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ORIGINAL ARTICLE

Exploring targets and signaling pathways of paeonol involved in relieving inflammation based on modern technology

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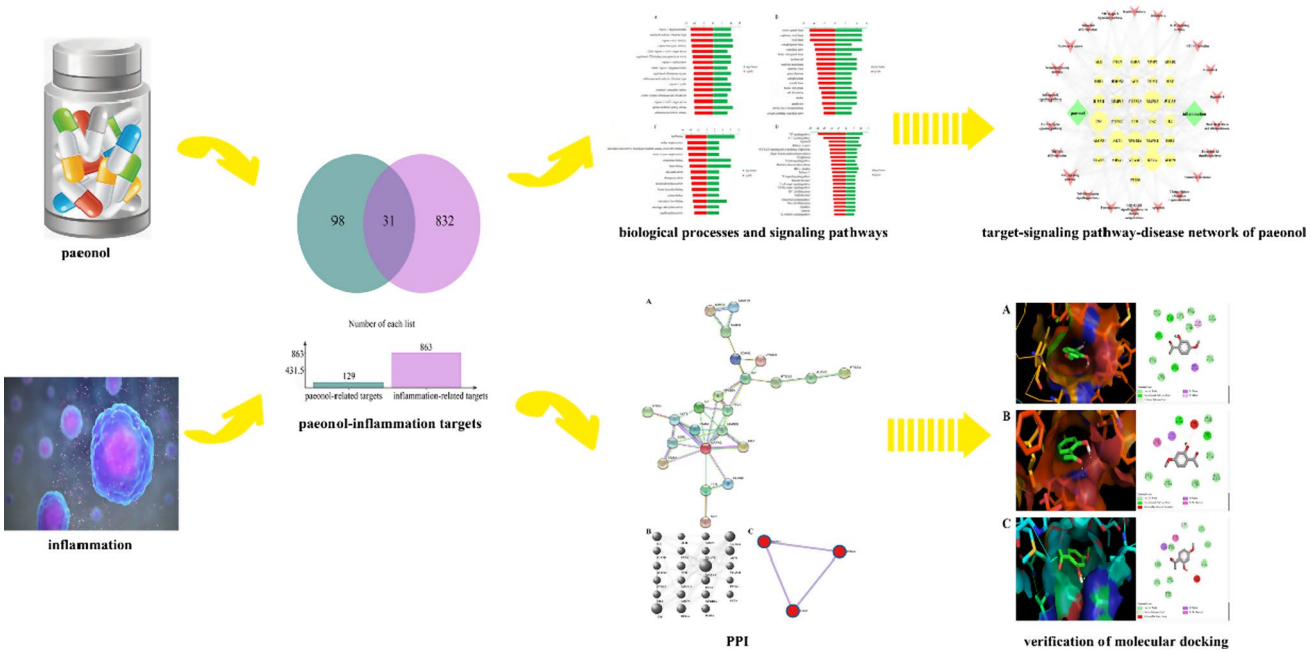
Abstract

Paeonol, derived from natural plants (*Moutan Cortex*), has a wide range of biological effects, including anti-inflammatory and antitumor effects as well as favorable effects against cardiovascular and neurodegenerative diseases. The anti-inflammatory action is the main pharmacological activity of paeonol and has the greatest clinical relevance. However, the anti-inflammatory mechanism of paeonol has not been reported in sufficient detail. We systematically analyzed the anti-inflammatory mechanism of paeonol using network pharmacological databases and platforms, including TCMSP, Swiss TargetPrediction, OMIM, DrugBank, TTD, Jevnn, STRING11.0, and Metascape. Furthermore, we used high-throughput molecular docking method to prove the results of the above analyses, providing a reference for exploring the mechanism of paeonol and developing targeted drugs.

Graphic abstract



Keywords Paeonol · Inflammation · Network pharmacology · Molecular docking · Target

Jian-hong Qi and Fang-xu Dong have contributed equally to this work.

Extended author information available on the last page of the article

Abbreviations

SUV	Solar ultraviolet
TOPK	T-LAK cell-derived protein kinase
MAPKs	Mitogen-activated protein kinase

ERK	Extracellular regulated protein kinase
ERBB2	Epidermal growth factor receptor 2
PPI	Protein–protein interaction network
GO	Gene ontology
KEGG	Kyoto encyclopedia of genes and genomes
BP	Biological Processes
CC	Cellular components
MF	Molecular functions
MMP9	Matrix metalloproteinase-9
TNF	Tumor necrosis factor

Introduction

Paeonol has shown many pharmacological effects in various experiments in vivo and in vitro. In addition to anti-inflammatory and antitumor effects, it positively influences cardiovascular and neurodegenerative diseases. Paeonol has been shown to alleviate solar ultraviolet (SUV)-induced skin inflammation by acting on T-LAK cell-derived protein kinase (TOPK) [1], and mitogen-activated protein kinase (MAPKs)/extracellular regulated protein kinase (ERK)/p38 signaling pathway is an important pathway used by paeonol to alleviate specific dermatitis [2]. In cell and molecular experiments, paeonol has significantly inhibited the growth and proliferation of gastric cancer cells and promoted their apoptosis, and the mechanism may be closely related to epidermal growth factor receptor 2 (ERBB2) [3]. Paeonol can prevent atherosclerosis by acting on miR-126 to reduce the formation of low-density lipoprotein [4]. In addition, paeonol can improve neurodegenerative diseases such as Alzheimer's disease and depression by reducing reactive oxygen species (ROS) level, thereby playing a neuroprotective role [5, 6].

Studies of anti-inflammatory activity of paeonol began in the sixties of the twentieth century [7]. According to previous research findings, the anti-inflammatory effect of paeonol is its most prominent pharmacological effect. To further increase the understanding of the anti-inflammatory activity and the development of targeted drugs, we explored the anti-inflammatory mechanism of paeonol by network pharmacology. Moreover, the interactions of paeonol with the core target proteins were virtually verified based on Autodock vina software.

Materials and methods

Screening of paeonol-related targets

We searched potential targets of paeonol based on TCMSP (https://tcmspw.com/tcmsp.php) [8] and the Swiss TargetPrediction (http://www.swisstargetprediction.ch/) [9]. We standardized the symbols of target proteins in accordance with the Uniprot protein database (https://www.uniprot.org/) [10].

Screening of inflammation-related targets

Using the key words related to inflammation, such as "inflammation," "arthritis," "dermatitis," "organ inflammation," "colitis," "periodontitis," and "stomatitis," we screened 863 high-scoring targets for inflammation based on disease databases, including OMIM (https://omim.org/) [11], DrugBank (https://www.drugbank.ca/) [12], and TTD (http://db.idrblab.net/ttd/) [13].

Construction of PPI network for anti-inflammatory targets of paeonol

To fully understand the interaction between paeonol-related targets and inflammation-related targets, we used the Jevnn platform (http://www.bioinformatics.com.cn/static/others/jvenn/example.html) [14] to intersect these interactions and create a Venn diagram.

To construct the protein–protein interaction network (PPI) model, we entered the common targets into STRING11.0 (https://string-db.org/) [15].

Enrichment analysis of paeonol-inflammatory targets' function and pathways

Using Metascape platform (http://metascape.org/gp/index.html) (Zhou et al., 2019) for Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment (Table 3), we entered the anti-inflammatory targets of paeonol and set the test parameters ($P < 0.01$) to obtain the main biological processes and signaling pathways.

Construction of paeonol targets signaling pathways network

Based on Cytoscape software, we drew paeonol targets signaling pathways network to further study the anti-inflammatory mechanism of paeonol.

Virtual verification of molecular docking

Molecular docking is a virtual drug design technique to verify the interaction between receptor and ligand. We used molecular docking technology to verify the interaction between paeonol and core targets, so as to provide theoretical support for the results of network pharmacology.

Results

Screening of paeonol-related targets

Using "paeonol" as the keyword, we searched and saved 129 possible target proteins of paeonol from the TCMSP and the Swiss TargetPrediction databases.

Screening of inflammation-related targets

In our previous review of paeonol, we found that the anti-inflammatory effect of paeonol mainly involved "arthritis," "dermatitis," "organ inflammation," "colitis," "periodontitis," and "stomatitis." Using these keywords, we found 863 inflammation-related and non-repetitive targets based on the disease databases.

Screening of core targets

In order to analyze the association network of paeonol anti-inflammatory targets, we had to find the intersection of paeonol-related targets and inflammation-related targets and identified 31 common targets as shown in Fig. 1.

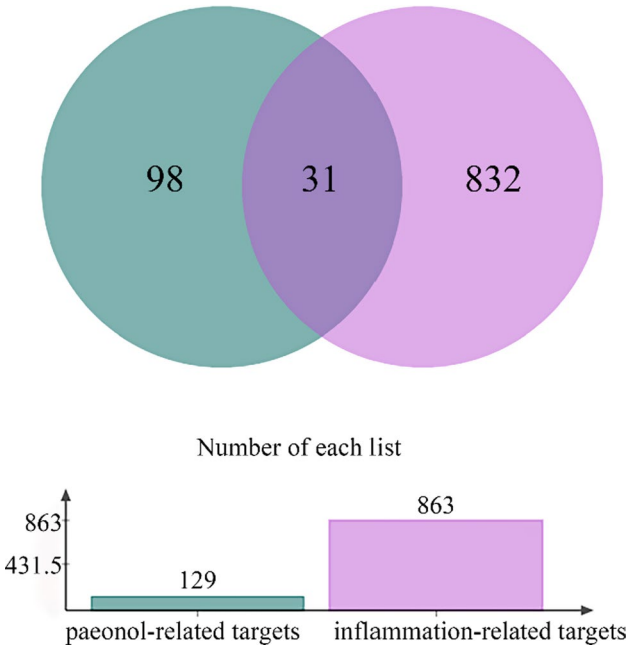


Fig. 1 Venn diagrams of paeonol-related targets and inflammation-related targets

Construction of PPI network for anti-inflammatory targets of paeonol

PPI network is an important means to show the importance of targets and their interactions. We constructed PPI network based on STRING11.0 platform and set the minimum interaction threshold (highest confidence ≥ 0.9). Finally, we obtained 23 relatively important targets in Fig. 2: RELA, TNF, AKT1, MAPK8, ALOX5, ESR1, NFKBIA, MMP9, IL2, VCAM1, RARA, ELANE, ALB, MET, ESR2, TTR, MMP3, PTEN, PTGS2, PTGS1, MAPK1, ICAM1, and MMP13. In particular, the module formed by MAPK1, RARA, and ESR2 may have potential biological significance for inflammation.

GO and KEGG analyses

We annotated and enriched the core targets on Metascape platform, and then analyzed their functions and pathways. GO analysis included the analysis of biological processes (BP), cellular components (CC), and molecular functions (MF). KEGG analysis focused on the enrichment and annotation of signaling pathways involved in paeonol anti-inflammatory actions. As shown in Fig. 3, we obtained 16 BP, 18 CC, 14 MF, and 22 signaling pathways, and most of these biological processes and signaling pathways are closely related to inflammation. In addition, TNF and IL-17 signaling pathways were the main signaling pathways detected (Table 1). Therefore, these results suggest that paeonol exerts anti-inflammatory effects through multitarget and multisignaling pathways.

Construction of paeonol targets signaling pathways network

To further explain the anti-inflammatory mechanism of paeonol, we used Cytoscape software to construct paeonol targets signaling pathways network. As shown in Fig. 4 and Table 2, there are 226 edges and 55 nodes in the network. In addition, the network also contains 31 targets and 22 signaling pathways. RELA and MAPK8 are the optimal targets, with the numerical value of degree 22 and the numerical value of closeness centrality 0.613636; TNF signaling pathway is the optimal target, with the numerical value of degree 17 and the numerical value of closeness centrality 0.514286. Therefore, paeonol may exert anti-inflammatory biological effects by acting on 33 main targets and 22 important signaling pathways.

Molecular docking of core targets

Virtual verification of 23 core targets obtained by PPI was carried out based on Autodock vina software [16]. The

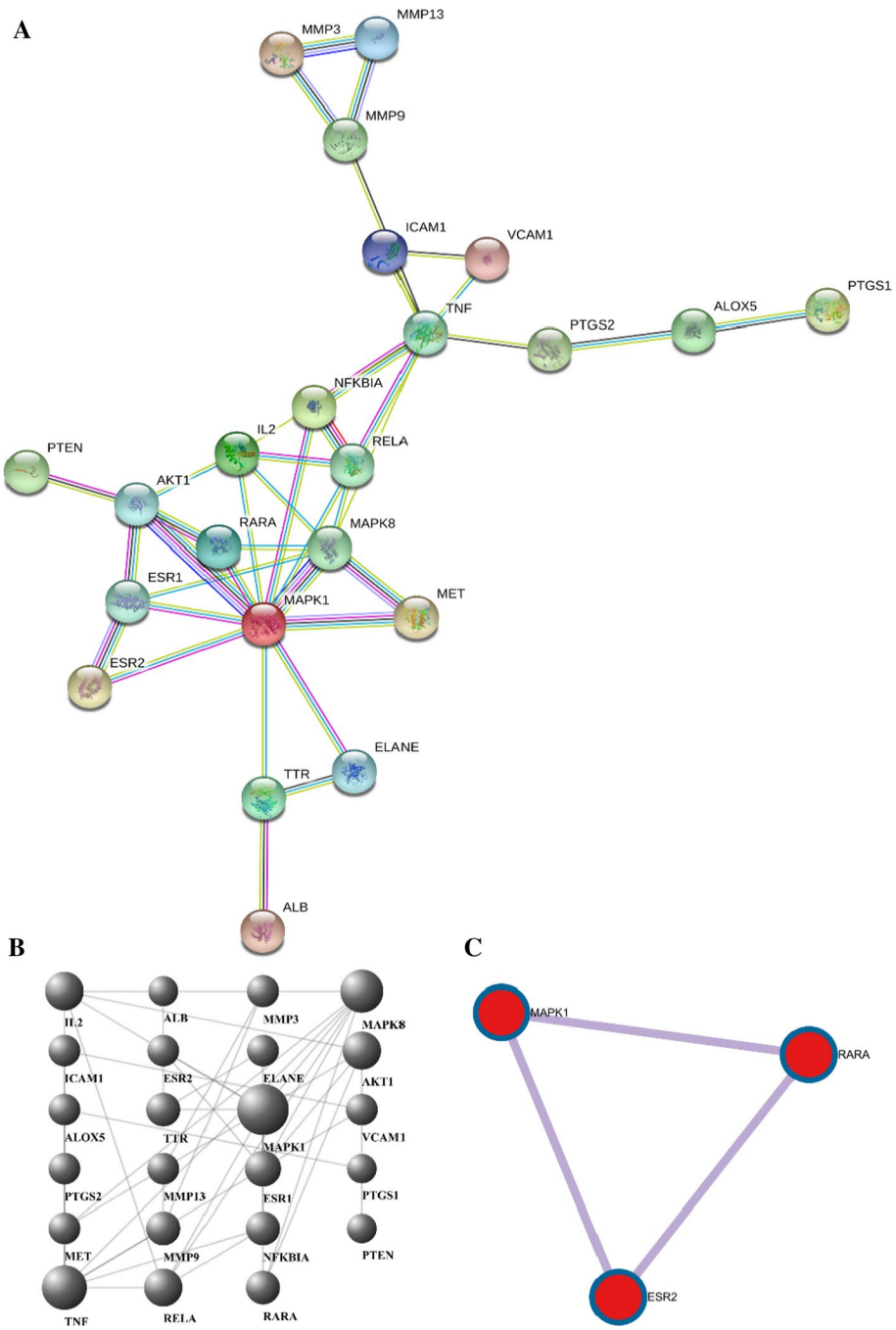


Fig. 2 PPI network for anti-inflammatory targets of paeonol. **a** Network nodes represent proteins: colored nodes mean the first shell of interactors. Node content: 3D structure of the protein. Edges of different colors represent protein–protein associations: light blue and purple edges mean known interactions (database & experiment); green, red, and blue edges mean predicted interactions (gene neighborhood, gene fusions, gene co-occurrence); yellow edges mean text mining; and black edges indicate co-expression. **b** The PPI network was processed by Cytoscape software: larger areas denote more important nodes. **c** Modules with potential biological significance in PPI

structures of target proteins (.pdb) and paeonol (.mol2) were downloaded from PDB database [17] and TCMSP database, respectively. Importantly, the screening of crystal structures for targets was based on the following principles: containing original ligand, high resolution, and high reliability. Paeonol was subjected to hydrogenation, charging, merging of non-polar hydrogen, and rotating chemical bonds by using AutodockTools software, and it was saved as PDBQT format file. The structures of target proteins were pretreated based on PyMol [18] and AutodockTools software, including hydrogenation, charging, definition of atomic types, merging of non-polar hydrogen, repairing of amino acid residues, removing water, ions, ligands, and excess amino acid chains, and finally saved as PDBQT files. Then, the config files of target proteins were created to set the parameters of grid box. The optimal binding energies between the 23 target proteins and paeonol were calculated by Autodock vina software. Smaller numerical values indicated stronger binding ability. The numerical values with binding energy less than − 5 kcal/mol account for 74% in Table 3, indicating that paeonol may

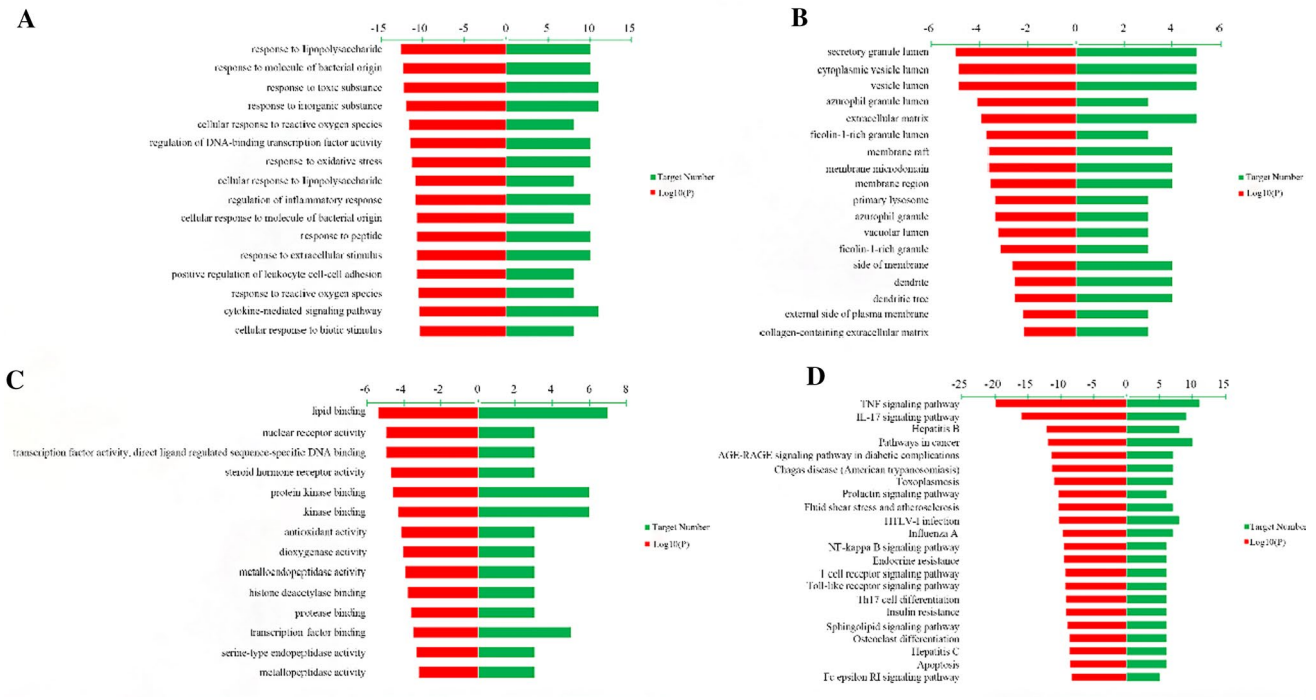


Fig. 3 GO and KEGG analyses of paeonol anti-inflammatory activity. **a** represents biological processes, **b** represents cellular components, **c** represents molecular functions, D represents signaling pathways

Table 1 Enrichment information of signaling pathways

Signaling pathway	Count	Log10 (P)	Targets
TNF signaling pathway	11	− 20.00294635	AKT1|ICAM1|MMP3|MMP9|NFKBIA|MAPK1|MAPK8|PTGS2|RELA|TNF|VCAM1
IL-17 signaling pathway	9	− 16.04429079	MMP3|MMP9|MMP13|NFKBIA|MAPK1|MAPK8|PTGS2|RELA|TNF
Hepatitis B	8	− 12.25489905	AKT1|MMP9|NFKBIA|MAPK1|MAPK8|PTEN|RELA|TNF
Pathways in cancer	10	− 11.97434934	AKT1|MET|MMP9|NFKBIA|MAPK1|MAPK8|PTEN|PTGS2|RARA|RELA
AGE-RAGE signaling pathway in diabetic complications	7	− 11.46555508	AKT1|ICAM1|MAPK1|MAPK8|RELA|TNF|VCAM1
Chagas disease (American trypanosomiasis)	7	− 11.37271885	AKT1|IL2|NFKBIA|MAPK1|MAPK8|RELA|TNF
Toxoplasmosis	7	− 11.05505232	AKT1|ALOX5|NFKBIA|MAPK1|MAPK8|RELA|TNF
Prolactin signaling pathway	6	− 10.35810608	AKT1|ESR1|ESR2|MAPK1|MAPK8|RELA
Fluid shear stress and atherosclerosis	7	− 10.35077372	AKT1|ICAM1|MMP9|MAPK8|RELA|TNF|VCAM1
HTLV-I infection	8	− 10.24468526	AKT1|ICAM1|IL2|NFKBIA|MAPK8|RELA|TNF|VCAM1
Influenza A	7	− 9.746401964	AKT1|ICAM1|NFKBIA|MAPK1|MAPK8|RELA|TNF
NF-kappa B signaling pathway	6	− 9.543195864	ICAM1|NFKBIA|PTGS2|RELA|TNF|VCAM1
Endocrine resistance	6	− 9.51542753	AKT1|ESR1|ESR2|MMP9|MAPK1|MAPK8
T-cell receptor signaling pathway	6	− 9.329065252	AKT1|IL2|NFKBIA|MAPK1|RELA|TNF
Toll-like receptor signaling pathway	6	− 9.303518428	AKT1|NFKBIA|MAPK1|MAPK8|RELA|TNF
Th17 cell differentiation	6	− 9.228377407	IL2|NFKBIA|MAPK1|MAPK8|RARA|RELA
Insulin resistance	6	− 9.228377407	AKT1|NFKBIA|MAPK8|PTEN|RELA|TNF
Sphingolipid signaling pathway	6	− 8.970385519	AKT1|MAPK1|MAPK8|PTEN|RELA|TNF
Osteoclast differentiation	6	− 8.715891959	AKT1|NFKBIA|MAPK1|MAPK8|RELA|TNF
Hepatitis C	6	− 8.695791279	AKT1|NFKBIA|MAPK1|MAPK8|RELA|TNF
Apoptosis	6	− 8.55937549	AKT1|NFKBIA|MAPK1|MAPK8|RELA|TNF
Fc epsilon RI signaling pathway	5	− 8.326499522	AKT1|ALOX5|MAPK1|MAPK8|TNF

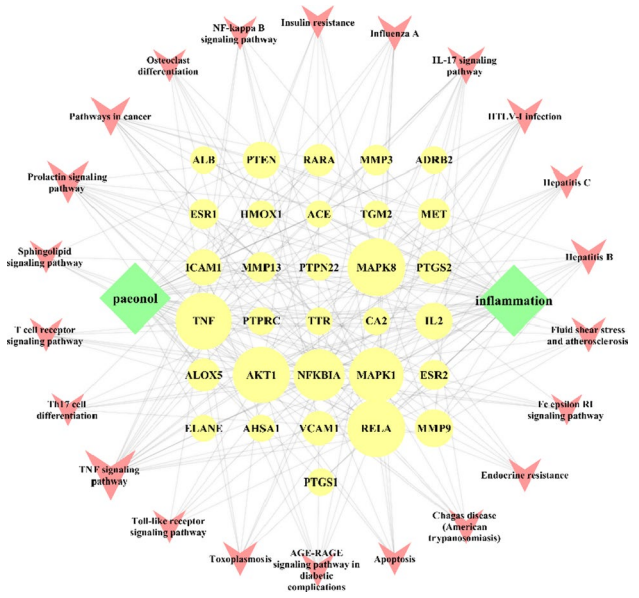


Fig. 4 Target-signaling pathway network of paeonol anti-inflammatory activity. From the inside to the outside: the circle is target, the diamond is paeonol and inflammation, and the inverted triangle is the signaling pathway. Node size: larger nodes indicate more important ones

have good binding activity with these target proteins [19]. In addition, the docking diagram of paeonol with the top three targets is shown in Fig. 5, and bonding types mainly include hydrogen bond and hydrophobic interaction.

Discussion

Inflammation is a spontaneous defensive response of the human body to "irritant." It usually manifests as redness, heat, swelling, and pain. "Irritant" refers to inflammatory factors, which can be divided into internal and external factors. Internal factors include tissue necrosis, accumulated metabolites, and allergic reactions. External factors include microorganisms (bacteria, viruses, fungi, parasites), physical factors (ultraviolet waves, mechanical damage, temperature), and chemical factors (strong acids, strong alkali, toxic substances). Generally, inflammation is beneficial to the body and helps the body to resist the attack of inflammatory factors. However, excessive inflammatory response can cause serious tissue damage and organ dysfunction [20]. Pruritus and organ damage are common diseases caused by inflammation. In addition, neurodegenerative diseases (Alzheimer's disease, depression, Parkinson's disease), cardiovascular disease, COVID-19, and cancer are also closely related to inflammation [21–23]. At present, nonsteroidal anti-inflammatory drugs are mainly used in the treatment of various inflammatory diseases, but there is a risk of gastrointestinal adverse reactions and hypersensitivity [24–26]. Paeonol has a wide range of pharmacological effects, of which the anti-inflammatory effect is the most important for clinical application, and the concern is that, paeonol has no obvious adverse reactions. Therefore, this study aimed to explore the molecular mechanism of paeonol anti-inflammatory action by network pharmacology and high-throughput molecular docking.

The anti-inflammatory effects of paeonol are mainly manifested in skin inflammation, arthritis, colitis, and organ damage. Paeonol alleviates UV-induced skin inflammation by inhibiting the release of IL-6, MMP-1, and TNF-α [27]. Targeting of the inflammatory factors is one of the important means to treat arthritis. Specifically, IL-1 plays a key role in the occurrence and development of arthritis. The paeonol-related inhibition of IL-1 can reduce the release of PGE2 and NO, thereby ensuring the normal life activities of chondrocytes [28]. The MAPK/ERK/p38 pathway is an important pathway used by paeonol in the treatment of colitis; it is related to the production of inflammatory factors and the clearance of free radicals [29]. Drugs, alcohol, obesity, and emotional agitation are important factors leading to liver injury. Paeonol exerts anti-inflammatory and antioxidant effects through the SIRT1/Nrf2/NF-κB signaling pathway, thereby reducing alcoholic hepatitis, which suggests that SIRT1 may be a potential drug target for the treatment of inflammation [30]. In China, paeonol has been successfully applied in the treatment of various inflammatory diseases for nearly 50 years [31], and it has achieved good curative effects. At present, paeonol preparations commonly used in clinical practice include paeonol ointment [32], paeonol cream [33], safflower paeonol ointment [34], paeonol injection [35], and compound paeonol dripping pill [36]. However, the poor oral bioavailability of paeonol limits its clinical application.

This study integrated the information from multiple databases and platforms to reveal the anti-inflammatory mechanism of paeonol by network pharmacology and verified the core targets by molecular docking. In the "target-signaling pathway network of paeonol anti-inflammatory action," we screened 22 core targets (e.g., RELA, MAPK8, TNF, AKT1, MAPK1, NFKBIA) and 33 main signaling pathways (e.g., TNF signaling pathway, Prolactin signaling pathway, Pathways in cancer, IL-17 signaling pathway) according to the "degree" value of nodes. The PPI network can find significant genes in the drug–target–disease network, and 23 core proteins such as ELANE, TNF, and MAPK8 were obtained. MAPK is one of the core targets in paeonol target-signaling pathway network (Fig. 4). It is an important kinase involved in intracellular and extracellular signal transduction. It is reported that pre-oral paeonol in rats can effectively reduce inflammatory diseases, including colitis, and the mechanism is related to the inhibition of the MAPK/

Table 2 Characteristic parameters of target-signaling pathway network

Type	Name	Degree	Closeness centrality
Target	RELA	22	0.613636
Target	MAPK8	22	0.613636
Target	TNF	21	0.6
Target	AKT1	21	0.6
Target	MAPK1	20	0.586957
Target	NFKBIA	18	0.5625
Target	MMP9	9	0.473684
Target	PTEN	8	0.465517
Target	IL2	8	0.465517
Target	ICAM1	8	0.465517
Target	VCAM1	7	0.457627
Target	PTGS2	6	0.45
Target	ALOX5	6	0.45
Target	RARA	5	0.442623
Target	MET	5	0.442623
Target	MMP3	4	0.435484
Target	MMP13	4	0.435484
Target	ESR2	4	0.435484
Target	ESR1	4	0.435484
Target	TTR	2	0.421875
Target	TGM2	2	0.421875
Target	PTPRC	2	0.421875
Target	PTPN22	2	0.421875
Target	PTGS1	2	0.421875
Target	HMOX1	2	0.421875
Target	ELANE	2	0.421875
Target	CA2	2	0.421875
Target	ALB	2	0.421875
Target	AHSA1	2	0.421875
Target	ADRB2	2	0.421875
Target	ACE	2	0.421875
Pathway	TNF signaling pathway	17	0.514286
Pathway	Prolactin signaling pathway	12	0.469565
Pathway	Pathways in cancer	10	0.453782
Pathway	IL-17 signaling pathway	9	0.446281
Pathway	Hepatitis B	8	0.439024
Pathway	HTLV-I infection	8	0.439024
Pathway	AGE-RAGE signaling pathway in diabetic complications	7	0.432
Pathway	Chagas disease (American trypanosomiasis)	7	0.432
Pathway	Toxoplasmosis	7	0.432
Pathway	Fluid shear stress and atherosclerosis	7	0.432
Pathway	Influenza A	7	0.432
Pathway	NF-kappa B signaling pathway	6	0.418605
Pathway	Endocrine resistance	6	0.418605
Pathway	T cell receptor signaling pathway	6	0.425197
Pathway	Toll-like receptor signaling pathway	6	0.425197
Pathway	Th17 cell differentiation	6	0.425197
Pathway	Insulin resistance	6	0.425197
Pathway	Sphingolipid signaling pathway	6	0.425197
Pathway	Osteoclast differentiation	6	0.425197

Table 2 (continued)

Type	Name	Degree	Closeness centrality
Pathway	Hepatitis C	6	0.425197
Pathway	Apoptosis	6	0.425197
Pathway	Fc epsilon RI signaling pathway	5	0.418605

Table 3 Optimal binding energies between paeonol and core targets

Rank	Target name	Protein name	PDB ID	Score (kcal/mol)
1	MMP9	Matrix metalloproteinase-9	6ESM	−7.4
2	MMP13	Collagenase 3	5B5O	−7.1
3	ALB	Albumin	6YG9	−6.8
4	PTGS2	Prostaglandin G/H synthase 2	5F19	−6.7
5	PTGS1	Prostaglandin G/H synthase 1	6Y3C	−6.7
6	MMP3	Stromelysin-1	1HY7	−6.6
7	RARA	Retinoic acid receptor alpha	3KMR	−6.4
8	MET	Hepatocyte growth factor receptor	4R1V	−6.3
9	ALOX5	Polyunsaturated fatty acid 5-lipoxygenase	3V98	−6.2
10	MAPK8	Mitogen-activated protein kinase 8	2XRW	−6
11	ESR1	Estrogen receptor	6VIG	−5.8
12	PTEN	Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN	1D5R	−5.7
13	MAPK1	Mitogen-activated protein kinase 1	4ZZN	−5.5
14	ESR2	Estrogen receptor beta	3OLL	−5.4
15	TTR	Transthyretin	4D7B	−5.3
16	IL2	Interleukin-2	4NEJ	−5.1
17	ELANE	Neutrophil elastase	5ABW	−5.1
18	TNF	Tumor necrosis factor	5UUI	−4.9
19	AKT1	RAC-alpha serine/threonine-protein kinase	1UNQ	−4.7
20	NFKBIA	NF-kappa-B inhibitor alpha	6Y1J	−4.7
21	ICAM1	Intercellular adhesion molecule 1	1IAM	−4.7
22	VCAM1	Vascular cell adhesion protein 1	1VCA	−4.6
23	RELA	Transcription factor p65	6NV2	−3.4

ERK/p38 signaling pathway [29]. TNF is one of the most important signaling pathways in paeonol target-signaling pathway network (Fig. 4). As a cytokine closely related to inflammation, it is a key indicator of many diseases. Paeonol can affect the expression of TNF-α, and TNF-α can activate NF-κB, thereby resulting in anti-inflammatory response. In addition, the functional modules including MAPK1, RARA, and ESR2 have important biological significance for the treatment of inflammation [37, 38]. According to the GO enrichment analysis results, the biological processes of paeonol anti-inflammatory action mainly involve response to inflammatory factors, regulation of DNA-binding transcription factor activity, and response to oxidative stress. Therefore, paeonol may play an anti-inflammatory role by regulating the related targets of these biological processes. The KEGG pathway analysis showed that paeonol anti-inflammation-related pathways mainly involved TNF signaling pathway and IL-17 signaling pathway. Allergic dermatitis is an inflammatory reaction of the skin caused by excessive immunity, and it belongs to allergic reactions. It has been reported that paeonol can reduce the release of lgE by regulating TNF and histamine, thereby playing an antiallergic role [39]. In addition, paeonol at different doses (200 and 400 mg/kg) has shown certain therapeutic effects on colitis in rats; specifically, it can block IL-17 signaling pathway and promote TGF-β1 production, thereby improving the pathological score of colon tissue [40]. Thus, TNF and IL-17-related signaling pathways may be an important molecular mechanism by which paeonol exerts its anti-inflammatory effects.

Molecular docking takes the active center of the target as the "docking pocket" and is an important means to verify the binding ability between drugs and targets, which can save a lot of time, manpower, material, and financial resources.

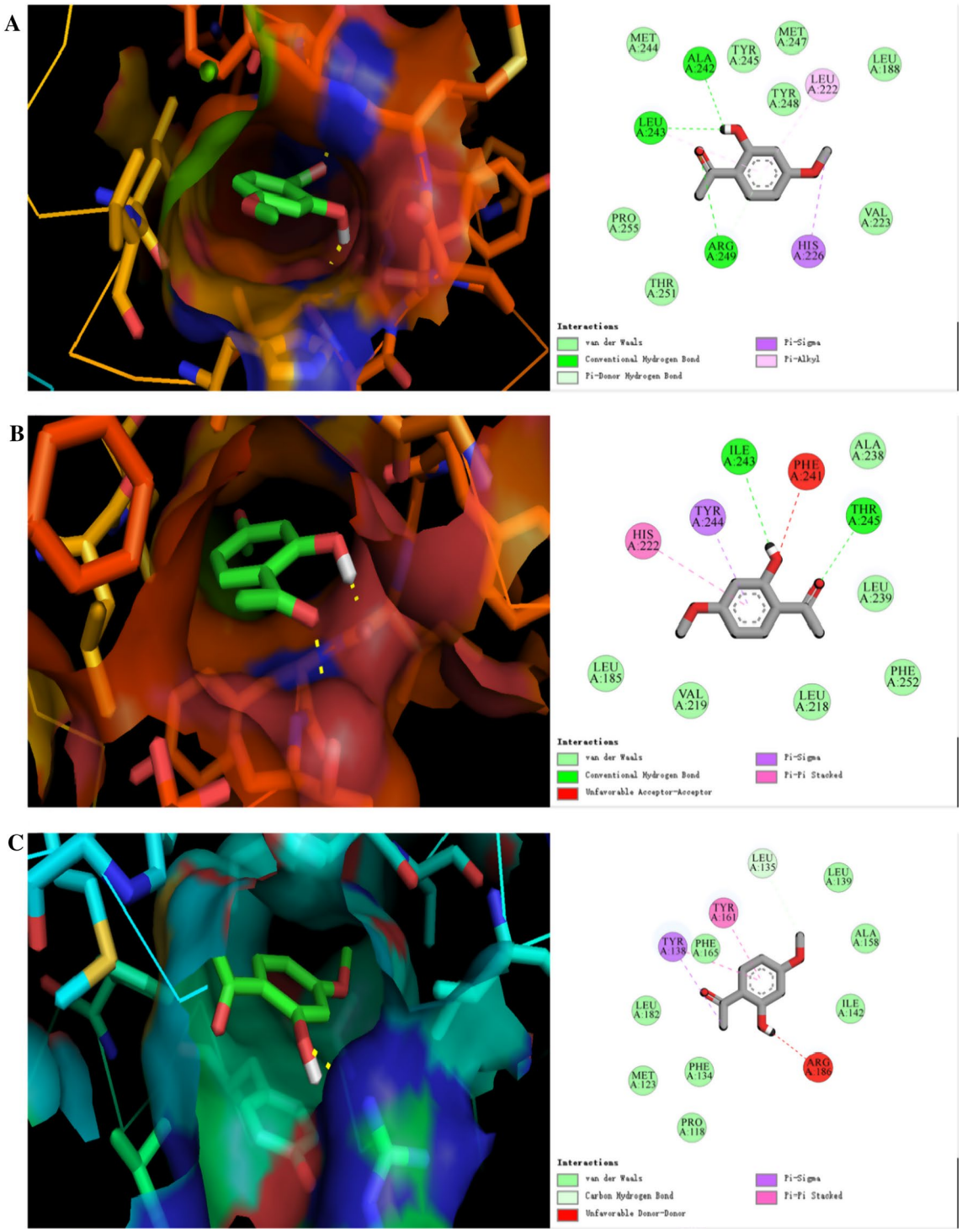


Fig. 5 Docking diagram of paeonol with the top three targets. **a** paeonol with MMP9, **b** paeonol with MMP13, and **c** paeonol with ALB; 3D diagram on the left and the 2D diagram on the right show the positions of active pockets and the types of interactions

Molecular docking results showed that the docking energy values were lower than 0, of which 74% were lower than − 5, indicating that paeonol has good affinity to these core targets. Importantly, MMP9 has the strongest binding affinity to paeonol. Among all the targets in the PPI network, MMP9, which can maintain the dynamic balance of extracellular matrix, is the target with the highest binding affinity to paeonol. In vitro experiments have shown that paeonol could

inhibit the growth, reproduction, and migration of tumor cells by regulating MMP9 in a concentration-dependent manner, and the mechanism was related to inflammation-related pathways such as NF-κB signaling pathway [41]. Therefore, it is speculated that MMP9 may be one of the important targets for paeonol to exert its anti-inflammatory effect.

In conclusion, paeonol exerts anti-inflammatory effects by acting on 22 targets and 33 signaling pathways, and it is closely related to the response to inflammatory factors, regulation of DNA-binding transcription factor activity, and response to oxidative stress. These potential targets have certain reference value for the study of paeonol targeted drugs.

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Authors' contributions J-HQ, F-XD, and X-LW have participated in the experiment and manuscript. J-HQ and F-XD have contributed equally to this work. X-LW have checked the contents of the manuscript and revised the language. In addition, X-LW gave guidance and effective suggestions on the overall manuscript design, data processing and discussion revision.

Availability of data and material The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

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