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Molecular docking technology and network pharmacology based on *Rhapontici Radix-Cremastrae Pseudobulbus* drug pair in treating breast cancer

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Abstract. – OBJECTIVE: Network pharmacology is a bioinformatics-based research strategy for identifying the mechanisms of drugs and promoting drug development. This study used network pharmacology to investigate the mechanism of the Loulu-Cremastrae Pseudobulbus drug pair treating breast cancer (BC).

MATERIALS AND METHODS: The ingredients and potential targets of the drug pair were searched with Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCSMP). National Center for Biotechnology Information (NCBI) and gene cards were used to search the targets of BC. Networks of "drugs-components-targets" and protein-protein interaction were constructed through Cytoscape. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis were carried out through common targets. Using AutoDock tool, molecular docking was performed to verify the binding between key targets and compounds.

RESULTS: Finally, we selected 6 active compounds from the drug pair. A total of 61 targets were associated with the drug pair, and 15,295 targets were related to BC. 55 common targets were obtained after the intersection. The key targets included Transcription factor Jun (JUN), Heat shock protein HSP 90-alpha (HSP90AA1), and Caspase-3(CASP3). 327 terms were obtained by GO analysis. 78 pathways ($p < 0.05$) were identified through KEGG analysis. Molecular docking indicated that important compounds combined well with key targets.

CONCLUSIONS: Various active compounds, including beta-sitosterol, 2-methoxy-9,10-dihydrophenanthrene-4,5-diol, and stigmasterol, can regulate multiple signaling pathways related to BC, such as the estrogen and prolactin signaling pathways, playing therapeutic roles in BC.

Key Words:
Rhapontici Radix-Cremastrae Pseudobulbus drug pair, Breast cancer, Molecular docking, Network pharmacology.

Introduction

Breast cancer (BC) is a serious threat to women's health, and it is the second-highest cancer among women[1]. BC is considered a heterogeneous malignant disease, and it has become a major public health problem worldwide[2]. Comprehensive therapy is the most commonly used treatment for BC, and surgery combined with radiotherapy, chemotherapy, molecular targeted therapy, immunotherapy, and endocrine therapy are the common methods[3]. However, these treatments have many adverse effects, for example, most chemotherapeutic drugs belong to chemosynthetic drugs. While inhibiting the development of tumor cells, they will inevitably cause excessive damage to normal tissues and cells, including bone marrow cells[4]. Traditional Chinese Medicine (TCM) is recognized for treating tumors in China.

Cremastrae Pseudobulbus can affect the phosphatidylinositol 3-kinase/protein kinase B signaling pathway and induce apoptosis in breast cancer cells. Moreover, it can inhibit tumor angiogenesis, invasion, and metastasis. It can be classified into stomach and large intestine meridians. It has functions in detoxification, carbuncle elimination, and knot dispersion. According to *Materia Medica*, it can "eliminate heat, toxin and pus", and *Cremastrae Pseudobulbus* is a high-frequency drug for the treatment of triple-negative breast

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cancer[5]. *Rhapontici Radix* can affect angiogenesis and induce apoptosis in tumor tissues[6]. Among the drugs with a high frequency of use in traditional Chinese medicine cases, are *Rhapontici Radix* and *Cremastrae Pseudobulbus*. However, the mechanism of the drug pair and its effect on breast cancer remains unclear.

With the development of bioinformatics, multi-pharmacology, and systems biology, drug discovery based on networks has become a new cost-saving method for drug development. The network pharmacology research methods have changed to a new "multi-target, multi-component" strategy[7]. Herbal medicines, such as the *Rhapontici Radix-Cremastrae Pseudobulbus* drug pair, have great potential in treating BC, using multi-target, multi-component synergies. The potential mechanism of *Rhapontici Radix - Cremastrae Pseudobulbus* against BC was studied by network pharmacology in our study. First, we searched for molecular targets for drug pairs. We then studied the intersection of targets and networks of molecular targets and breast cancer-related target sharing, and we carried out molecular docking to explore the interaction of key components with breast cancer target binding. Our research elucidated the mechanism of action on drug therapy for breast cancer and promoted new drug development.

Materials and Methods

Target Prediction Associated with BC

We obtained targets associated with BC using the National Center for Biotechnology Information Database (NCBI, https://www.ncbi.nlm.nih.gov/)[8] and GeneCards (https://www.genecards.org/)[9] by searching "breast cancer" and the species was set as "Homo sapiens". 4,744 targets were searched in NCBI, and 15,253 targets were searched in GeneCards. A total of 15,295 targets were found after removing repeated targets.

Collection of Compounds and Targets Related to Rhapontici Radix-Cremastrae Pseudobulbus Drug Pair

Based on Chinese herbal medicines, Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, http://ibts.hkbu.edu.hk/LSP/tcmsp.php), we obtained the compounds and targets of the *Rhapontici Radix-Cremastrae Pseudobulbus* drug pair[10]. OB $\geq$ 30% and drug-likeness (DL) $\geq$ 0.18 were set as the standards[11], bioactive components were selected, and related targets of each component were obtained. With a Venn diagram, common targets of the drug pair and BC were obtained. These genes were potential targets of the drug pair treating BC.

Protein-Protein Interaction

Protein-protein interaction (PPI) network was constructed through common genes. The common targets were imported into the STRING (https://string-db.org/) database[12]. Using Cytoscape (version 3.7.1)[13], the PPI network was visualized. Then, we calculated degrees to identify key targets[14]. The top 10 targets were considered to be dominant targets. Based on Molecular Complex Detection (MCODE), we carried out cluster analysis of the PPI network.

Network Construction

To investigate the mechanism of the *Rhapontici Radix-Cremastrae Pseudobulbus* drug pair treating BC, a drug-component-target network was constructed through Cytoscape (version 3.7.1[13]).

Gene Ontology and Pathway Analysis

Through ClueGO in Cytoscape, we analyzed KEGG pathways and gene ontology (GO) of potential targets. Set the KEGG pathway analysis and GO enrichments were considered significant with a p-value < 0.05[14].

Molecular Docking

Based on the RCSB Protein Data Bank (http://www.pdb.org/), we downloaded the hub proteins' crystal structures of the *Rhapontici Radix-Cremastrae Pseudobulbus* drug pair. Then, we modified the conformations of proteins with AutoDock Tools 1.5.6, including water removal, amino acid optimization, computation of charge, and hydrogen addition. Using Chem 3D, three-dimensional chemical structures of ligands were created and their energy was minimized. Saved results in MOL2 format. Saved the data in pdbqt format as docking ligand. Used autogrid4 and autodock4 for docking and used Discovery Studio 2019 to visualize the results.

Results

Identification of Components and Targets

Rhapontici Radix-Cremastrae Pseudobulbus have two common components (Figure 1A). There were 41 components of *Rhapontici Radix-Cremastrae Pseudobulbus* drug pair obtained through TCMSP, according to the standard of OB $\geq$ 30% an d DL $\geq$ 0.18, 7 components were screened (Fig-

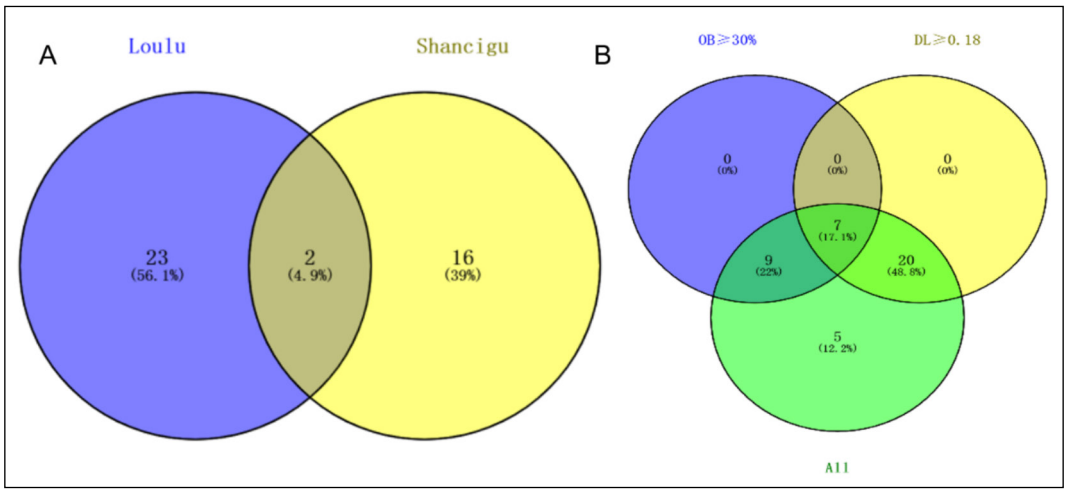

Figure 1. Venn diagram of drug pair of *Rhapontici Radix - Cremastrae Pseudobulbus* screening of bioactive compounds: (**A**) Common constituents of *Rhapontici Radix - Cremastrae Pseudobulbus*. **B**, Venn diagram: 41 components (green section), and 7 bioactive components screened by two ADME-related models (blue section stands for the components of OB ≥ 30%, yellow section stands for DL ≥ 0.18).

ure 1B). We displayed the chemical name, formula, and molecular weight of the 7 components in Table I. After removing compounds without targets, 6 compounds remain. We acquired 61 potential targets from TCMSP. After the intersection with targets of BC, 55 common targets were obtained (Figure 2A). The network of drug-compound targets is presented in Figure 2B.

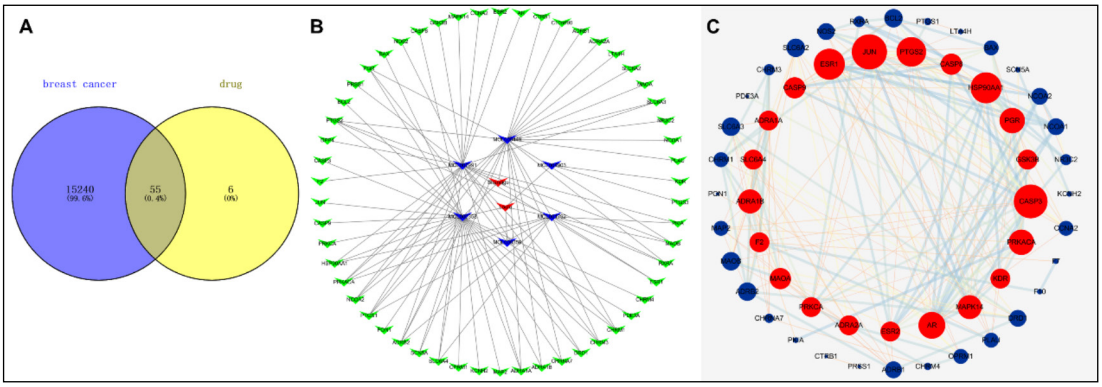

Figure 2. Common-target network. **A**, Mapping of Drug pair of *Rhapontici Radix - Cremastrae Pseudobulbus* related targets and breast cancer related targets, 55 common targets were showed. **B**, Construction of Drug pair of *Rhapontici Radix -Cremastrae Pseudobulbus* component-target visual network, Green for medicine, blue for ingredients, green for target. **C**, Interaction network of proteins related to the treatment of breast cancer by Drug pair of *Rhapontici Radix - Cremastrae Pseudobulbus*. The red nodes represented the big hub nodes. The node size was proportional to the target degree in the network.

Table I. The active compounds and their properties.

Mol ID	Molecule Name	MW	OB (%)	DL	Source
MOL000449	Stigmasterol	412.77	43.82985	0.75665	Shancigu
MOL007991	2-methoxy-9,10-dihydrophenanthrene-4,5-diol	242.29	44.96763	0.18129	Shancigu
MOL001792	DFV	256.27	32.76272	0.18316	Loulu
MOL000358	beta-sitosterol	414.79	36.91391	0.75123	Loulu
MOL000359	sitosterol	414.79	36.91391	0.7512	Loulu
MOL004903	liquiritin	418.43	65.69011	0.73893	Loulu
MOL007939	diosbulbin B	344.39	43.01105	0.70221	Loulu

Mol: molecule; MW: molecule weight; OB: Oral Bioavailability; DL: drug-likeness.

Table II. Information of top 10 potential antidepressant targets from drug pair of Rhapontici Radix - Cremastrae Pseudobulbus.

Name	Degree	Clustering Coefficient	Neighborhood Connectivity	Closeness Centrality	Betweenness Centrality
JUN	21	0.428571	11.57143	0.581395	0.101812
CASP3	20	0.4	11.75	0.581395	0.144443
HSP90AA1	18	0.48366	12.11111	0.531915	0.076242
ESR1	18	0.535948	12.38889	0.505051	0.029823
PTGS2	17	0.463235	11.82353	0.531915	0.101324
AR	15	0.580952	12.93333	0.480769	0.019108
PRKACA	14	0.296703	10.35714	0.485437	0.114445
PGR	14	0.571429	12.92857	0.480769	0.023907
ADRA1B	13	0.333333	8.307692	0.462963	0.053344
MAPK14	13	0.692308	14	0.471698	0.006243

JUN: Jun Proto-Oncogene, AP-1 Transcription Factor Subunit; CASP3: Caspase 3, Apoptosis-Related Cysteine Peptidase; HSP90AA1: Heat Shock Protein 90 Alpha Family Class A Member 1; ESR1: Estrogen Receptor 1; PTGS2: Prostaglandin-Endoperoxide Synthase 2; AR: Androgen Receptor; PRKACA: Protein Kinase, cAMP-Dependent, Catalytic, Alpha; PGR: Progesterone Receptor; ADRA1B: Adrenoceptor Alpha 1B; MAPK14: Mitogen-Activated Protein Kinase 14.

Analysis of PPI Network

The common targets were related to the establishment of the PPI network. There were 55 nodes and 222 edges, as shown in Figure 2C. The average degree of the node was 8.07, the local clustering coefficient was 0.519. In addition, 5 network clusters were obtained (Figure 3A-E). The top 10 targets were *JUN*, *CASP3*, *HSP90AA1*, *ESR1*, *PTGS2*, *AR*, *PRKACA*, *PGR*, *ADRA1B* and *MAPK14* (Table II, Figure 3F).

Gene Ontology Enrichment Analysis

36 biological process terms were obtained ($p < 0.05$; Figure 4A), and G protein-coupled amine and adrenergic and adrenergic receptor activities were the top ones. In cellular component analysis (Figure 4B), dopaminergic synapse, plasma membrane raft, and caveola were in the lead. In terms of molecular function (Figure 4C), for instance, nitric oxide synthase activity, scaffold protein binding, and negative regulation of protein binding were at the top.

Table III. Molecular docking scores of 3 components and 2 target proteins (kcal/mol).

Receptor / ligand	HSP90AA1	JUN
MOL000449	-9.5	-8.2
MOL007991	-8.7	-8.2
MOL000358	-5.3	-8.2

JUN: Jun Proto-Oncogene; HSP90AA1: Heat Shock Protein 90 Alpha Family Class A Member 1.

KEGG Pathway Enrichment Analysis

According to the 55 potential targets, more than 40 pathways (Figure 4D, $p < 0.05$) were selected for the next analysis, including arginine and proline metabolism, complement and coagulation cascades, progesterone-mediated oocyte maturation, endocrine, thyroid hormone signaling pathway, and other factor-regulated calcium reabsorption were at the top. In these pathways, arginine and proline metabolism have the lowest *p*-value and the most target enrichment.

Molecular Docking Results and Analysis

Molecular docking analysis predicted the interaction between important compounds (MOL000449, MOL007991, and MOL000358) and key targets. Three ligands and two targets (JUN and HSP90AA1) showed good interactions. The free energy of binding is displayed in Table III. We found traditional hydrogen bonding and van der Waals forces were two main forces. The structural model, binding mode, and binding site of key targets and important compounds are shown in Figures 5-7.

Discussion

As a malignant tumor that occurs in the gland epithelial tissue of the breast, the pathogenesis of BC is rather complicated and may be related to heredity, endogenous and exogenous hormones, radiation exposure, obesity, benign breast diseases, alcohol intake, and other factors[16]. Although BC can be treated through surgery, endocrine

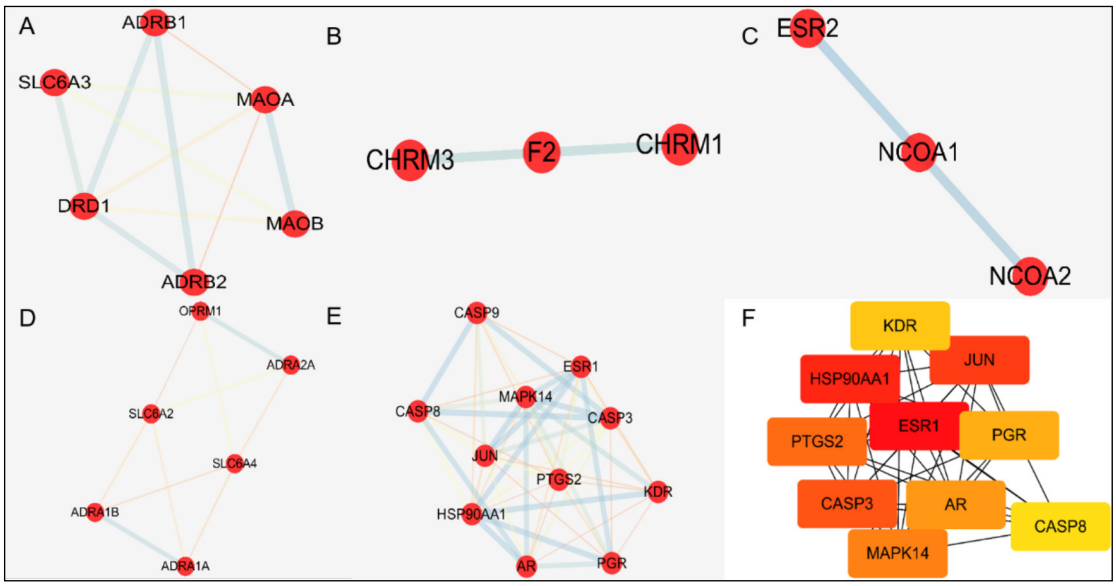

Figure 3. Subnetwork graph of protein-protein interaction and top ten hub targets. **A**, Score=4.4. **B**, Score=3. **C**, Score=3. **D**, Score=4. **E**, Score=10. **F**, The top ten targets screened out.

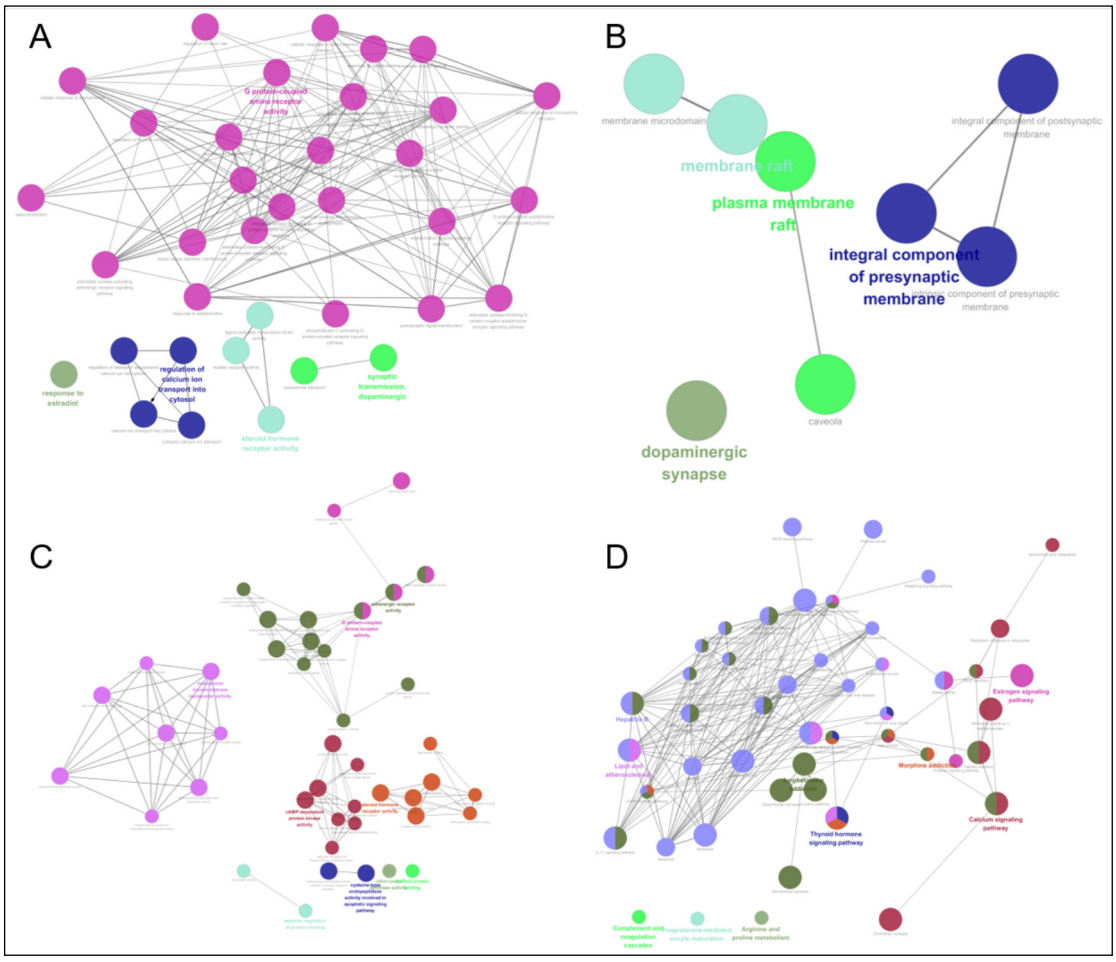

Figure 4. Enrichment of GO and KEGG pathway of Drug pair of *Rhapontici Radix - Cremastrae Pseudobulbus in* the treatment of breast cancer. **A**, Biological process (BP) analysis. **B**, Cellular component (CC) analysis. **C**, Molecular function (MF) analysis. **D**, Enriched KEGG pathways analysis.

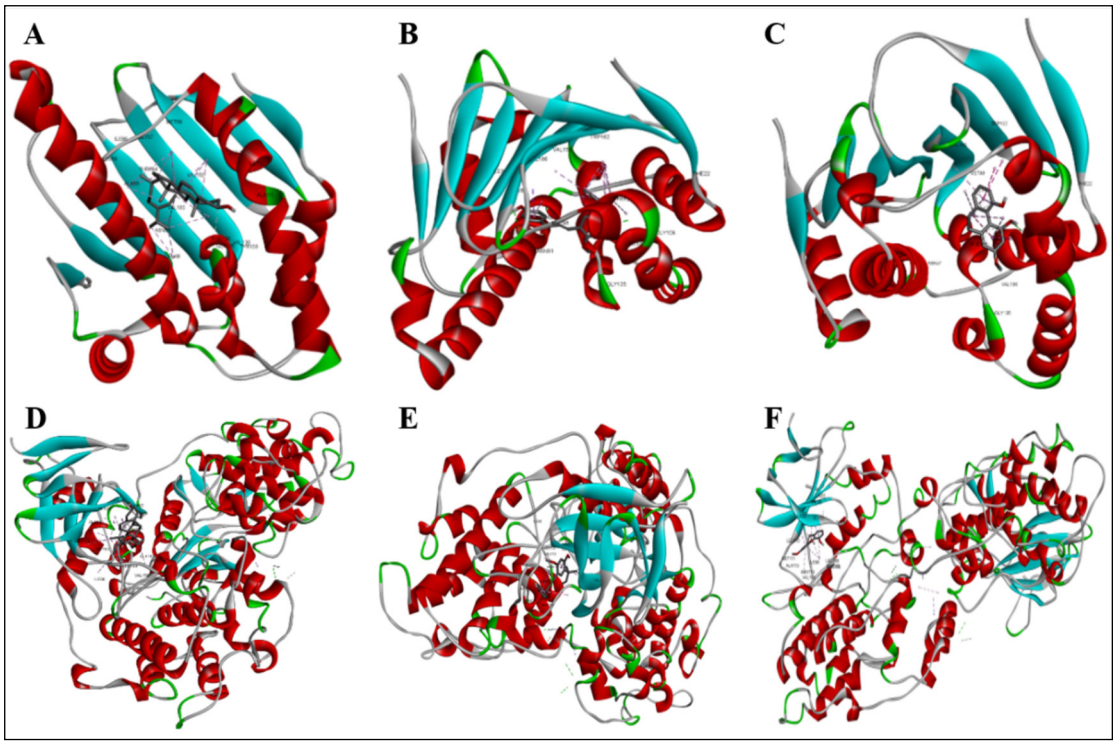

Figure 5. 2 targets were JUN and HSP90. The top 3 compounds were Stigmasterol, beta-sitosterol, 2-methoxy-9,10-dihydrophenanthrene-4,5-diol. Structural model of active ingredients with hub targets. **A**, Structural model of HSP90AA1 with beta-sitosterol. **B**, Structural model of HSP90AA1 with Stigmasterol. **C**, Structural model of HSP0AA1 with 2-methoxy-9,10-dihydrophenanthrene-4,5-diol. **D**, Structural model of JUN with beta-sitosterol. **E**, Structural model of JUN with Stigmasterol. **F**, Structural model of JUN with 2-methoxy-9,10-dihydrophenanthrene-4,5-diol.

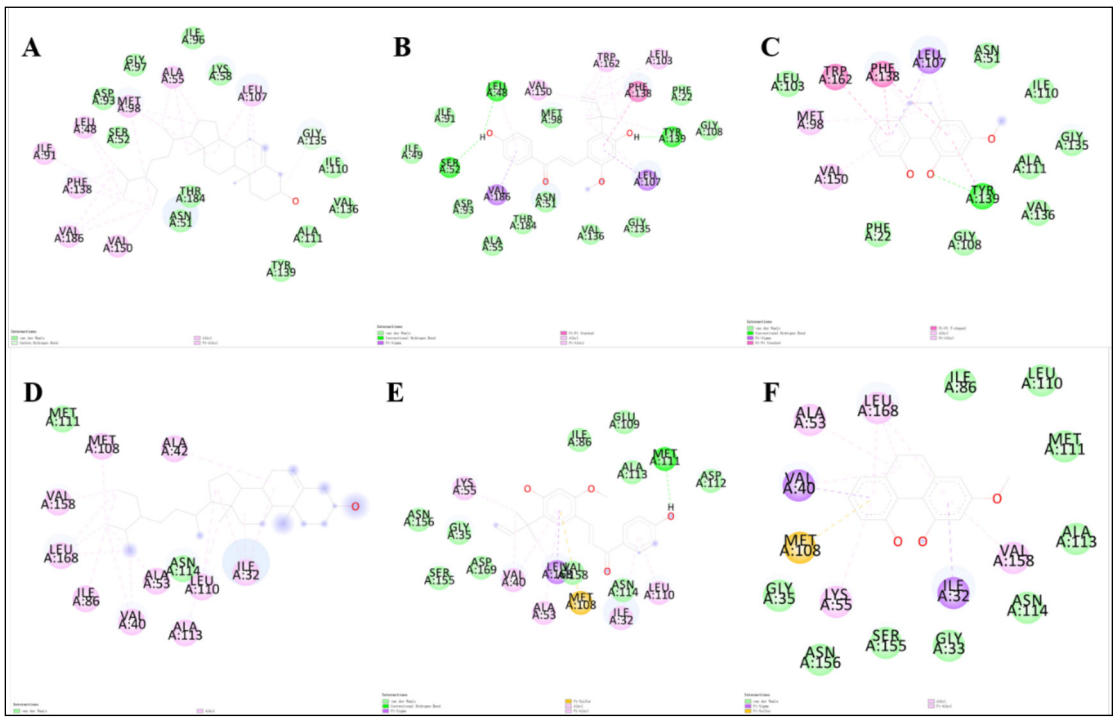

Figure 6. Binding site of active ingredients with hub targets. **A**, Structural model of HSP90AA1 with beta-sitosterol. **B**, Structural model of HSP90AA1 with Stigmasterol. **C**, Structural model of HSP0AA1 with 2-methoxy-9,10-dihydrophenanthrene-4,5-diol. **D**, Structural model of JUN with beta-sitosterol. **E**, Structural model of JUN with Stigmasterol. **F**, Structural model of JUN with 2-methoxy-9,10-dihydrophenanthrene-4,5-diol.

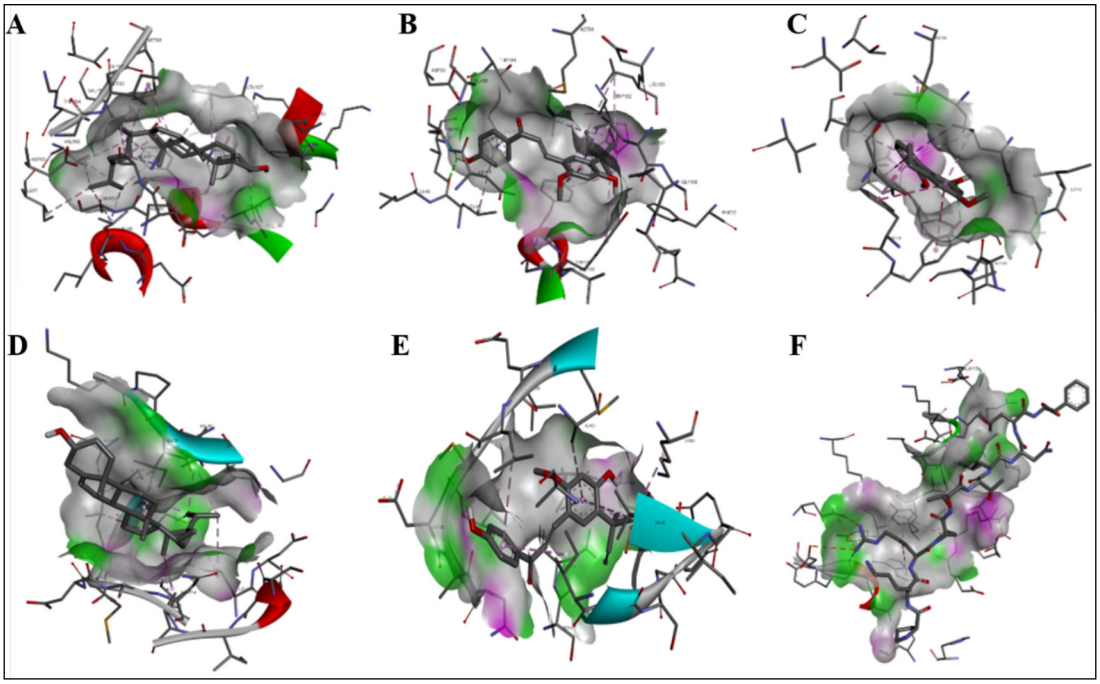

Figure 7. Binding mode of proteins and different ligands. **A**, Structural model of HSP90AA1 with beta-sitosterol. **B**, Structural model of HSP90AA1 with Stigmasterol. **C,** Structural model of HSP0AA1 with 2-methoxy-9,10-dihydrophenanthrene-4,5-diol. **D**, Structural model of JUN with beta-sitosterol. **E**, Structural model of JUN with Stigmasterol. **F**, Structural model of JUN with 2-methoxy-9,10-dihydrophenanthrene-4,5-diol.

therapy, chemotherapy, radiotherapy, and targeted therapy, 35%-40% of patients show recurrence and metastasis after the operation, which cannot be cured and eventually increases the risk of death[2]. The emergence of targeted drugs has led to a breakthrough in BC treatment. The earliest target drug is ER antagonist, which is now the basis of endocrine therapy for breast cancer. It is widely used in clinics[17]. Mature anti-HER-2 therapy has a good therapeutic effect in neoadjuvant therapy, adjuvant therapy, and late treatment[18]. PARP inhibitors have found new vitality for patients with breast cancer and BRCA1/2 mutation[19]. Targeted therapy is effective and has few adverse reactions and obvious advantages in clinical applications. However, few targeted drugs used in breast cancer cannot meet the needs of patients with breast cancer.

Rhapontici Radix - Cremastrae Pseudobulbus drug pair has a good curative effect on BC[20]. The mechanism of action was elucidated by network pharmacology. Sitosterol can be used as an effective autophagic agent. Llaverias et al[21] found that phytosterol can inhibit tumor growth in hereditary breast cancer. Other studies[22] indicated that sitosterol has a therapeutic effect on breast cancer.

Oestrogen is a category of steroid hormones playing important roles in the regulation of normal breast epithelium growth; increased risk of BC is related to excessive exposure to oestrogen[23]. In all of the study cases, estrogen resulted in significant softening of BC cells, while cells grown in hormone-free media resulted in increased elastic and viscoelastic moduli under study. In addition, fluorescence microscopy revealed changes in the distribution of E-cadherin in cells cultured under estrus conditions. In addition, contact among cells seems to be weakened. Atomic Force Microscopy (AFM) imaging can support these results, which showed surface roughness change, cell height, and cell-to-cell contact after estrogen treatment[24].

Stigmasterol, 2-methody-9,10-dihydrophenanthrene-4, 5-diol, and beta-sitosterol were important components for treating BC in *Rhapontici Radix - Cremastrae Pseudobulbus* drug pair. In terms of targets, *JUN* had the largest degree. *JUN* has a certain relationship with the proliferation and angiogenesis of breast cancer. *JUN* gene protein is closely related to angiogenesis. The *VEGF* gene promoter contains four *Ap-1* binding sites. The synthesis of *VEGF* was increased under hypoxia or anoxia. The overexpression of *JUN* leads to the reduction of the sensitivity of breast can-

cer cells to tamoxifen[25]. Therefore, *JUN* targeted therapy is an effective new method to prevent tumor angiogenesis[26]. *CASP3* ranks second. The expression of *CASP3* protein was low in many tumor tissues[27]. In addition, the expression of *CASP3* gradually decreased in breast adenosis, breast fibroadenoma, and breast cancer, and the lower the expression rate of *CASP3* protein in breast cancer, the higher the clinical stage. Therefore, in future research, targets with higher levels, such as *JUN* and *CASP3,* are effective therapeutic targets. Studies[28] at epidemiological, cellular, and genetic levels suggest that the pathogenesis of human breast cancer involves polypeptide hormone prolactin.

Conclusions

Our research presents insights into the mechanism of the anti-breast cancer effect of the *Rhapontici Radix -Cremastrae Pseudobulbus* drug pair. By using network pharmacology, potential targets can be experimentally verified.

Conflict of Interest
The authors declare that they have no conflict of interests.

Data Availability
All data are available upon request by contacting the corresponding author.

Funding
No funding was used in this study.

Authors' Contributions
YJX and CT designed the research, JPQ and HQG collected and processed the data, and ZWW and QL wrote the manuscript. All authors acknowledged and approved the final version of the manuscript.

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Ethics Approval and Informed Consent
This manuscript does not require ethical approval and informed consent.

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