Mechanism of *Camellia nitidissima* Chi in Treating Premature Ovarian Failure Based on Network Pharmacology and Molecular Docking

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Abstract [**Objectives**] This study was conducted to explore active components and molecular biological mechanisms of *Camellia nitidissima* Chi in the treatment of premature ovarian failure (POF). [**Methods**] The active components and corresponding targets of *C. nitidissima* Chi were retrieved through literature and the TCMSP database. POF-related disease targets were identified using the OMIM and Genecards databases. A PPI network was constructed using the STRING database and Cytoscape 3.10.2. A herb-active component-target-pathway network diagram was also constructed with Cytoscape 3.10.2. The CytoNCA plugin was used to screen out the top five core targets and core active components. GO and KEGG enrichment analyses of the intersecting targets were performed using DAVID. Finally, molecular docking was conducted using Auto Dock to verify the interaction between core targets and active components, and visualization was done using PyMol. [**Results**] A total of 26 active components and 461 targets of *C. nitidissima* Chi were identified, with 154 intersecting targets related to POF. The core components of the herb included 1,1'-bi-2-naphthol, 3',4-O-dimethylcedrusin, eriodictyol, quercetin, and vanillin. The PPI network revealed that the main targets were epidermal growth factor receptor (EGFR), protein kinase B1 (AKT1), proto-oncogene Src (SRC), hypoxia-inducible factor 1α (HIF1A), and estrogen receptor 1 (ESR1). KEGG enrichment analysis revealed 10 pathways closely related to POF, mainly involving the PI3K-Akt signaling pathway, chemical carcinogenesis-reactive oxygen species, endocrine resistance, and the HIF-1 signaling pathway. Molecular docking results showed that the core active components had strong binding activity with the targets. [**Conclusions**] *C. nitidissima* Chi has multi-component, multi-target, and multi-pathway characteristics in the comprehensive treatment of POF, providing informational support for its clinical application.

Key words *Camellia nitidissima* Chi; Premature ovarian failure; Network pharmacology; Molecular docking

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Premature ovarian failure (POF) refers to the premature decline of ovarian function in women before the age of 40, which is characterized by the decrease of the number and quality of follicles, the imbalance of reproductive hormones, and menstrual disorder or amenorrhea, which leads to the decline or even loss of fertility. The disease is often accompanied by other health problems and increases the risk of death, which seriously affects women's physical and mental health. In recent years, the incidence of POF has increased year by year, and there is a younger trend[1]. There are many reasons for POF, including environment, heredity, metabolism, hormone imbalance, immune abnormality, physical or chemical factors, *etc.*[2], but its exact pathogenesis has not been fully clarified. At present, hormone replacement therapy and immunosuppressants are mainly used in clinic to relieve POF symptoms. However, long-term use of these therapies may bring side effects, such as increasing the risk of breast cancer and cardiovascular diseases[3]. Therefore, it is expected to provide a new treatment strategy for POF patients by looking for effective traditional Chinese medicine replacement therapy.

Camellia nitidissima C. W. Chi (CNC) is a unique Chinese medicine in Guangxi. It is an evergreen shrub or small tree of *Camellia* in Theaceae, belonging to non-toxic plants, and mainly grows in the southwest of China. 90% of the world's wild camellia is only distributed in Shiwan Mountain in Fangchenggang City, Guangxi, so it is known as the "giant panda in the plant world" and the "queen of tea family"[4], and it is one of the traditional medicinal plants of Zhuang nationality in Guangxi. The medicinal value of *C. nitidissima* Chi was first seen in *Compendium of Materia Medica*. It has been used by Zhuang people in Guangxi for a long time and has important medicinal and edible value. According to *Guangxi Chinese Herbal Medicine Standard*, *C. nitidissima Chi* has the functions of clearing away heat and toxic materials, resisting bacteria and inflammation, promoting diuresis to reduce edema, and protecting liver and preventing cancer. Modern pharmacological research further found that *C. nitidissima* Chi is rich in natural active ingredients such as tea polyphenols, tea polysaccharides, total flavonoids and total saponins[4–5], and has many pharmacological effects such as lowering blood sugar, lowering blood lipid, lowering blood pressure, and resisting oxidation, inflammation and tumor[4–12]. Therefore, through network pharmacology and molecular docking technology, the mechanism of action of *C. nitidissima* Chi with multiple components, multiple targets and multiple channels was studied, and its active components and potential mechanism of regulating premature ovarian failure (POF) were explored, aiming to provide theoretical support for future experimental research and its clinical application in infertility-related diseases.

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Methods

Collection and screening of active components in *C. nitidissima* Chi

The main active components of *C. nitidissima* Chi were collected in traditional Chinese medicine systems pharmacology database and analysis platform (TCMSP)[13] by screening with oral bioavailability (OB) ≥30% and drug-like (DL) ≥0.1 as the degree values, and the effective active ingredients reported in the literature were collected simultaneously. Molecular structures were collected through TCMSP and PubChem (https://pubchem.ncbi.nlm.nih.gov/).

Screening of targets corresponding to active components of *C. nitidissima* Chi

Swiss Target Prediction (http://www.swisstargetprediction.ch/)[14] database and TCMSP database were adopted to screen targets related to active components of *C. nitidissima* Chi under the screening condition of probability greater than 0. The screening was limited to "Homo sapiens". The target information finally obtained was standardized to obtain standard gene names.

Screening of POF disease-related targets

With "Premature ovarian failure" as the key word, Online Mendelian inheritance in man (OMIM)[15] and GeneCards[16] databases were searched. Deduplication was performed after screening and merging the retrieved data.

Establishment of network diagram of protein-protein interaction network (PPI) between *C. nitidissima* Chi and POF

Https://bioinformatics.psb.ugent.be/webtools/Venn/ was used to intersect the active components of *C. nitidissima* Chi with POF-related targets. Multiple proteins were selected from STRING database[17] to analyze the interaction between the intersecting targets, and the results of STRING were visualized by Cytoscape software, thus further constructing a "CNC-active component-target-pathway-disease" network diagram.

Signal path enrichment analysis

The intersecting targets were imported into DAVID database[18], and related pathway information of Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) was obtained. The top five results of related pathways were extracted for analysis and interpretation, and visualized analysis was performed through the Bioinformatics online platform.

Molecular docking verification

The information of core targets was downloaded from RCSB (https://www.rcsb.org/)[19] database, and the protein structures were pre-processed by PyMOL software. The 3D structures of core active components were downloaded from PubChem, and molecular docking was carried out by AutoDock software. The docking results were visualized by PyMOL.

Results

Screening of potential active components of *C. nitidissima* Chi

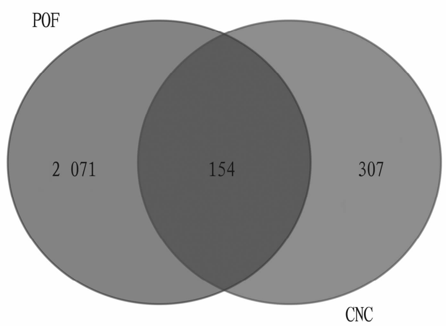
According to previous literature reports and TCMSP database, 26 kinds of effective active components of *C. nitidissima* Chi were screened out, as shown in Table 1.

Table 1 Active components of *C. nitidissima* Chi

Active component	Molecular formula	Pubchem ID
Quercetin	$C_{15}H_{10}O_7$	5280343
Kaempferol	$C_{15}H_{10}O_6$	5280863
4-Isobutyl-phenol	$C_{10}H_{14}O$	123212
Gallic acid	$C_7H_6O_5$	370
Benzyl alcohol	C_7H_8O	244
Cis-linaloloxide	$C_{10}H_{18}O_2$	529304
Phenethyl alcohol	$C_8H_{10}O$	6054
2,6-Dimethyl-3,7-octadiene-2,6-diol	$C_{10}H_{18}O_2$	5352451
Decyl isobutyl ester	$C_{22}H_{40}O_4$	66983857
Linalool	$C_{10}H_{18}O$	6549
Fenchyl alcohol	$C_{10}H_{18}O$	15406
Palmitic acid	$C_{16}H_{32}O_2$	985
Protocatechuate	$C_7H_6O_4$	72
Vanillin	$C_8H_8O_3$	1183
3'4-O-dimethylcedrusin	$C_{21}H_{26}O_6$	124426
Eudesmin	$C_{22}H_{26}O_6$	325601
1,2-Dimethoxybenzene	$C_8H_{10}O_2$	7043
Isovaleric acid	$C_5H_{10}O_2$	10430
Catechol	$C_6H_6O_2$	289
4-Methylcatechol	$C_7H_8O_2$	9958
2-Methoxy-4-vinylphenol	$C_9H_{10}O_2$	332
Pentadecanoic acid	$C_{15}H_{30}O_2$	13849
Luteolin	$C_{15}H_{10}O_6$	5280445
1,1'-Bi-2-naphthol	$C_{20}H_{14}O_2$	11762
Eriodictyol	$C_{15}H_{12}O_6$	440735
Benzoic acid-2-hydroxy-methylester	$C_8H_8O_3$	4133

Construction of *C. nitidissima* Chi-active component-target-disease Venn diagram

There were 461 active targets corresponding to 26 active components of *C. nitidissima* Chi, and 2 225 POF targets were searched. Next, 154 common target genes were obtained by intersection of the two types of targets, and a Venn diagram was made by Venn website (https://bioinformatics.psb.ugent.be/webtools/Venn/), as shown in Fig. 1.



POF: Premature ovarian failure; CNC: *C. nitidissima* Chi.

Fig. 1 Venn diagram of *C. nitidissima* Chi active components and premature ovarian failure targets

Establishment of protein-protein interaction (PPI) network

The relationship of the intersecting targets were analyzed in the STRING website with medium confidence analysis, and 152 nodes and 2 582 edges were obtained. The results of protein interaction in the TSV format were imported into the 3. 10. 2 version of Cytoscpe for visualization. According to the degree values, a higher value indicated a bigger node and darker color. Five core targets were selected, namely epidermal growth factor receptor (EGFR), protein kinase B1 (AKT1), proto-oncogene (SRC), hypoxia-inducible factor 1α (HIF1A) and estrogen receptor 1 (ESR1), as shown in Fig. 2.

A *C. nitidissima* Chi-active component-target-pathway network diagram was constructed. According to the number of targets of each component interacting with POF, the top five were 1,1'-bi-2-naphthol, 3'4-O-dimethylcedrusin, eriodictyol, quercetin and vanillin, as shown in Fig. 3.

GO and KEGG pathway analysis

GO function enrichment analysis includes biological process (BP), cellular component (CC) and molecular function (MF). The 154 intersecting targets were input into DAVID database for GO analysis. The biological process item of *C. nitidissima* Chi in treating POF involved protein phosphorylation, apoptotic process, negative regulation of apoptotic process, signal transduction, *etc.* The cell component item included cytosol, nucleus and cytoplasm. The molecular function item involved protein binding, ATP binding, homologous protein binding, *etc.* The top 10 biological processes, cell components and molecular functions were screened and plotted as a histogram (Fig. 4).

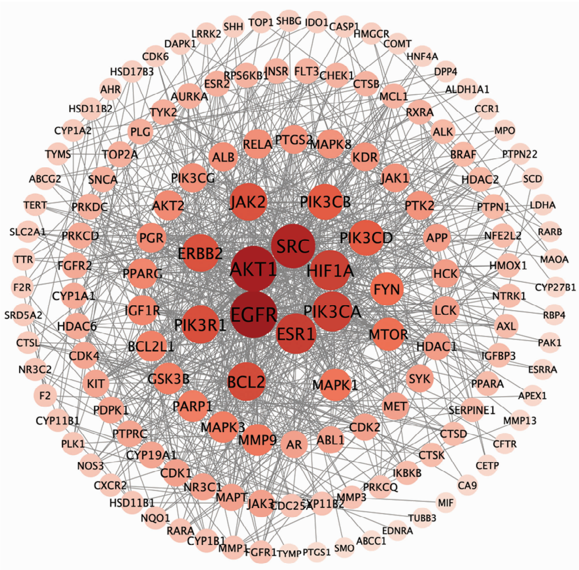


Fig. 2 Premature ovarian failure-*C. nitidissima* Chi target PPI network diagram

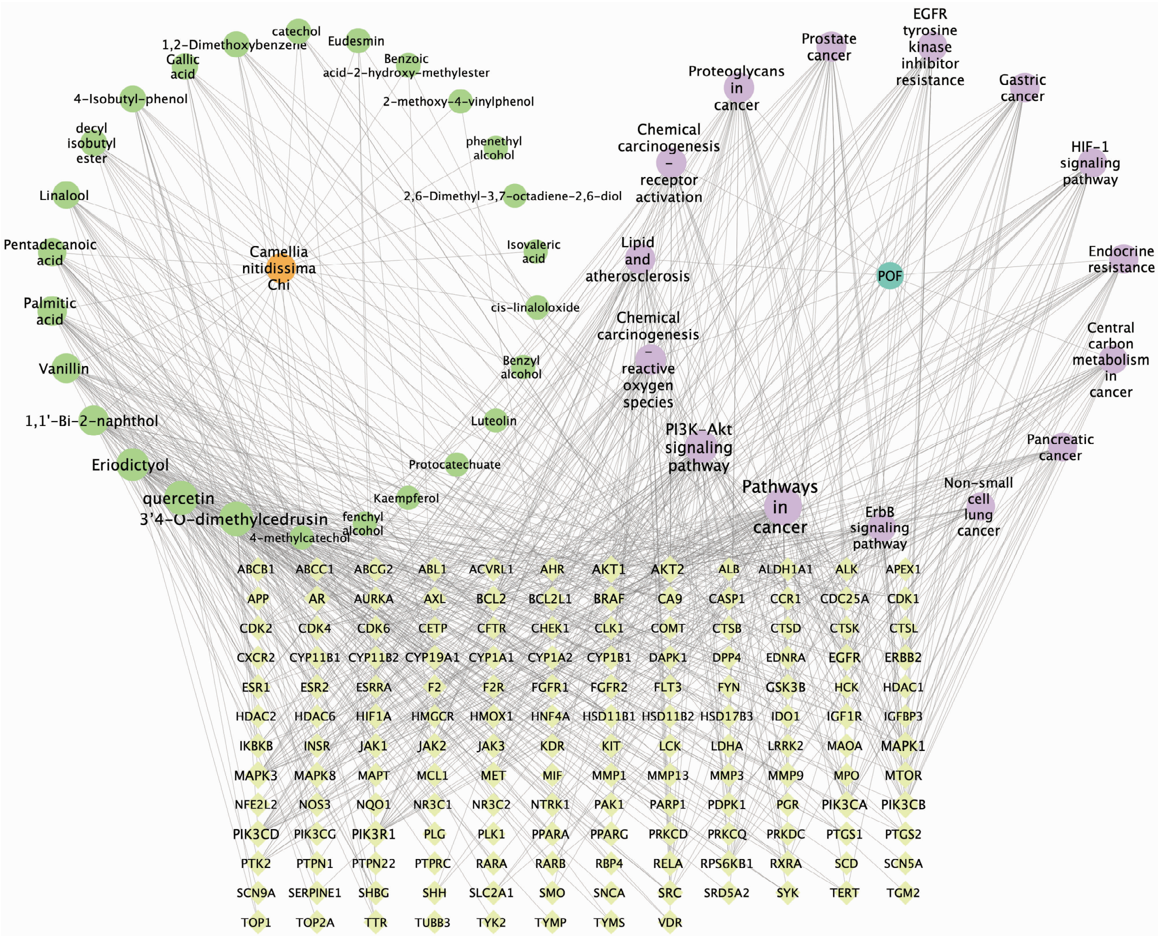
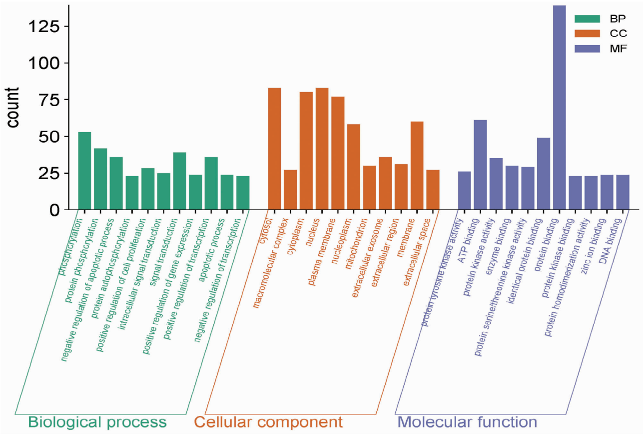


Fig. 3 *C. nitidissima* Chi-active component-target-pathway network diagram



BP: Biological process; CC: cell component; MF: molecular function.

Fig. 4 GO function enrichment histogram of the top ten BP, CC and MF functions corresponding to common target genes

Through the analysis of KEGG pathway, the top ten related signal pathways where the intersecting targets were enriched were selected, as shown in Fig. 5. The related pathways were mainly PI3K-Akt signal pathway, chemical carcinogenesis-reactive oxygen species, endocrine resistance, HIF-1 signal pathway and so on.

Molecular docking

Five key targets, AKT1, EGFR, HIF1A, PIK3CA, and SRC, were selected for molecular docking with five core active components, namely 1,1'- bi -2- naphthol, 3'4-O-dimethylcedrusin, eriodictyol, quercetin, and vanillin. The binding energies are shown in Table 2, and the binding energies were all less than −4.5 kcal/mol, indicating that the core active components of the herb had strong docking activity with key targets, and the possibility of action was great. The binding sites were visualized by PyMOL software, as shown in Fig. 6.

Table 2 Binding energy of core targets and core active components

	AKT1	EGFR	HIF1A	PIK3CA	SRC
1,1'-Bi-2-naphthol	−5.7	−6.0	−4.8	−5.9	−8.3
3'4-O-dimethylcedrusin	−9.4	−8.4	−8.7	−8.8	−7.3
Palmitic acid	−6.5	−5.7	−5.2	−5.4	−5.0
Quercetin	−8.6	−7.5	−7.0	−7.7	−8.7
Vanillin	−8.2	−7.8	−7.2	−9.5	−5.5

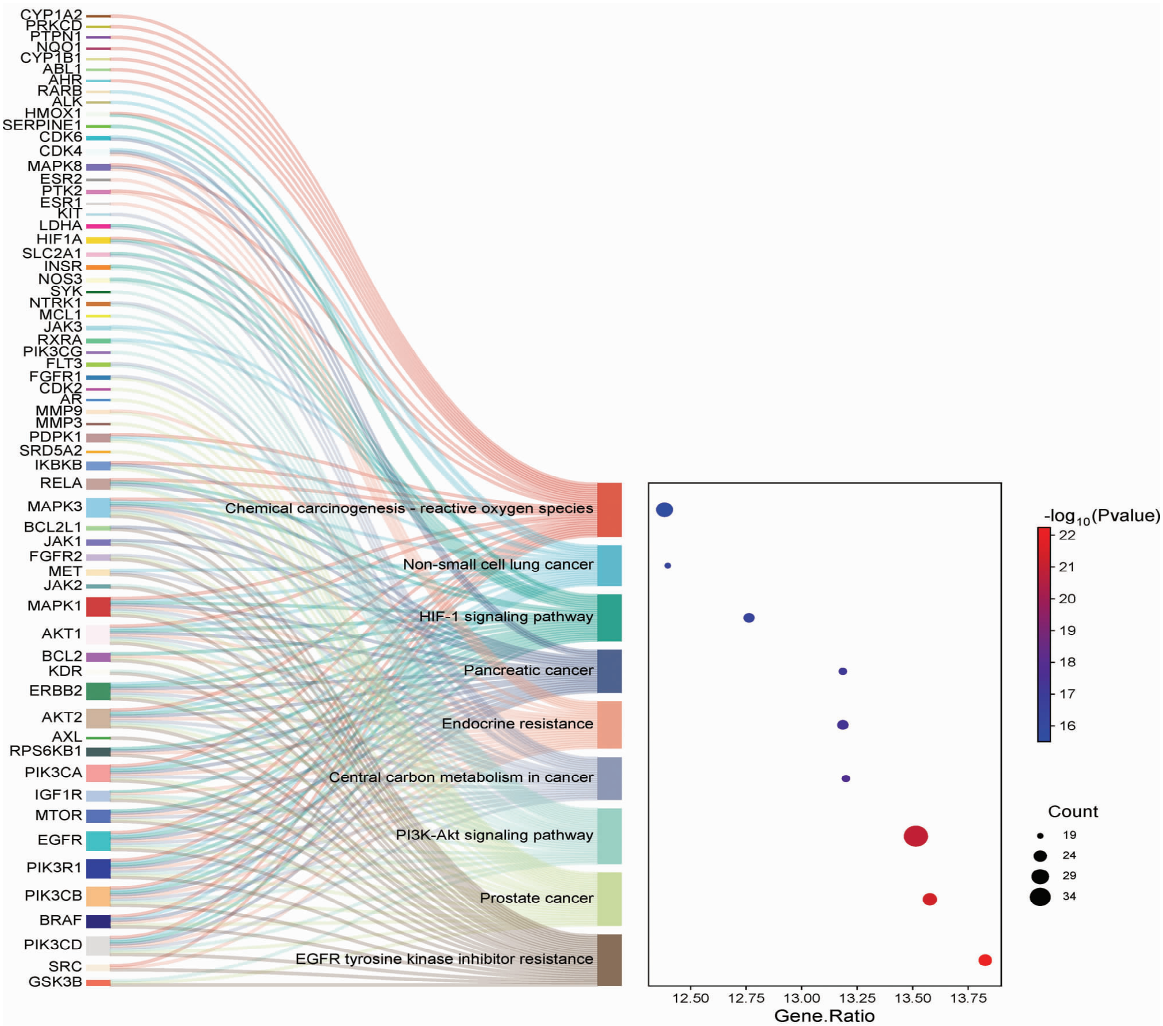


Fig. 5 KEGG pathway enrichment diagram of the top ten related signal pathways corresponding to common target genes

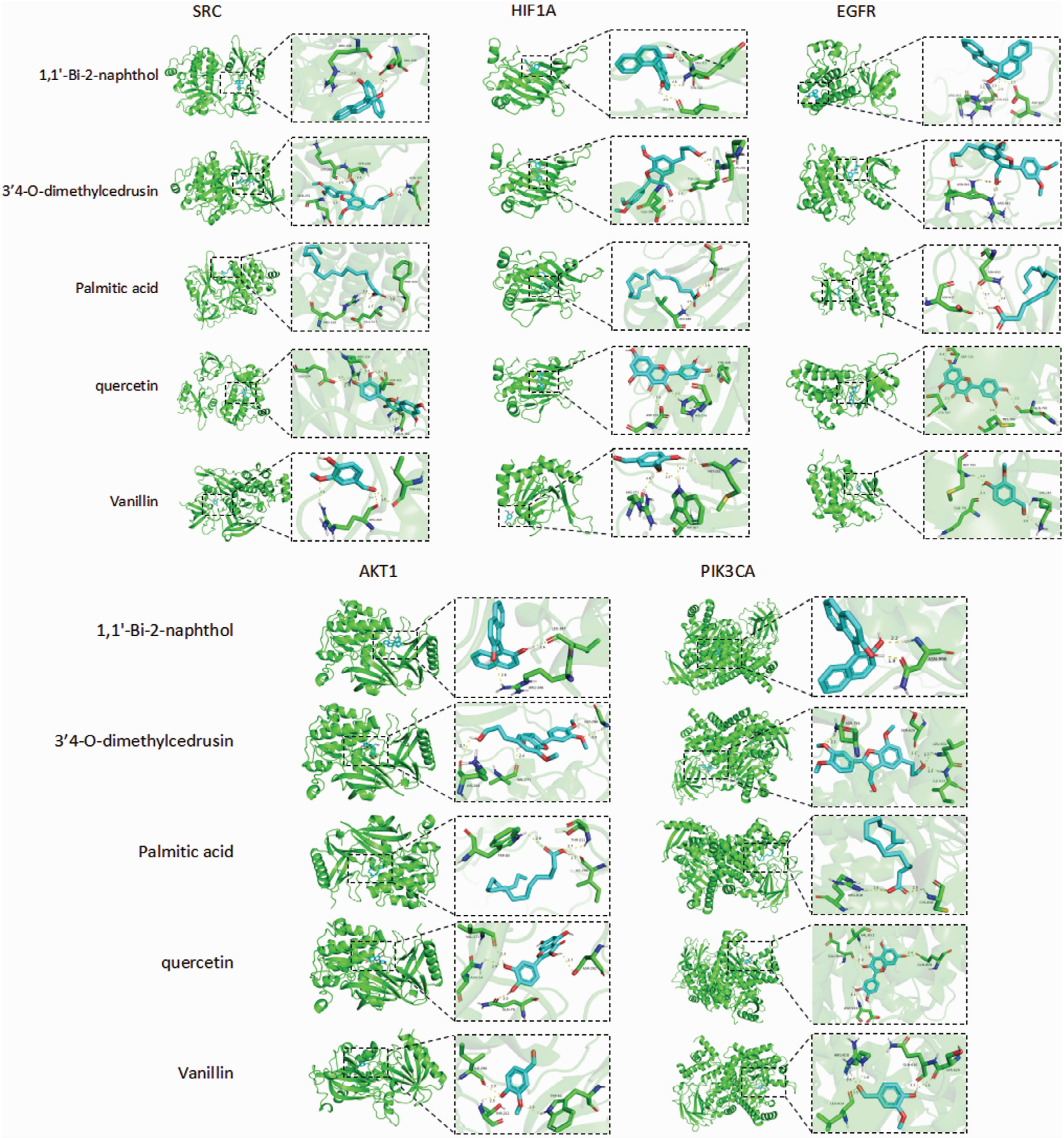


Fig. 6 Model diagram of docking between effective components of the herb and key target molecules

Discussion

C. nitidissima Chi is a traditional medicinal and edible plant of Zhuang nationality in Guangxi, which is rich in many natural active ingredients such as tea polyphenols, tea polysaccharides, total flavonoids, total saponins, tea pigments, anthocyanins, vitamins and trace elements[4-5], and has remarkable effects in lowering blood sugar, lowering blood pressure, and resisting oxidation, inflammation and tumor[4-12]. In daily life, *C. nitidissima* Chi is often used as health tea and widely consumed. Previous studies have shown that patients with premature ovarian failure (POF) are often accompanied by the increase of ovarian oxidative stress (OS) and inflammatory reaction. Therefore, the antioxidant and anti-inflammatory properties of *C. nitidissima* Chi may provide potential therapeutic ideas for the prevention and treatment of POF. According to the research of network pharmacology, the key active components of *C. nitidissima* Chi in regulating premature ovarian failure included 1,1'-bi-2-naphthol, 3'4-O-dimethylcedrusin, eriodictyol, quercetin and vanillin. Existing studies have shown that these plant compounds have significant pharmacological effects in viral resistance, tumor inhibition, oxidative regulation, and inflammation reduction. For example, quercetin has been proved to reduce the oxidative stress damage of endometrial stromal cells induced by hydrogen peroxide[20]. Eriodictyol has the effects of regulating oxidative stress, relieving inflammation, inhibiting tumor and resisting obesity[21]. Vanillin also plays a significant role in reducing inflammation, regulating oxidation reaction and inhibiting endometrial lesions[22]. Therefore, *C. nitidissima* Chi shows the regulatory effect on premature ovarian failure through the synergistic effect of its various active components, indicating its potential in treating this disease.

Further research found that the core targets of *C. nitidissima* Chi in regulating premature ovarian failure included AKT1, HIF1A, EGFR, PIK3CA, SRC and so on. AKT1 plays a key role in cell proliferation, migration, metabolism and apoptosis[23-24]. Up-regulation of HIF1A helps cells to survive in hypoxic environment, and its absence will increase the invasion and metastasis of pancreatic cancer cells[25]. EGFR plays an important regulatory role in cell growth and differentiation, especially under the stimulation of follicle-stimulating hormone (FSH), which plays an important role in regulating the growth of follicles[26]. PIK3CA is a common mutant gene in many cancers, and the joint mutation with ARID1A will promote tumor inflammatory signal transduction and tumor growth in ovarian clear cell carcinoma[27]. GO analysis showed that these target genes were mainly enriched in biological processes such as protein phosphorylation, apoptotic process, negative regulation of apoptotic process and signal transduction. KEGG enrichment analysis showed that the treatment of premature ovarian failure with *C. nitidissima* Chi involved many signal pathways in, including PI3K-Akt pathway, chemical carcinogenesis and reactive oxygen species, HIF-1 signal pathway and endocrine resistance.

Based on the results of molecular docking, it was found that there was good binding activity between 3'4-O-dimethylcedrusin and AKT1, quercetin and SRC, and vanillin and PIK3CA. Therefore, it is speculated that *C. nitidissima* Chi may regulate cell growth, apoptosis and proliferation in reproductive system through these targets. Its different active components are stably bonded with the targets related to premature ovarian failure through multiple targets to exert a therapeutic effect. To sum up, the network analysis framework of "*C. nitidissima* Chi-active component-intersecting target-POF" was constructed by using the network pharmacology method, and enrichment analysis was performed by screening core targets and main components. It was concluded that the regulatory effect of *C. nitidissima* Chi on POF was the result of the synergistic effect of various active components, which was verified by molecular docking technology. This study provides a research basis for further exploring the molecular mechanism of active components of *C. nitidissima* Chi in treating POF. In the future, animal experiments will be used to explore and verify relevant targets and pathways, so as to provide scientific basis and guidance for clinical application.

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(such as cellulose, lignin and ash) needed for the cultivation of edible fungi. Zhong *et al.* [8] carried out the cultivation experiment of *P. ostreatus* with the mixture of bamboo shavings, sawdust and straw as the main raw materials. The results showed that the formula with half of bamboo shavings and half of sawdust and straw achieved the highest yield and the biological efficiency reached 42%. However, there are few studies on the safety of cultivating edible fungi with bamboo shavings, such as excessive heavy metal content, pesticide residues, chemical reagents and other quality and safety issues. In this study, the suitable addition of Chinese medicine residue and bamboo shavings to partially replace sawdust for mycelial culture of *A. auricula* in large test tubes was discussed, providing reference for the preparation of original strain and mushroom production in the next step. Meanwhile, the breeding of strains adaptive to byproducts, the optimization of substrate formulas and how to improve the yield and quality of fruiting bodies need further study.

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