Regular article

Study on the mechanism of Zedoary turmeric oil combined with docetaxel in the treatment of breast cancer based on network pharmacology and molecular docking technology

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Abstract

In order to reveal the multi-target pharmacological mechanism of Zedoary turmeric oil combined with docetaxel in the treatment of breast cancer, we used network pharmacology and molecular docking. The targets of docetaxel were retrieved from the Swiss Target Prediction database. The active components of *Curcuma* Zedoary turmeric were screened using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), with criteria set as oral bioavailability OB ≥ 30% and drug-likeness DL ≥ 0.1. Potential targets of these components were subsequently predicted. Breast cancer-related targets were retrieved from the OMIM and GeneCards databases. The Venny tool was used to identify 177 overlapping targets between docetaxel, Zedoary turmeric oil, and breast cancer, followed by protein-protein interaction (PPI) analysis. Gene Ontology (GO) functional enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the Metascape database. A drug-breast cancer-KEGG pathway target network was constructed using Cytoscape 3.8.0. Molecular docking was employed to verify the binding ability between drugs and core targets. Results showed that the combined treatment may exert anti-breast cancer effects through key targets such as MAPK1, PIK3CA, and HSP90AA1, primarily implicating the biological process of protein phosphorylation and engaging the PI3K-Akt signaling pathway. This study successfully predicted the key targets and enriched pathways of Zedoary turmeric oil combined with docetaxel for breast cancer treatment, providing new insights for further research and development.

Keywords: Zedoary turmeric oil; docetaxel; breast cancer; network pharmacology; molecular docking

1 Introduction

Breast cancer is the most common malignant tumor and the second leading cause of cancer-related deaths among women worldwide, posing a significant threat to female health [1]. In recent years, increasing life pressures from various aspects such as work, family, and society have disrupted normal estrogen levels in women, leading to a rising incidence of breast cancer among younger populations. It is predicted that in the next 25 years, the incidence and mortality of breast cancer in developed countries could increase by up to 60%.

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According to the 2022 Breast Cancer Diagnosis and Treatment Guidelines [2], comprehensive treatment strategies are primarily adopted, including multiple therapeutic approaches such as surgery, radiotherapy, chemotherapy, endocrine therapy, targeted therapy, and traditional Chinese medicine.

Breast cancer is a heterogeneous disease with several molecular subtypes, including Luminal A, Luminal B, HER2-positive, and triple-negative breast cancer (TNBC). Luminal A and B subtypes are hormone receptor-positive, which respond well to endocrine therapy. HER2-positive breast cancer is characterized by amplification of the HER2 gene and is treated with HER2-targeted therapies. TNBC, which lacks estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, is associated with aggressive behavior, poor prognosis, and limited treatment options. Recent studies have highlighted the importance of subtype-specific therapies for improved clinical outcomes. For example, TNBC frequently exhibits dysregulation of the PI3K/AKT pathway and high expression of heat shock proteins, making it a potential target for combination therapy [3-5].

Docetaxel, a taxane-based chemotherapeutic agent, exhibits potent anticancer activity by stabilizing microtubule assembly and inhibiting depolymerization. It exerts antitumor effect by binding to the β-tubulin subunit of microtubules, stabilizing microtubule polymerization, arresting the cell cycle at the G2/M phase, and inhibiting mitosis [3]. Despite its therapeutic efficacy in the treatment of various cancers including prostate cancer, breast cancer, and brain cancer, docetaxel causes significant adverse effects, greatly affecting clinical treatment progress [6,7]. Additionally, chemoresistance may develop during treatment, which is a major cause of chemotherapy failure [8,9]. Currently, combination therapy is widely used in clinical practice. Combination therapy involves administering two or more treatments with different mechanisms of action to overcome drug resistance, reduce effective chemotherapy doses, and minimize side effects. Synergistic combination therapy helps improve therapeutic outcomes. Recently, there has been considerable focus on developing bioactive components from natural plants with anticancer activity. The main bioactive component extracted from the dried rhizomes of Zedoary turmeric is volatile oil. This oil contains various components such as curcumol, β-elemene, and curdione. These compounds have been shown to exert multi-target antitumor effects against various malignancies, including breast cancer and liver cancer.

Network pharmacology studies the material basis of drug actions on organisms at the molecular level, reveals intrinsic molecular mechanisms, and discovers new drug targets and molecular mechanisms related to drug activity [8,9]. This study employed network pharmacology methods to integrate compound database mining, bioinformatics databases, and network analysis. This integrated approach facilitates a shift from the “one drug, one target” strategy of chemical drugs to a “one drug, multiple targets” approach (Fig. 1). By establishing a drug-target-KEGG pathway network, we explored the multi-target mechanism of Zedoary turmeric oil combined with docetaxel in breast cancer treatment at the gene and pathway levels, providing a foundation and direction for clinical drug therapy and the development of new drug targets [10].

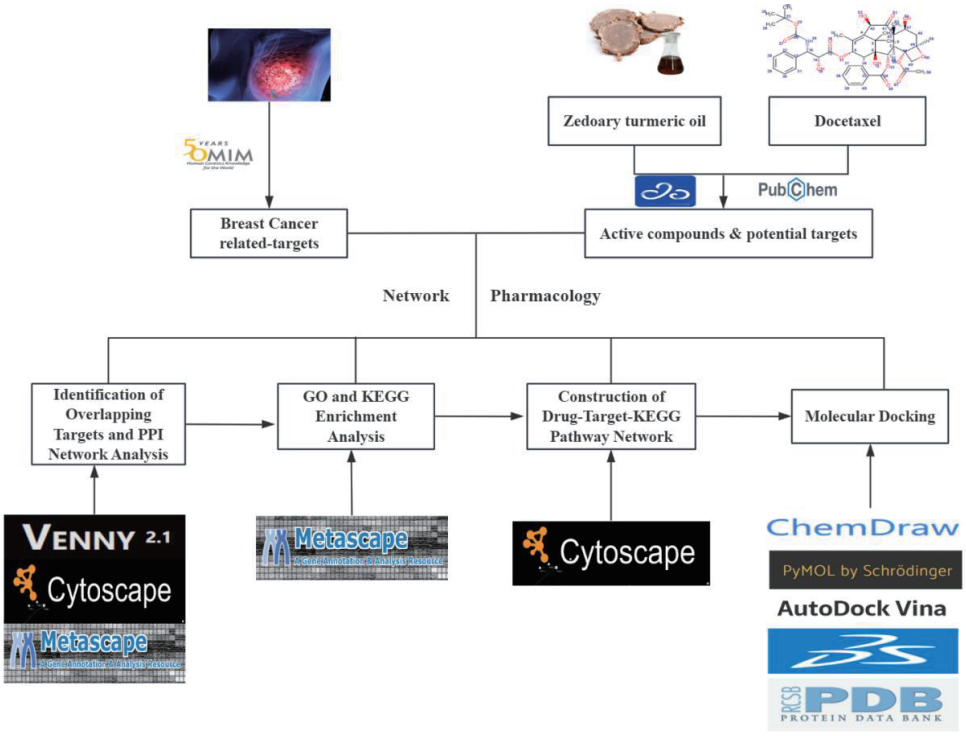

Fig. 1 Flow chart of network pharmacology

2 Materials and methods

2.1 Screening of targets for Zedoary turmeric oil, docetaxel, and breast cancer

The 2D and 3D structures of docetaxel were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The structural formulas were imported into the SwissTargetPrediction database (http://www.swisstargetprediction.ch/) to predict drug targets. Using the TCMSP platform, active compounds of Zedoary turmeric were retrieved with "Ezhu" as the search term and screened using criteria of human oral bioavailability OB ≥ 30% and drug-likeness DL ≥ 0.1. Literature mining from domestic and international databases was used to supplement and consolidate active components obtained through both approaches, and targets corresponding to the active compounds of Zedoary turmeric were obtained. To acquire comprehensive breast cancer targets, multiple databases were integrated for analysis, including the OMIM database (https://www.omim.org/) and GeneCards database (https://www.genecards.org/), using "breast cancer" as the search term. Targets from each database were integrated and deduplicated establish a final count of disease-associated targets.

2.2 Identification of overlapping targets and PPI network analysis

The Venny tool (https://bioinfogp.cnb.csic.es/tools/venny/index.html) was used to identify overlapping targets between drugs and disease. These targets were imported into the STRING database (https://string-db.org/) to generate a TSV file of protein interactions. This file was used in Cytoscape 3.8.0 to construct a protein interaction network. Finally, topological data analysis of the network was performed using the Network Analyzer tool.

2.3 GO and KEGG enrichment analysis

Overlapping genes were imported into the Metascape database (https://metascape.org/gp/index.html). With the species set to human, analyses were conducted for Cellular Component (CC), Molecular Function (MF), Biological Process (BP), and KEGG enrichment. Online analysis was performed using the bioinformatics platform.

2.4 Construction of drug-target-KEGG pathway network

The drug-target-KEGG pathway network was constructed using visualization software Cytoscape 3.8.0.

2.5 Molecular docking

ChembioDraw 3D software was used to draw the 3D chemical structures of docetaxel and key components of Zedoary turmeric oil, which were energy-minimized and exported as PDB files. The PDB database (https://www.rcsb.org/) was used to screen PDB files of key target proteins. PyMOL software was used to determine protein chains. AutoDock software was used to process receptors and ligands through dehydration, hydrogen addition, charge calculation, and other operations. Semi-flexible molecular docking was performed using AutoDock Vina 1.1.2 to determine optimal binding sites and calculate binding energies. Finally, Discovery Studio software was used for visualization and mapping.

3 Results

3.1 Analysis results of targets for Zedoary turmeric oil, docetaxel, and breast cancer

Based on the 2D and 3D chemical structures of docetaxel (Fig. 2), 107 drug-related targets were identified from the SwissTargetPrediction database. Using the TCMSP database, 17 active compounds meeting the criteria of OB > 30% and DL > 0.10 criteria were screened. This set was supplemented by 14 additional compounds identified through literature mining, resulting in a final list of 31 active ingredients. Corresponding potential protein targets for these 31 compounds were obtained from the TCMSP platform; 2D structural diagrams were acquired from the PubMed database and imported into SwissTargetPrediction to obtain protein targets. Targets obtained through both methods were integrated with duplicates removed, and 577 protein targets were obtained. Through GeneCards and OMIM databases, 15,298 breast cancer targets were retrieved. Targets with scores > 10 were selected and duplicates were removed, resulting in 2,136 targets.

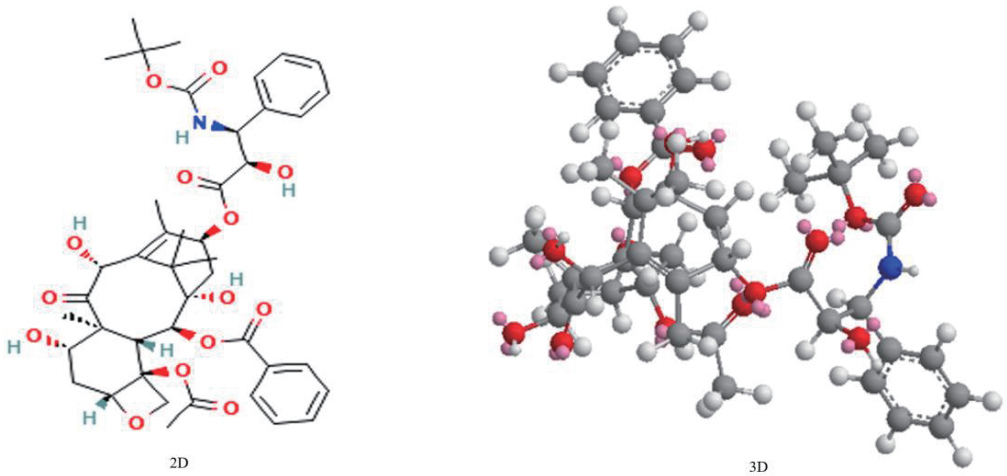

Fig. 2 2D and 3D structures of docetaxel

3.2 Key targets and PPI topological network analysis

Venny analysis identified 177 overlapping targets between disease and drug targets. These 177 targets were imported into the STRING database with confidence set to 0.900 and non-interacting proteins hidden. The TSV file of protein interactions was exported to obtain the PPI network diagram. Topological network analysis was conducted using Cytoscape 3.8.0 software, with darker colors and larger areas of the nodes indicating higher degree values. The thickness of connecting lines between targets represents the combined score, with thicker lines indicating closer connections between target proteins. MAPK3, SRC, MAPK1, AKT1, HSP90AA1, PIK3R1, PIK3CA, CDK1, JUN, and ESR1 were the top-ranked target proteins (Fig. 3), suggesting these target genes may play key roles in docetaxel treatment of breast cancer.

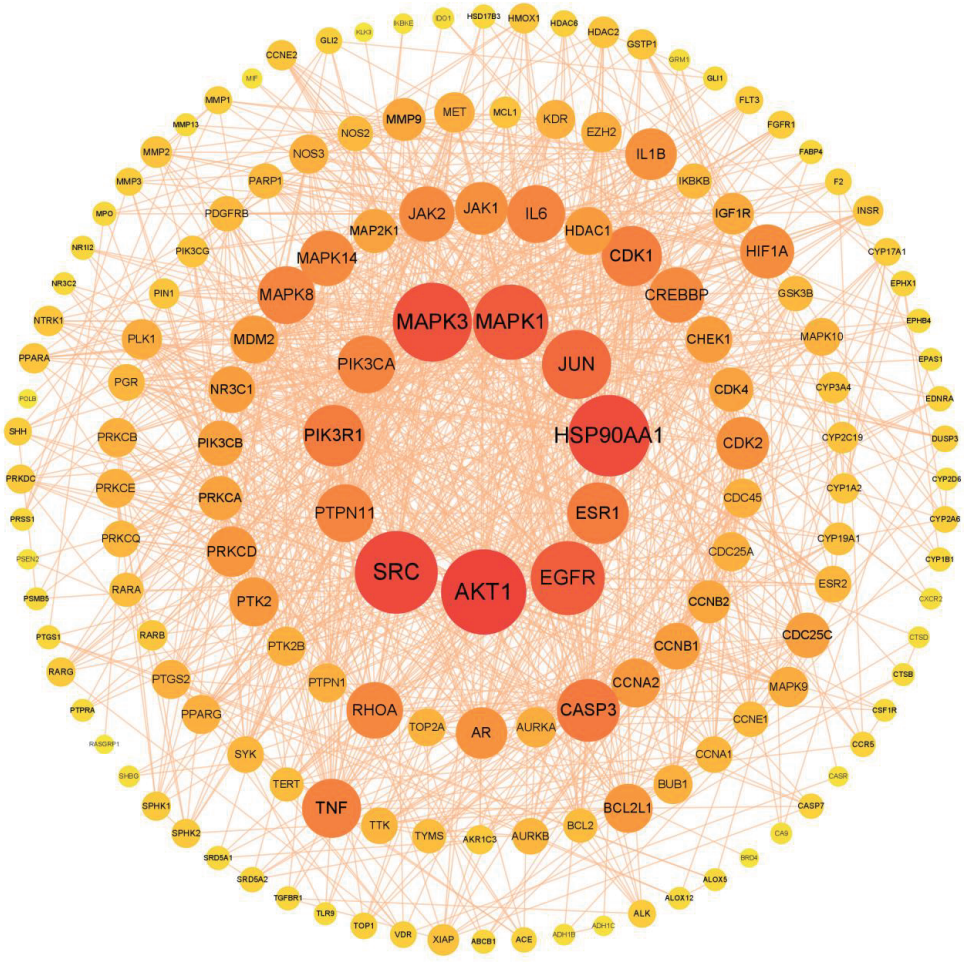

Fig. 3 PPI network of overlapping targets for docetaxel and breast cancer

3.3 Molecular mechanism of combined treatment

GO and KEGG enrichment analyses of the 177 overlapping targets identified 1,985 biological processes (BP), 99 cellular components (CC), and 203 molecular functions (MF). The top 10 terms ranked by *P*-value for each category were plotted as bar charts (Fig. 4). Macroscopic biological evaluation of these proteins based on GO enrichment results showed that these key anti-breast cancer

targets are mainly located in membrane rafts, membrane microdomains, transferase complexes, phosphorus-containing group transfer complexes, and protein kinase complexes. Molecular functions primarily involve protein kinase activity, phosphotransferase activity, and transcription factor binding. Biological processes mainly include protein phosphorylation, response to hormones, positive regulation of phosphorylation, regulation of kinase activity, and positive regulation of cell death.

KEGG enrichment analysis identified 192 pathways. Based on *P*-value and count value, bubble charts were generated to display the top 10 enriched pathways (Fig. 5). These proteins mainly participate in pathways such as cancer pathways, hepatitis B, lipid and atherosclerosis, progesterone-mediated oocyte maturation, AGE-RAGE signaling pathway in diabetic complications, and PI3K-Akt signaling pathway. The cancer pathway was most prominent with the highest enrichment degree, suggesting it might be an important pathway for drug treatment of breast cancer. Subgroup analysis revealed that the PI3K-Akt pathway is particularly relevant for TNBC.

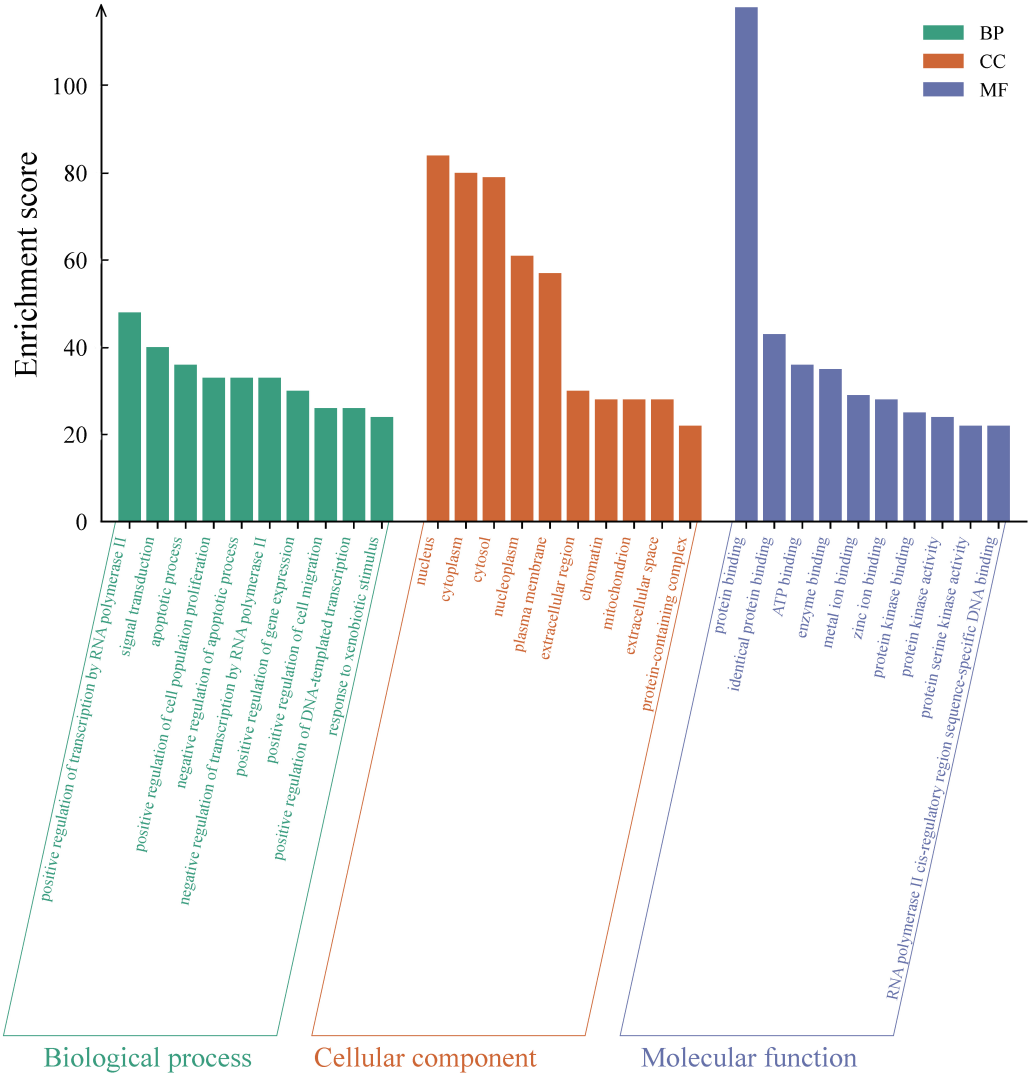

Fig. 4 GO enrichment analysis for docetaxel against breast cancer

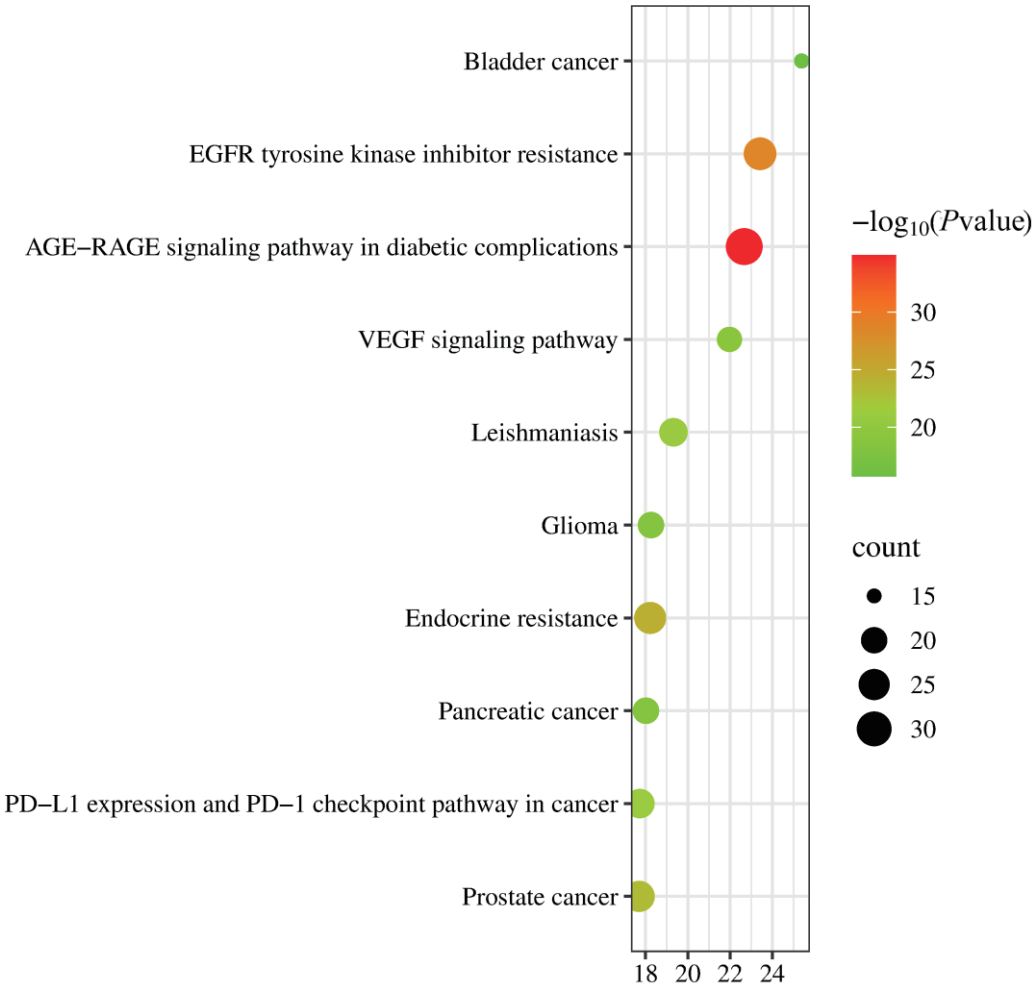

Fig. 5 KEGG pathway enrichment analysis for docetaxel against breast cancer

3.4 Construction of disease-drug-KEGG pathway target network

A network diagram with 218 nodes and 1,350 edges was constructed using Cytoscape 3.8.0 software (Fig. 6). Specifically, the combined treatment of Zedoary turmeric oil and docetaxel for breast cancer may exert molecular mechanisms through multiple biological processes in multiple nodes and multiple KEGG enrichment pathways. In the network diagram, the target proteins with the highest degree values were CYP19A1 (Degree = 28), JAK2 (Degree = 19), MAPK1 (Degree = 18), PIK3CA (Degree = 16), and AKT1 (Degree = 11). These targets are speculated to be the core targets for treating breast cancer. Core targets are associated with multiple KEGG enrichment pathways, such as cancer pathways, PI3K-Akt pathway, lipid and atherosclerosis, hepatitis B, AGE-RAGE signaling pathway, and progesterone-mediated oocyte maturation pathway. The main active components of ZTO include *β*-elemene, curcumol, and curdione, which are highlighted in the network as key nodes. The term "ZTO" refers to Zedoary Turmeric Oil, the standardized extract from Curcuma zedoaria.

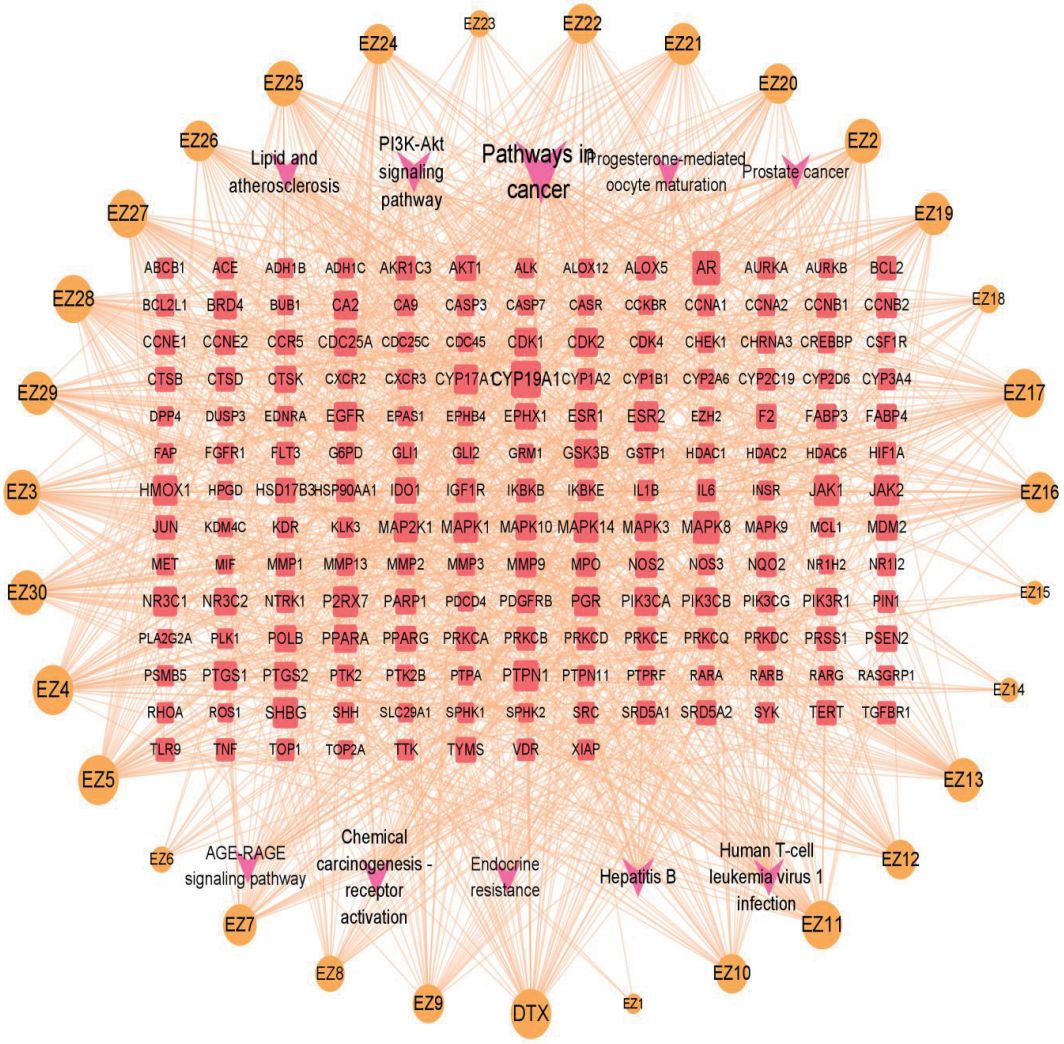

Fig. 6 Disease-drug-KEGG pathway target network

3.5 Molecular docking of Zedoary turmeric oil active components and docetaxel with core targets

Using AutoDock 4.2 software, structures were modified through ligand dehydration, hydrogen addition, and charge calculation. Semi-flexible molecular docking was performed using AutoDock Vina 1.1.2 to determine optimal binding sites and calculate binding energies (Table 1). Finally, PyMOL and Discovery Studio software were used for visualization and mapping (Figs. 7-9). The stability of docking conformations was analyzed based on the binding affinity. Lower binding affinity indicates more stable binding and stronger interaction forces between active components and core targets. Molecular docking of key targets analyzed from PPI and disease-drug-KEGG pathway target networks with key components of Zedoary turmeric oil (*β*-elemene, curcumol, curdione) and docetaxel showed binding energies less than -7 kcal/mol, suggesting these targets might be key targets for drug treatment of breast cancer. The most stable

target for drug docking was PIK3CA, with a binding energy of -17.1 kcal/mol for docetaxel. For ZTO components, *β*-elemene showed strong binding with MAPK1 (-8.9 kcal/mol) and HSP90AA1 (-8.5 kcal/mol). With active components as ligands and key targets as receptors, van der Waals forces, Pi-Sigma interactions, and other non-covalent interactions between ligands and receptors play key roles in the binding affinity of complexes. The ligand interacts with multiple residues on PIK3CA protein through van der Waals forces, such as TYR240, ALA220, PHE223, VAL224, and ASP190 residues. Residues ASN127 and ARG852 on PIK3CA protein function through Pi-Sigma. Additionally, compounds can exert affinity through interactions such as Alkyl, Pi-Alkyl, conventional Hydrogen Bond, and Carbon Hydrogen Bond with other residues. Therefore, given these interactions and docking energies, the substrate binds tightly and deeply to the amino acid cavity, indicating that small molecules are well-suited for the receptor binding pocket.

Table 1 Molecular docking binding energies (kcal/mol) of key components with core target

PDB ID	Gene	Docetaxel	*β*-elemene	Curcumol	Curdione
4ZZN	MAPK1	−14.8	−8.9	−9.4	−9.5
7L1C	PIK3CA	−17.1	−8.7	−9.5	−8.7
1UNR	AKT1	−12.5	−7.5	−7.8	−7.8
3T0H	HSP90AA1	−12.7	−8.5	−9.1	−8.9

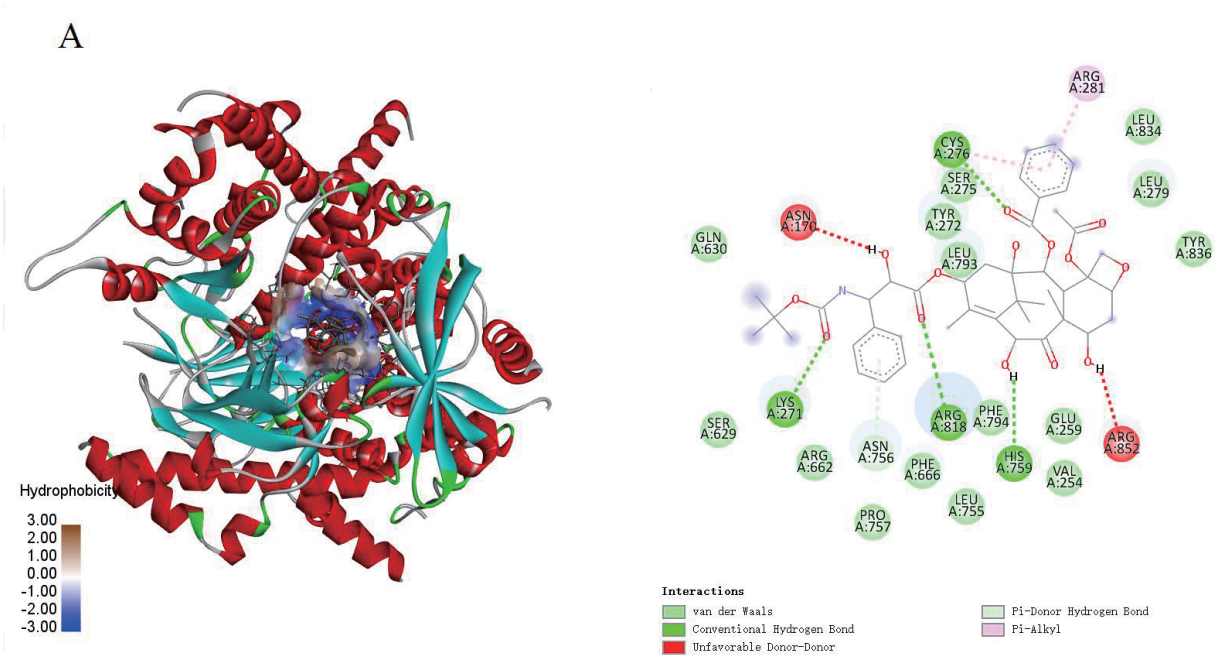

Fig. 7 Molecular docking diagram of docetaxel and PIK3CA

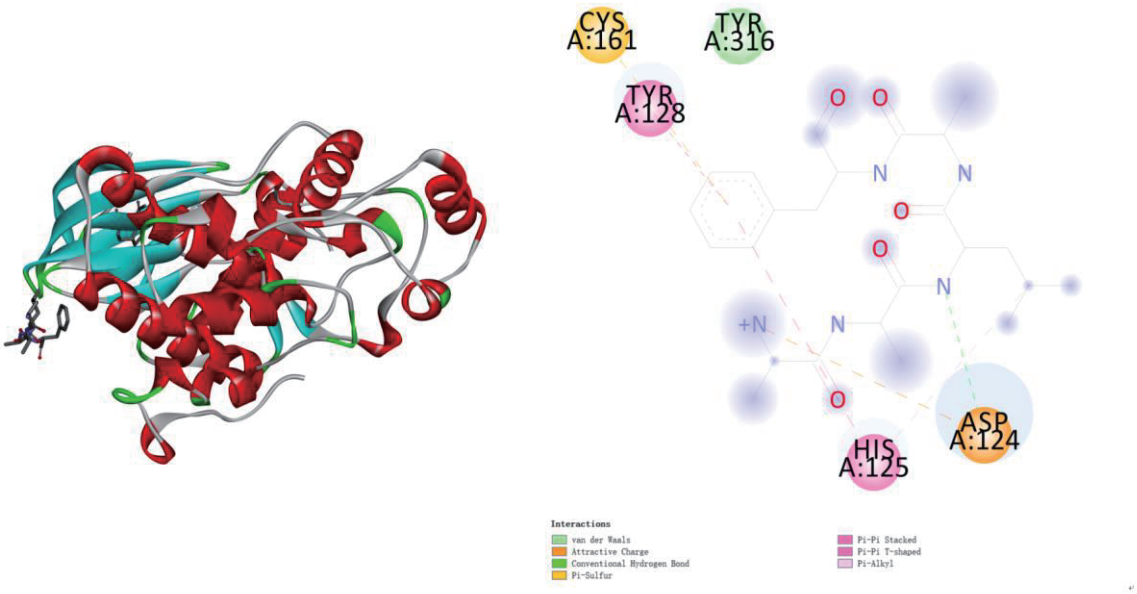

Fig. 8 Molecular docking diagram of β-elemene and MAPK1

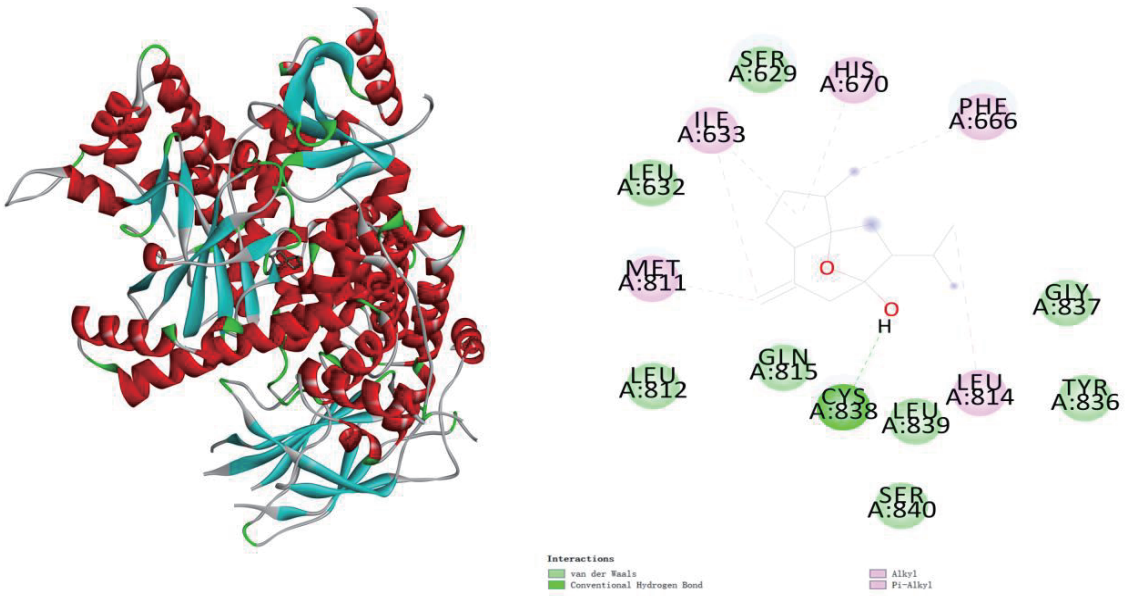

Fig. 9 Molecular docking diagram of curcumol and PIK3CA

4 Discussion

Docetaxel is a widely used chemotherapeutic drug for targeted metastatic breast cancer, but long-term use can lead to drug resistance and toxicity in cancer patients. Therefore, we had combined it with Zedoary turmeric oil, an extract from the natural antitumor plant Zedoary turmeric, to overcome resistance and reduce the effective dose of chemotherapy, thereby minimizing side effects [11]. To elucidate the pharmacological mechanism by which Zedoary turmeric oil and docetaxel

synergistically treat breast cancer, this study integrated network pharmacology and molecular docking. We systematically explored the relevant treatment targets, biological processes, and pathways to identify new therapeutic targets and predict related molecular markers for breast cancer treatment.

PPI network was constructed based on the overlapping targets between disease and drugs, predicting core targets such as MAPK3, SRC, MAPK1, AKT1, HSP90AA1, PIK3R1, PIK3CA, CDK1, JUN, and ESR1. MAPK, also known as extracellular signal-regulated kinase (ERK), encodes proteins involved in various cellular processes such as proliferation, differentiation, transcriptional regulation, and development [12,13]. ERK mediates mitogen-induced proliferation signals from the cell membrane to the nucleus through phosphorylation of 90 kDa ribosomal S6 kinase (p90RSK2) [14]. MAPK mutations are associated with many human cancers, including breast cancer, prostate cancer, and ovarian cancer [15,16]. Heat shock protein 90-alpha (HSP90AA1) is a molecular chaperone protein that plays an important role in tumor development and is highly expressed under stimulating conditions such as trauma, infection, and tumors. Newly formed HSP90AA1 can be secreted into the extracellular environment or enter the nucleus to stimulate immune memory formation and participate in tumor formation. Experiments have demonstrated that HSP90AA1 plays important roles in DNA damage regulation, cell cycle regulation, gene expression, and carcinogenesis. In cancer cells, HSP90AA1 stimulates cell survival, growth, and invasion, serving as a cancer biomarker [17]. Liu et al. used online databases and clinical parameters to detect the diagnostic value of plasma HSP90AA1 in breast cancer, finding that HSP90AA1 in the HSP90 family is a promising diagnostic and prognostic biomarker for breast cancer [18]. Additionally, HSP90AA1 promotes cancer cell proliferation, metastasis, invasion, and epithelial-mesenchymal transition in various diseases, indicating that HSP90AA1 might be a potential target for cancer treatment, including breast cancer. In molecular docking, PIK3CA showed the strongest binding ability with docetaxel, suggesting that efficacy might be enhanced through this target. Studies have found activating mutations in PIK3CA in approximately 30-40% of cancer patients. As a member of the PI3K protein family, PIK3CA can induce overactivation of the α isoform of phosphatidylinositol 3-kinase. Mutations in this gene can lead to abnormal activation of the PI3K/AKT pathway, promoting unlimited cell proliferation, inhibiting tumor cell apoptosis, and causing abnormal cell differentiation [19]. Therefore, PIK3CA mutations are closely related to carcinogenesis. Current research has found that PIK3CA mutations are associated with the occurrence and development of breast cancer [20,21]. Correlating with breast cancer clinical staging, PIK3CA mutations may serve as a risk factor for poor prognosis in hormone receptor-positive breast cancer patients, making it a biological target for exploring new treatment strategies for hormone receptor-positive breast cancer patients [22,23].

In addition to screening key targets, this study constructed a drug-target-KEGG pathway network based on GO and KEGG enrichment pathway results, facilitating exploration of the important mechanisms of Zedoary turmeric oil and docetaxel in the treatment of breast cancer. BP results showed a high correlation with protein phosphorylation. Protein phosphorylation is an important post-translational modification in tissues and cells. When affected by the microenvironment, abnormal protein phosphorylation can occur, leading to the onset of various malignant diseases. Therefore, these differential phosphorylation modifications can serve as potential targets for disease detection or treatment, especially in cancer, since phosphorylation modifications in cancer cells and the tumor microenvironment often differ significantly from

normal cells. Tang et al. [24] screened and identified plasma phosphorylated protein markers associated with recurrence of ER-positive breast cancer, identifying 9 differentially expressed phosphorylated protein markers compared to newly diagnosed patients, providing new markers for monitoring breast cancer treatment efficacy [25]. Relevant literature reports that clinically, phosphorylated AKT can be detected to assess survival, prognosis, and outcomes in breast cancer patients. High expression of phosphorylated AKT can increase expression of downstream P16 protein in cancer cells, enhancing cancer cell infiltration and adhesion, thereby affecting the degree of breast cancer deterioration [26]. Additionally, it is related to responses to hormones, regulation of kinase activity, and positive regulation of cell death. KEGG enrichment showed that the mechanism of action may involve the AGE-RAGE signaling pathway and PI3K-Akt signaling pathway. Studies show that about 20% of breast cancer patients exhibit lymphedema during clinical treatment [27]. Activation of the AGE-RAGE axis can participate in activating multiple downstream signaling pathways, such as oxidative stress, inflammation, and fibrosis in diabetic nephropathy [28,29]. Core drugs may inhibit the activation of the AGE-RAGE axis, thereby regulating the progression of diabetic nephropathy and exerting edema-reducing effects. The PI3K/AKT signaling pathway is activated by enzyme-linked receptors and is crucial for cell differentiation, proliferation, energy and glucose metabolism, apoptosis, cellular response to oxidative stress, and angiogenesis. In breast cancer, the PI3K pathway shows mutations in genes encoding catalytic and regulatory subunits. The most common mutations are located in exons 9 and 20, identified in tumor tissues and circulating DNA from all breast cancer subtypes [30,31]. Mutations in breast cancer also occur in RTK receptors such as HER2, whose phosphorylation leads to PI3K/AKT activation [32,33]. In summary, research on mutations in the PI3K/AKT signaling pathway and their inhibitors may be truly beneficial for patients diagnosed with breast cancer. Additionally, AKT1, a subtype of AKT, is an important downstream target in the PI3K/AKT signaling pathway, regulating tumor growth, proliferation, apoptosis, survival, and invasiveness of tumor cells. Breast cancer development is often manifested as alterations in PI3K/AKT signaling, and malignant tumor formation may be related to AKT overexpression, which participates in local tumor growth [34]. AKT1 can regulate the cell cycle, mitigate the effects of cell cycle inhibitors, and thereby affect tumor growth [35]. Therefore, it can be inferred that the mechanism of Zedoary turmeric in treating breast cancer may involve regulating the key target AKT1 on the PI3K/AKT signaling pathway, participating in the biological process of cell cycle regulation to exert anticancer effects.

5 Conclusion

This study elucidated the multi-target pharmacological mechanism of docetaxel in treating breast cancer from the perspective of network pharmacology and molecular docking. The drug may exert anti-breast cancer effects through key targets such as MAPK1, PIK3CA, and HSP90AA1, via biological processes including protein phosphorylation, response to hormones, and positive regulation of cell death, as well as through enriched pathways such as the AGE-RAGE signaling pathway, PI3K-Akt signaling pathway, and progesterone-mediated oocyte maturation pathway. Since computational methods in systems biology may yield predictions inconsistent with actual results, our research group plans to conduct *in vitro* and *in vivo* experiments in subsequent studies to further validate the predicted results.

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