, 11 belong to Cortex Moutan, 13 belonged to Paeoniae Radix Alba, 15 belonged to *Wolfiporia cocos* and 23 belonged to Persicae Semen. 69 active ingredients corresponded to 275 related target genes. Finally, we obtained 120 target genes by Universal Protein (UniProt) resource standardizing target and gene information and removing duplicates. Table 1 shows the active components and main targets of the Guizhi Fuling capsule.

Chronic pelvic inflammatory disease targets and its common targets with Guizhi Fuling capsule were determined. Collecting the genes of chronic pelvic inflammatory disease by GeneCards, we obtained 2917 genes related to chronic pelvic inflammatory disease. 61 drug-disease intersection targets were obtained after the screening (fig. 1).

Drug-target network construction was assembled using the effective active ingredients and targets. The drug data network construction showed that 161 nodes, 308 edges and 3.230 average neighbors formed an interaction relationship (fig. 2).

PPI network construction of drug-disease intersection targets was determined. We performed PPI information network visualization by importing 61 common targets into the STRING database (fig. 3A). According to the top 30 MCC scores and degrees, we identified the vital targets (fig. 3B and fig. 3C) and screened out 33 vital targets by integrating MCC and degree screening results (Table 2). The cell components enriched by Cellular Component (CC) mainly included dopaminergic synapse, immunological synapse, integral component of presynaptic membrane, caveolae, an intrinsic component of presynaptic membrane, and so on. The primary cell functions of Molecular Function (MF) enrichment were dopamine binding, 3',5'-cyclic-Adenosine Monophosphate (cAMP) phosphodiesterase activity, catecholamine binding, cAMP binding and steroid hormone receptor activity. KEGG pathway enrichment analysis of top 20 genes (fig. 4), Biological Process (BP) pathway enrichment analysis of top 20 genes (fig. 5), CC pathway enrichment analysis of top 20 genes (fig. 6), MF pathway enrichment analysis of top 20 genes (fig. 7).

TABLE 1: SOME ACTIVE COMPONENTS OF GUIZHI FULING CAPSULE

Molecular ID	Active ingredients	OB (%)	DL	Drug
MOL000492	(+)-Catechin	54.83	0.24	*Cinnamomi ramulus*, Cortex Moutan, Paeoniae Radix Alba
MOL001930	Benzoyl paeoniflorin	31.27	0.75	Cortex Moutan, Paeoniae Radix Alba
MOL000359	Sitosterol	36.91	0.75	*Cinnamomi ramulus*, Cortex Moutan, Paeoniae Radix Alba
MOL001925	Paeoniflorin	68.18	0.4	Cortex Moutan, Paeoniae Radix Alba
MOL000211	Mairin	55.38	0.78	Cortex Moutan, Paeoniae Radix Alba
MOL000422	Kaempferol	41.88	0.24	Cortex Moutan, Paeoniae Radix Alba
MOL000358	Beta-sitosterol	36.91	0.75	*Cinnamomi ramulus*, Paeoniae Radix Alba

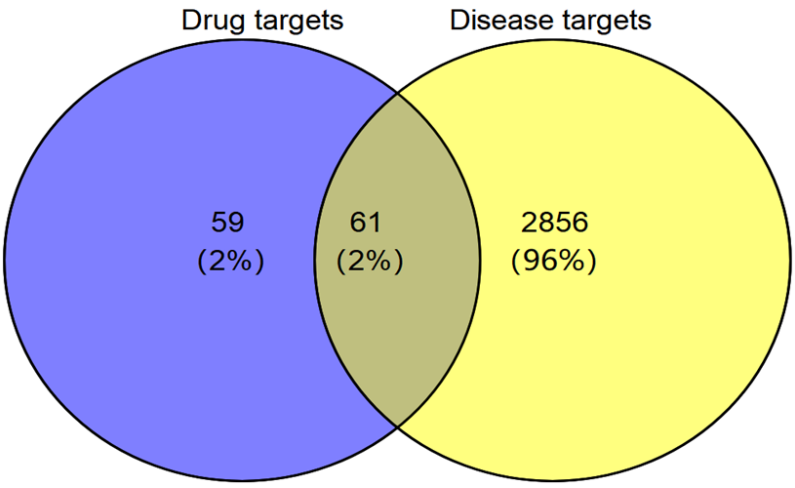

Fig. 1: Venn diagram of common targets of Guizhi Fuling capsule-chronic pelvic inflammatory disease

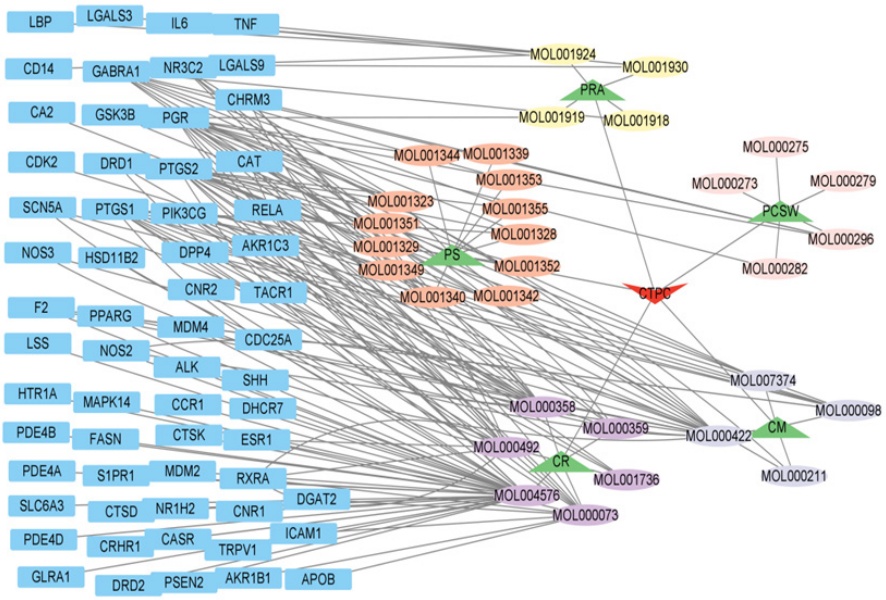

Fig. 2: Drug-active ingredient-target network diagram
Note: CR: *Cinnamomi ramulus*; CM: Cortex Moutan; PRA: Paeoniae Radix Alba; PCSW: *Poria cocos* (Schw.) Wolf; PS: Persicae Semen and CTPC: Cinnamon Twig and Poria capsule, (Red triangle): Drug; (Green triangle): Active Chinese medicine; (Oval): Active ingredient and (Rectangle): Potential target of the drug

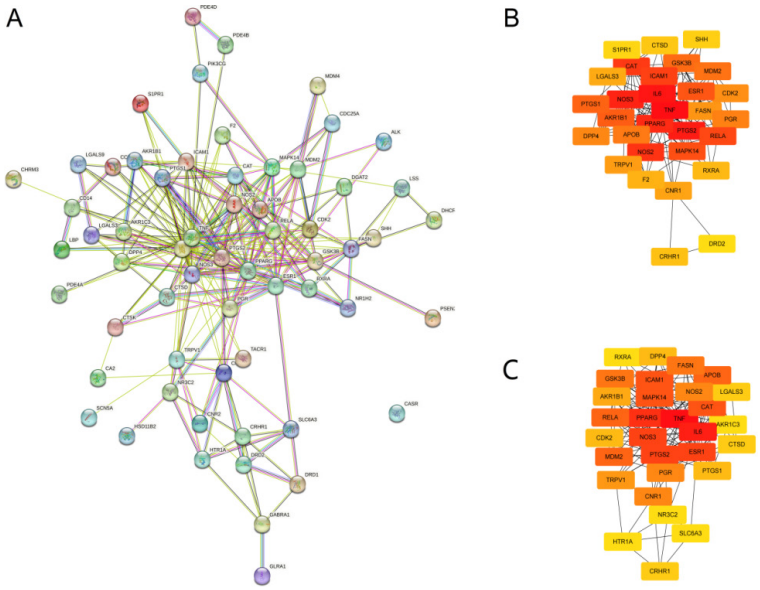

Fig. 3: Drug-disease intersection target PPI network diagram

TABLE 2: MCC AND DEGREE ALGORITHM TOPOLOGY ANALYSIS RESULTS (TOP 30)

Gene symbol	MCC	Gene symbol	Degree
TNF	42871	TNF	36
IL6	42817	IL6	34
PTGS2	39258	PPARG	25
NOS3	37706	ESR1	19
PPARG	36786	PTGS2	19
NOS2	25224	NOS3	19
CAT	24132	MAPK14	15
ICAM1	18150	ICAM1	15
RELA	15864	CAT	15
MAPK14	13084	RELA	13
ESR1	5939	APOB	13
AKR1B1	5766	MDM2	13
PTGS1	5046	GSK3B	12
GSK3B	4585	FASN	12
MDM2	3728	NOS2	11
APOB	2418	CNR1	11
PGR	2174	PGR	11
DPP4	1560	TRPV1	10
CDK2	842	AKR1B1	9
FASN	386	CDK2	8
TRPV1	255	PTGS1	8
CNR1	143	DPP4	8
LGALS3	128	LGALS3	7
F2	120	CRHR1	7
RXRA	36	CTSD	7
CRHR1	28	RXRA	6
CTSD	26	NR3C2	6
SHH	25	DRD2	6
S1PR1	24	HTR1A	6
DRD2	20	SLC6A3	6

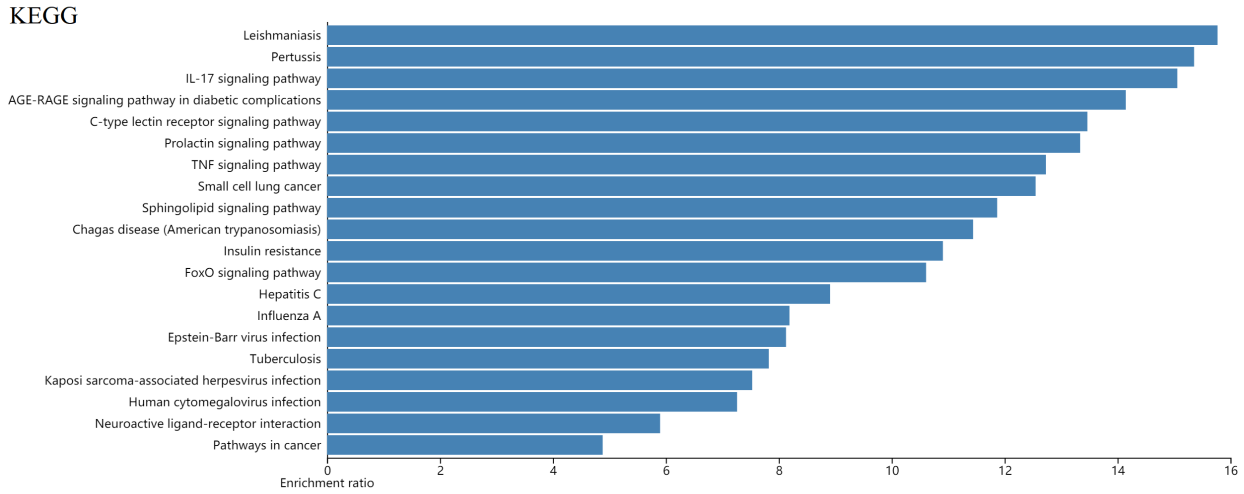

Fig. 4: KEGG pathway enrichment analysis of top 20 genes

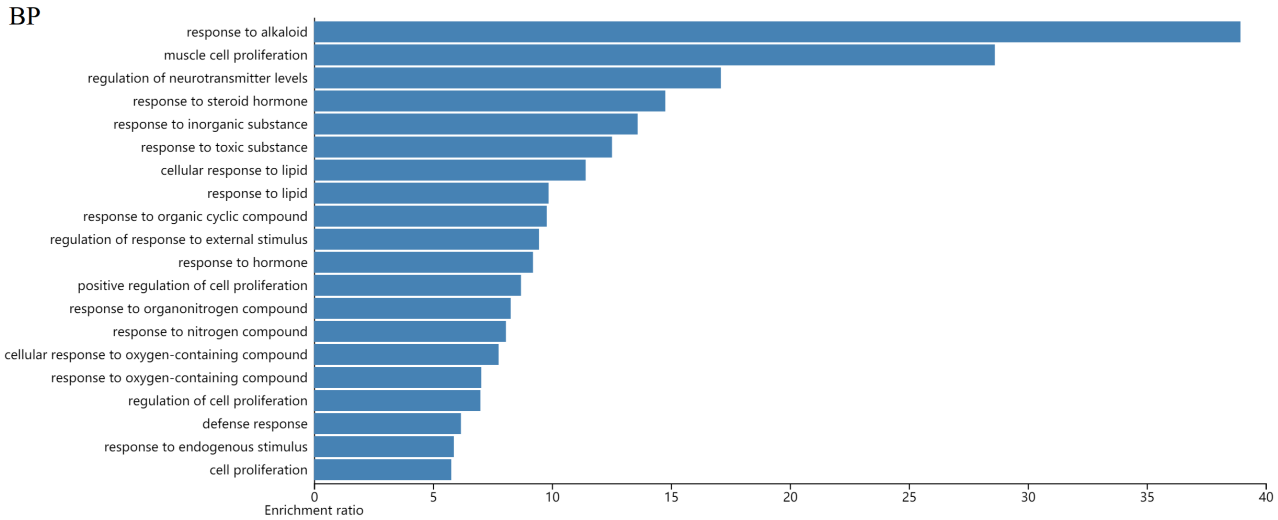

Fig. 5: BP pathway enrichment analysis of top 20 genes

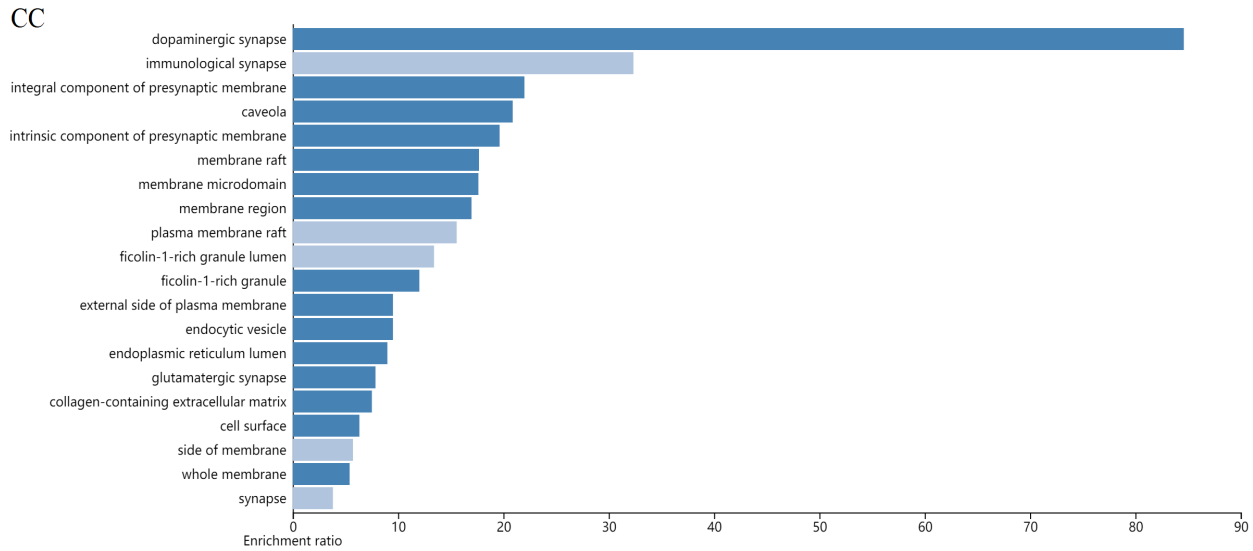

Fig. 6: CC pathway enrichment analysis of top 20 genes
Note: ( ): False Discovery Rate (FDR)≤0.05 and ( ): FDR>0.05

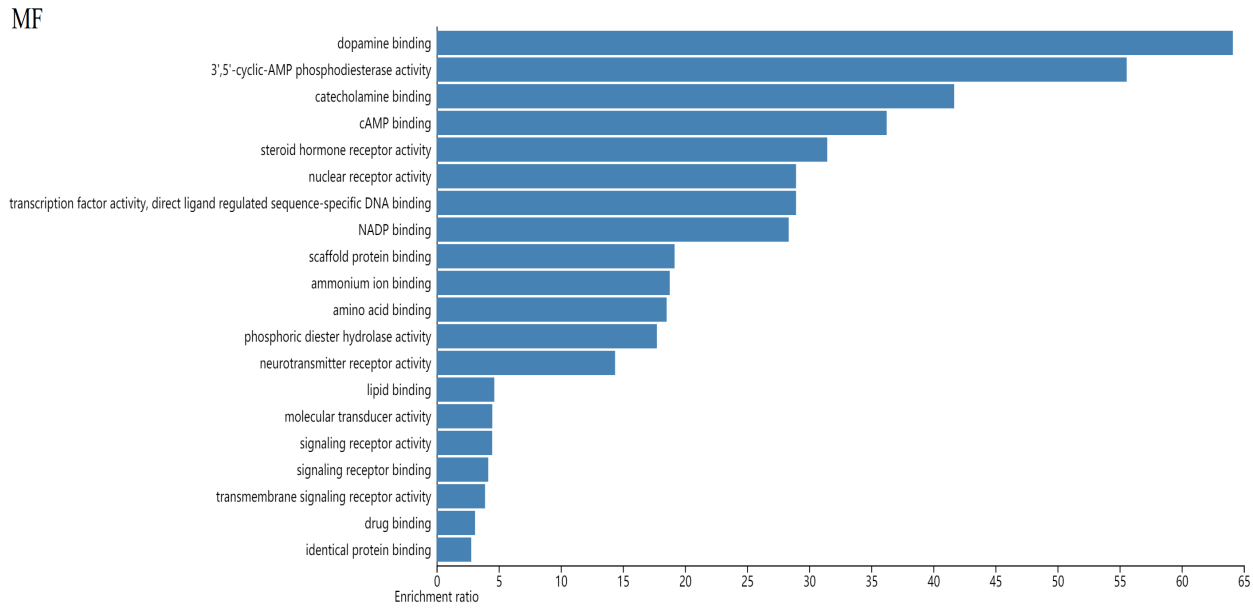

Fig. 7: MF pathway enrichment analysis of top 20 genes

Molecular docking was performed according to the binding energies. When the binding energy of protein molecules and ligand molecules is <-5 kcal/mol^{-1}, it suggests having a high probability of a combination. In this study, we performed molecular docking between the vital components of OB>50 % (enantiomer of catechin, paeoniflorin, mairin) and the core targets of degree >20 Tumor Necrosis Factor (TNF), Interleukin 6 (IL6), Peroxisome Proliferator-Activated Receptor Gamma (PPARG). The results showed that the binding energy of the vital components to the core target molecules was >-5 kcal/mol^{-1} (Table 3 and fig. 8).

The etiology of chronic pelvic inflammatory disease is very complex and stubborn and some patients have poor physical fitness. In the absence of timely and thorough treatment for pelvic inflammatory disease, the condition is often prone to recurrence seriously affecting the quality of life of female patients. Chronic pelvic inflammatory disease is closely related to the inflammatory state of the body. However, the relationship between immune processes and inflammation is difficult to understand[14]. Research has shown that Guizhi Fuling capsule has various active effects such as anti-inflammatory, analgesic, anti-tumor, regulating smooth muscle and endocrine, and enhancing immunity[15]. Guizhi Fuling capsules are composed of various traditional Chinese medicine compounds. It has certain advantages in clinical treatment of chronic pelvic inflammatory disease with complex pathogenesis. But currently, medical experts have not reached a consensus on the mechanism of action of Guizhi Fuling capsules in the treatment of chronic pelvic inflammatory disease. Based on the connection and relationship analysis of biological network nodes, network pharmacology has constructed a multi-level network of "chemical components, predicted targets, and signaling pathways", and comprehensively analyzed the effects of traditional Chinese medicine compounds. It can reflect the multi component, multi target and multi pathway characteristics of traditional Chinese medicine compounds, which is also related to diseases. This is in line with the basic principles of holistic view and syndrome differentiation and treatment in traditional Chinese medicine. Therefore, it is necessary to apply network pharmacology to explore the mechanism of action of Guizhi Fuling capsules in chronic pelvic inflammatory disease.

TABLE 3: MOLECULAR DOCKING BINDING ENERGY (KCAL/MOL^{-1}) OF VITAL COMPONENTS AND CORE TARGETS

Active ingredients	TNF	IL6	PPARG
(+)-Catechin	-5.68	-6.62	-5.15
Paeoniflorin	-5.33	-7.82	-5.98
Mairin	-8.25	-8.41	-7.32

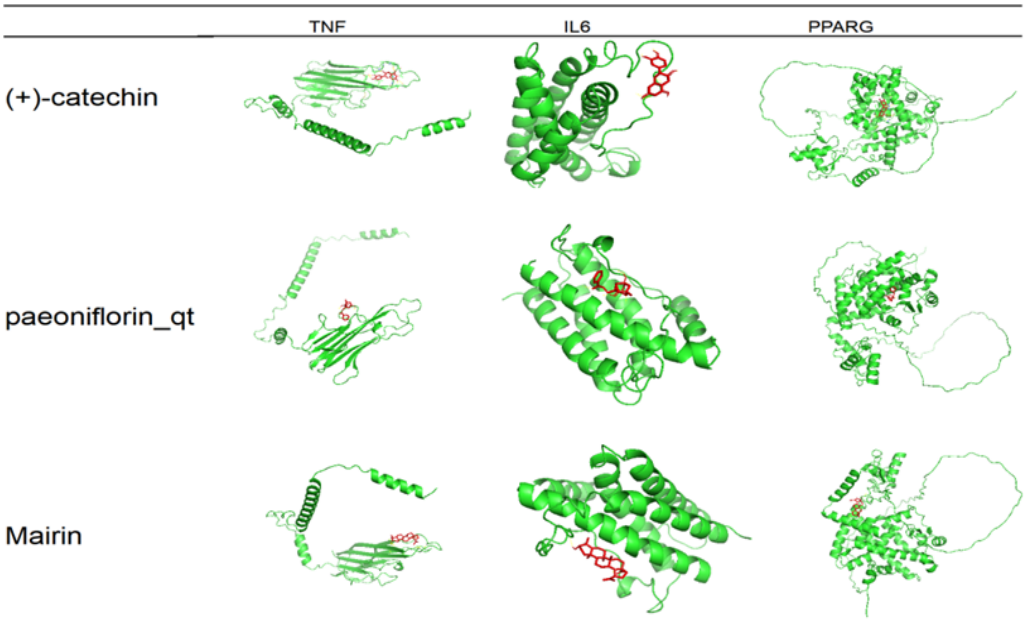

Fig. 8: Molecular docking mode of vital components and core targets

In this study, we construct the 'drug-compound-target-disease' network of Guizhi Fuling capsule in chronic pelvic inflammatory disease treatment by the network pharmacology method, and 69 active components and 120 target genes were obtained mainly involving target genes TNF, IL-6, PPARG, Estrogen Receptor 1 (ESR1), Prostaglandin-Endoperoxide Synthase 2 (PTGS2), Nitric Oxide Synthase 3 (NOS3), etc. As per the results of GO enrichment and KEGG pathway enrichment analysis, leishmaniasis, pertussis, IL-17 signaling pathway, Advanced Glycation Endproducts-Receptor for Advanced Glycation Endproducts (AGE-RAGE) signaling pathway in diabetic complications, C-type Lectin Receptor (CLR) signaling pathway, response to alkaloid, muscle cell proliferation, regulation of neurotransmitter levels, dopaminergic synapse, immunological synapse, dopamine binding, cAMP phosphodiesterase activity may be a mechanism of Guizhi Fuling capsule on chronic pelvic inflammatory disease.

TNF-Alpha (α) and IL-6 are effective immunological indicators to reflect the severity of infection in patients, and their levels will be significantly increased in women with pelvic inflammatory disease[16]. TNF-α is involved in the body's inflammatory response, which can chemoattract complements, effect the cells and promote their aggregation to the site of infection. IL-6 can accelerate the release of superoxide dismutase and lysosomal enzymes. It acts on various inflammatory and anti-inflammatory cytokines in chronic pelvic inflammatory disease[17]. PPARG influences chronic inflammation and oxidative stress[18]. ESR1 is related to the mechanism of action of icariin on knee osteoarthritis[19], which is similar to the results of this study. PTGS2 is a cyclooxygenase and peroxidase in the prostaglandin biosynthesis pathway. It is a C20-type oxylipin mainly derived from arachidonic acid and plays a central role in the inflammatory response[20]. This study found that TNF, IL6, PPARG, ESR1, PTGS2, and other genes are closely related to chronic pelvic inflammatory disease, but their roles need to be further studied.

IL-17 is a highly multifunctional pro-inflammatory cytokine, and it is essential for various processes, including host defense, tissue repair, the pathogenesis of inflammatory diseases, and cancer progression[21]. The IL-17 signaling pathway mainly induces the release of inflammatory factors by regulating downstream Mitogen-Activated Protein Kinase (MAPK). Studies have pointed that the destruction of IL-17 (secukinumab, ixekizumab, and brodalumab) signals in the skin can treat psoriasis[22]. The AGE-RAGE regulates the release of inflammatory factors mainly by inducing oxidative stress and acting on downstream Jun N-terminal Kinase (JNK), Extracellular signal-Regulated protein Kinases 1 and 2 (ERK1/2), and Serine/Threonine Kinase (Akt). Studies have shown that overexpression of Nonsteroidal Anti-inflammatory drug-activated Gene-1/Growth Differentiation Factor 15 (NAG-1/GDF15) can inhibit renal and systemic inflammation in mice, the AGE/RAGE axis, its downstream inflammatory molecules and adhesion molecules[23]. Another study showed that the AGE-RAGE signaling pathway in diabetic complications is one of the main signaling pathways involved in the anti-cholestasis process of the San-Huang-Chai-Zhu Formula (SHCZF)[24]. We reviewed the medical literature and found few studies on leishmaniasis and pertussis signaling pathways. So, we believe that the consistency of the mechanism of Guizhi Fuling capsule in chronic pelvic inflammatory disease treatment needs to be verified by basic experiments. Based on network pharmacology and molecular docking technology, this study analyzes the mechanism of Guizhi Fuling capsule in chronic pelvic inflammatory disease treatment, which can guide the clinical application of Guizhi Fuling capsule to a certain extent. In addition, traditional Chinese medicine components applications such as *Cinnamomi ramulus*, *Wolfiporia cocos*, Cortex Moutan, Persicae Semen, and Paeoniae Radix Alba has gradually attracted the attention of material application[25]. These may become a new topic worth of further studies because of improving the bioavailability of Guizhi Fuling capsule and its use as an auxiliary drug (bioavailability of the leading drug improving).

In summary, Guizhi Fuling capsule may treat chronic pelvic inflammatory disease through several active ingredients and targets effects in *Cinnamomi ramulus*, Cortex Moutan, *Radix Paeoniae Alba*, Poria and Semen Persicae and may affect leishmaniasis, pertussis, IL-17 signaling pathway, and other multi-pathways. In this study, by constructing a network of components-targets-pathways-chronic pelvic inflammatory disease

of Guizhi Fuling capsule, we predicted and summarized the targets and pathways of Guizhi Fuling capsule, which could provide direction and ideas for further research of Guizhi Fuling capsule. However, this study also has limitations. Our research is based on network pharmacology and molecular docking methods that uses only database data to predict the mechanism of action of Guizhi Fuling capsule in treating chronic pelvic inflammatory disease, which can help to discuss the possible active ingredients, targets and signaling pathways of Guizhi Fuling capsules theoretically. Secondly, there are many chemical components in Guizhi Fuling capsules and many components which have not been further analyzed due to not meeting the screening conditions for OB≥30 % and DL≥0.18. Next, it is also required to conduct basic experiments to verify the pharmacological effects of Guizhi Fuling capsules.

Conflict of interests:

The authors declared no conflict of interests.

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