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RESEARCH ARTICLE

The Potential Effects and Mechanisms of *Rhododendron molle* against Rheumatoid Arthritis Based on Network Pharmacology and Molecular Docking

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ARTICLE HISTORY

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Abstract: ***Background*:** Rheumatoid arthritis (RA) is a self-inflammatory disease with increasing global morbidity and high disability. The Chinese herbal medicine *Rhododendron molle* G. Dons has been conventionally used to control RA without side effects for hundreds of years, but its effect and mechanism for anti-RA are still unclear.

***Objective*:** The objective of this study is to study the potential effect and mechanism of *R. molle* against RA from the perspective of action targets and molecular pathways.

***Methods*:** In this study, systemic network pharmacology was used to explore the potential effect and mechanisms of *R. molle* against RA, including drug active components collection, target prediction, PPI network construction, and GO and KEGG pathway enrichment analyses. At last, molecular docking was carried out to estimate the pharmacological effects and mechanisms.

***Results*:** A total of 19 drug-active compounds from *R. molle* and 188 potential therapeutic targets for RA were screened. According to the results of molecular docking, the interaction between 4 key active compounds (rhodojaponin III, quercetin, kaempferol, rhodojaponin VI) and 10 core target proteins (TNF, AKT1, ALB, IL-1β, TP53, EGFR, CASP3, MMP9, PTGS2, BCL2) is the closest. The results of enrichment analysis showed that the most enriched pathways were pathways related to inflammation, human T-cell leukemia virus type I infection, PI3K-Akt and IL-17.

***Conclusion*:** The Chinese herbal medicine *R. molle* may regulate multiple pathways by interacting with multiple drug-active compounds and core targets, and cause the patient's immune system to respond accordingly, reducing the release of inflammatory factors, and relieving joint pain.

Keywords: *Rhododendron molle*, rheumatoid arthritis, network pharmacology, molecular docking, action target, drug active compound.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a self-inflammatory disease characterized by chronic inflammation and bone damage, and it ranks first among inflammatory joint lesions [1, 2]. RA has a chronic course, stable progression, and a high incidence of accompanying diseases, significantly reducing the overall quality of life of patients. In severe cases, it can cause damage to systemic organs throughout the body and disability [3, 4]. The global incidence of RA is approximately 0.3%-1% and approximately 0.42% in China [5].

The pathogenesis of RA is complex, and most medical researchers believe that this disease belongs to autoimmune diseases, which are related to genetic, infectious, immune, and other factors [6]. However, its exact pathogenesis in clinical practice is still not fully understood [7]. At the cellular level, the balance between osteoblasts and osteoclasts in the bone tissue of RA patients is disrupted, and the formation of normal bone tissue is hindered [8]. The number of fibroid-like synovial cells (FLS) in the patient's joint area significantly increases [2]. From a molecular level perspective, cytokines such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), nitric oxide synthase (iNOS) and prostaglandin E2 (PGE2) are considered key cytokines in the pathogenesis of RA [9-11]. Wnt/β-catenin signaling pathway, 3-phosphate inositol kinase, protein kinase B (PI3K/Akt) signaling pathway, mitogen-activated protein kinase (MAPK) signaling pathway, and fluid artery congee signal pathway may play an important role in the pathogenesis of RA [12].

At present, the treatment of RA is limited to reducing joint inflammation, alleviating pain, maximizing joint func-

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tion, and slowing down the rate of deterioration [13], and the mainstream drugs used for treatment include non-steroidal anti-inflammatory drugs (NSAID), disease-improving anti rheumatic drugs (DMARD), corticosteroids [9, 14]. However, the use of these stem cell-derived therapeutics has toxic side effects, such as hypertension, myocardial infarction, nephrotoxicity, nausea, abdominal pain, ulcers, and gastrointestinal bleeding [11]. The newly developed small molecule targeted drugs, such as tofacitinib [15] and baricitinib [16], have significant therapeutic effects on key links in the pathogenesis of RA. However, the types of these drugs are not diverse enough, and not many patients can afford them [17]. Therefore, there is an urgent need to develop drugs for the treatment of RA with low toxicity, good efficacy, and reasonable prices.

Natural plants were important candidates for drug screening, with abundant natural resources that can effectively treat diseases and usually have no obvious side effects [18]. Research has found that *Tripterygium wilfordii* Hook. f. [19], *Paeonia lactiflora* Pall. [20], and *Glycyrrhiza uralensis* Fisch. [21] can all alleviate symptoms related to RA, making them candidate drugs for RA treatment. *Rhododendron molle* G. Dons is a traditional Chinese medicine, also known as Naoyanghua. According to ancient medical monographs, its roots, flowers, and fruits have analgesic, anti-inflammatory, and insecticidal effects [22]. Recently, our research has found that the extract of leaves from *R. molle* has significant anti-inflammatory and antioxidant activities [18, 23]. It has been found that 10 compounds in *R. molle* exhibit significant inhibitory activities against nitric oxide production in lipopolysaccharide-induced RAW264.7 mouse macrophages. We speculate that *R. molle* has enormous potential for anti-RA. So far, over 100 monomeric compounds have been isolated and identified from *R. molle*, including several major categories such as diterpenes, triterpenes, flavonoids, lignans, *etc*. [24, 25]. However, it requires lots of time and energy to evaluate the pharmacological properties and molecular mechanisms of these compounds, which limits further research and utilization of *R. molle*.

Network pharmacology is a discipline that combines pharmacology, bioinformatics and network pharmacology methods, which can quickly predict the interactions between various chemical components and action targets in drugs. Molecular docking technology is a simulation method to predict the interaction mechanism between small-molecule ligands and receptors [26]. They have been successfully used to predict and validate some plant components for treating complex diseases. For example, through these methods, researchers have found that kukoamine A in *Lycium chinense* Miller. can be used as a targeted therapeutic drug for osteoporosis [27], while safflomin C and safflower-yellow-B in *Carthamus tinctorius* L. can be used for combating myocardial ischemia [28]. In this study, modern network pharmacology and molecular docking technology were used to evaluate the anti-RA effect of more than 100 active compounds in *R. molle*. The important action targets and the potential molecular mechanism for RA with *R. molle* were predicted. This study provided a theoretical basis for the potential effects and molecular mechanisms of *R. molle* for RA.

2. MATERIALS AND METHODS

2.1. Drug Active Component and Action Target

According to the literature [29, 30] and the information provided by the analysis platform of the Chinese herbal systems pharmacology database (TCMSP, https://old.tcmsp-e.com/) [31], the components with oral bioavailability (OB) ≥30% and drug-likeness activity (DL) ≥0.18 were set as the thresholds for selecting drug active components in this study. It should be noted that the *R. molle* used in the name of the prescription of "Naoyanghua" [32]. So, when searching in the TCMSP database, enter "Naoyanghua" as the keyword. In addition, to make the prediction results more scientific and accurate, the previously reported active components that might have anti-inflammatory activity in *R. molle* were also added as drug-active components.

Subsequently, the action targets of the drug active components of *R. molle* from the TCMSP were recorded. In addition, for drug active components not included in TCMSP, the top 30 action targets of each of them were predicted by the online database PharmMapper (http://www.lilab-ecust.cn/pharmmapper/).

2.2. Acquisition of Potential Therapeutic Target

With "Rheumatoid Arthritis" as the keyword, action targets related to RA were searched in GeneCards (https://www.genecards.org/) database, and the targets of "score>1.0" were selected as RA-related targets. The action targets of drug active components were intersected with the RA disease-related targets, and then the Venn diagram was plotted to obtain the common targets, which were the potential therapeutic targets for the treatment of RA.

2.3. Interaction Network between Target and Component

Based on previous analytic results, the data pairs of drug active components in *R. molle* and potential therapeutic targets were imported into Cytoscape 3.9.1 software. An *R. molle*-drug active components-targets map was constructed.

2.4. GO Enrichment Analysis and KEGG Pathway Analysis

The David platform (https://david.ncifcrf.gov/) [33] was used to conduct GO enrichment analysis on biological process (BP), cell component (CC), and molecular function (MF), as well as KEGG pathway enrichment analysis on potential therapeutic targets for RA of *R. molle*. The enriched data was imported into the online tool Weishengxin (https://www.bioinformatics.com.cn/) to draw bubble and bar charts for GO enrichment analysis and KEGG enrichment analysis, in order to provide a more vivid analysis.

2.5. Drawing of PPI Network and Screening of Core Target

The screened potential therapeutic targets (Intersection targets) were submitted to the string platform (https://cn.string-db.org/), and we defined the species as "Homo sapiens". Then, a potential therapeutic target protein

interaction (PPI) map for the treatment of RA with *R. molle* was obtained. In order to more clearly demonstrate the regulatory role of core proteins in the PPI network, the original PPI network diagram was visualized and analyzed using Cytoscape 3.9.1 software. In addition, core targets (Hub targets) were obtained through the software's CytoHub plugin in Cytoscape 3.9.1.

2.6. Molecular Docking

Molecular docking validation was performed between the top 10 core targets and their corresponding drug-active components of *R. molle*. The crystal structures of the target protein (3D structure file in PDB format) were taken from the PDB database (https://www.rcsb.org/), and Pymol software was used for crystal water removal, hydrogenation, and charge addition processing. The SDF structures file of the drug active components in *R. molle* were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Molecular docking was calculated using AutoDockTools 1.5.7 software and the binding energy was calculated based on the scoring function. The generated results were simulated using Pymol software to display binding sites and chemical bonds.

3. RESULTS

3.1. Drug Active Components

A total of 9 drug active components were screened from TCMSP with OB≥30% and DL≥0.18, and all of the information is summarized in Table **1**. Those 9 active components were sorted in the descending order of OB value, numbered Rm1-Rm9. In order to evaluate more active compounds related to anti-RA in *R. molle*, other 10 monomeric compounds from the literature [31, 34-36] were supplemented. Those 10 drug active components were sequentially numbered as Rm10-Rm19, and their information is also shown in Table **1**. Due to the fact that the active components Rm10-Rm19 are not included in the TCMSP database, their OB and DL values are unknown.

3.2. Potential Therapeutic Target

According to the retrieval of the TCMSP database and the prediction of PharmaMapper website, a total of 294 action targets in 19 drug-active compounds of *R. molle* were collected. Total 5790 RA-related targets were obtained from the GeneCards database, of which 3893 met the screening criteria and were included in the study. A total of 188 common intersections for 294 action targets from *R. molle* and

Table 1. Drug-active components of *R. molle.*

Short Form	Active Components	OB (%)	DL	References
Rm1	*psi*-rhodomyrtoxin	68.43	0.63	[31]
Rm2	*α*-isosparteine	68.35	0.21	[31]
Rm3	rhodojaponin III	64.97	0.56	[31, 34-36]
Rm4	kalmanol	61.61	0.50	[31]
Rm5	andromedotoxin	55.97	0.61	[31]
Rm6	isorhamnetin	49.60	0.31	[31]
Rm7	grayanotoxin III	47.01	0.48	[31]
Rm8	quercetin	46.43	0.28	[31]
Rm9	kaempferol	41.88	0.24	[31]
Rm10	rhodojaponin I	-	-	[36]
Rm11	rhodojaponin II	-	-	[36]
Rm12	rhodojaponin VI	-	-	[34-36]
Rm13	rhodojaponin VII	-	-	[36]
Rm14	*2-O*-methylrhodomollein XI	-	-	[36]
Rm15	*2-O*-methylrhodojaponin VI	-	-	[35]
Rm16	*6-O*-acetylrhodomollein XXI	-	-	[36]
Rm17	grayanotoxin XV III	-	-	[36]
Rm18	rhodomollein XI	-	-	[36]
Rm19	rhodomolin I	-	-	[36]

3893 RA disease-related targets were obtained by Venny online analysis tool, which were potential therapeutic targets of *R. molle* for treating RA. The venny diagram is shown in Fig. (**1**). *R. molle*-drug active components-targets map, shown in Fig. (**2**), which was obtained by connecting each drug active component to its corresponding potential therapeutic target. It can be found that among the 19 active components, except for Rm2 which only corresponds to 1 target, all other active components contain multiple potential therapeutic targets. Rm8 contains a maximum of 99, Rm1 contains 21, and Rm10 contains 16. And different components often contain the same target. For example, both Rm3 and Rm12 contain ALB, while Rm13 and Rm17 both have MAPK8.

3.3. GO and KEGG Enrichment Analyses

GO enrichment analysis of gene function of 188 potential therapeutic targets was carried out at three levels: biological process (BP), cellular component (CC), and molecular function (MF). A total of 876 BP-related items, 97 CC-related items, and 177 MF-related items were enriched. The top 20 terms in the 3 categories above are shown as bubble charts in Figs. (**3A-C**). The top ten with the smallest *P* value of each part (a total of 30 terms) were selected as prominent biological processes, including the main response to apoptosis, response to inflammation, response to lipopolysaccharides, and other biological activities that are closely related, Fig. (**3D**).

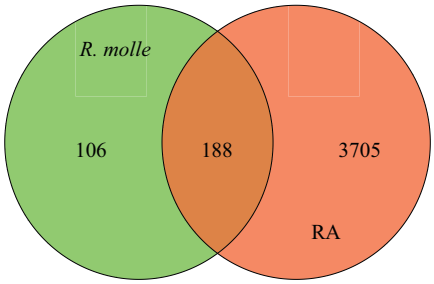


Fig. (1). Venn diagram of common targets of *R. molle*-RA. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

According to the results of KEGG pathway enrichment analysis, 170 signaling pathways were acquired that were involved in the possible mechanism by which *R. molle* treatment affects RA and shows the top 20 pathways in Fig. (**4**). The active components in *R. molle* primarily target the response to pathways in cancer, PI3K-Akt signaling

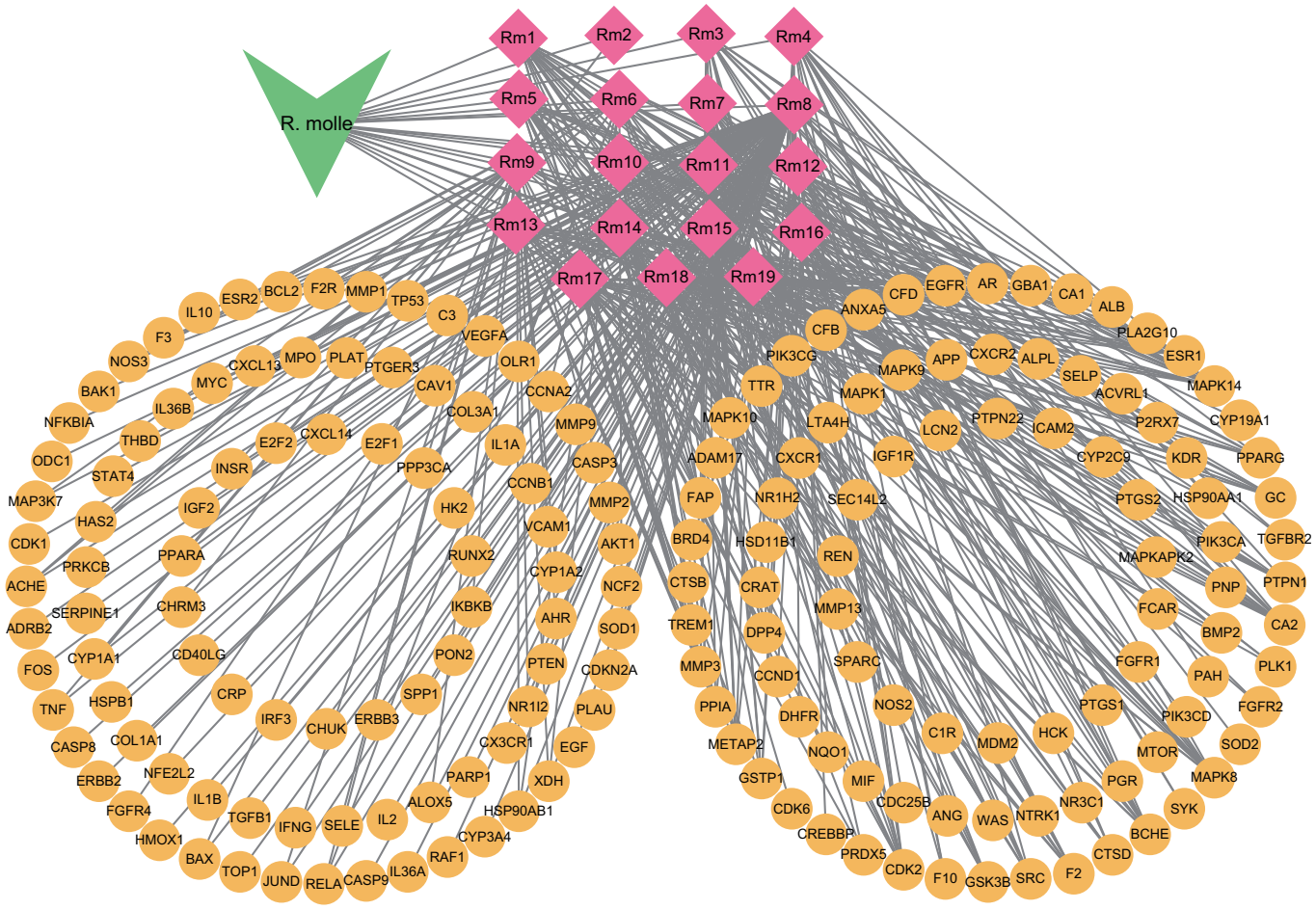


Fig. (2). *R. molle*-Drug active components-Targets map. The pink diamond represents 19 drug active components, the yellow circle represents 188 potential therapeutic targets, and the gray solid line represents the corresponding relationship. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

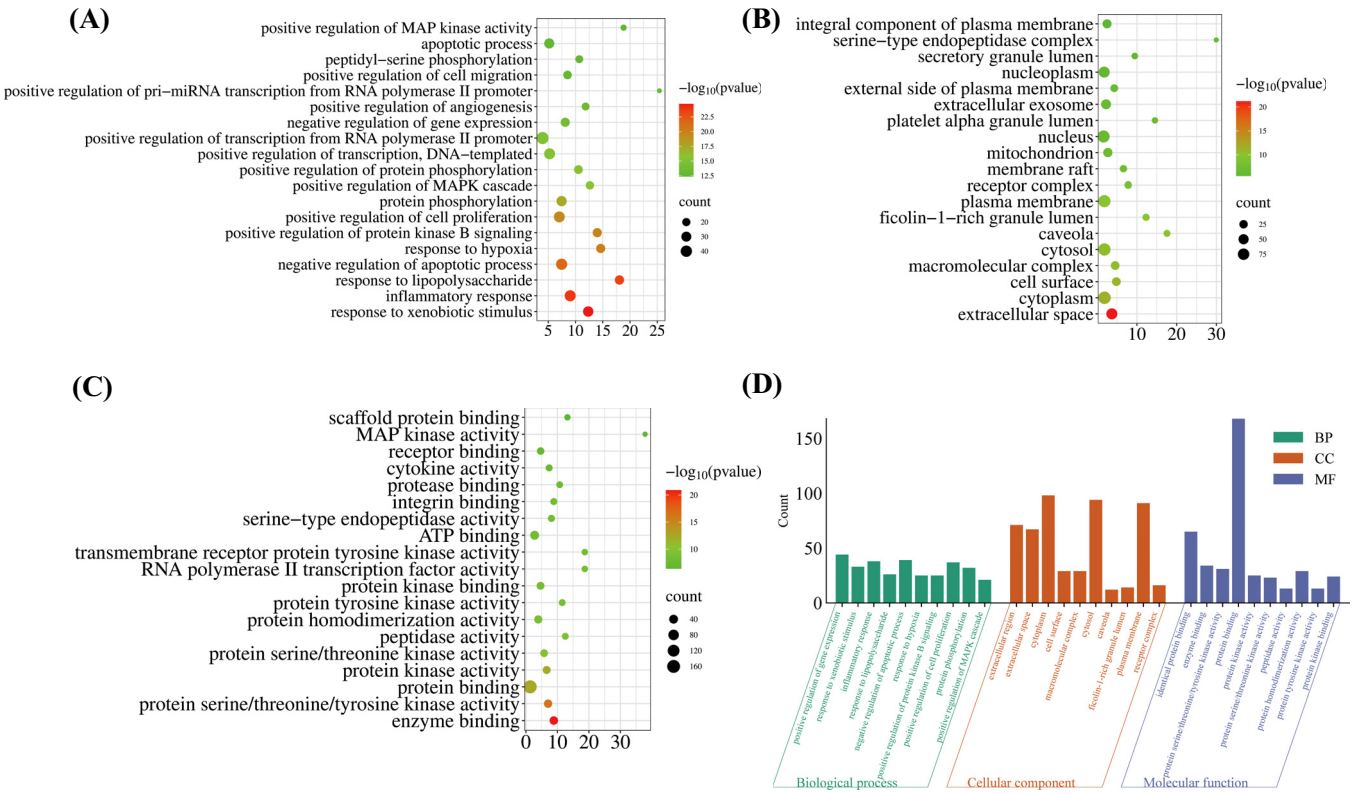


Fig. (3). GO enrichment results of potential therapeutic targets. (**A**) Bubble plot of the biological process category terms; (**B**) Bubble plot of the cellular component category terms; (**C**) Bubble plot of the molecular function category terms; (**D**) The results of target gene counting in the key process of GO enrichment. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

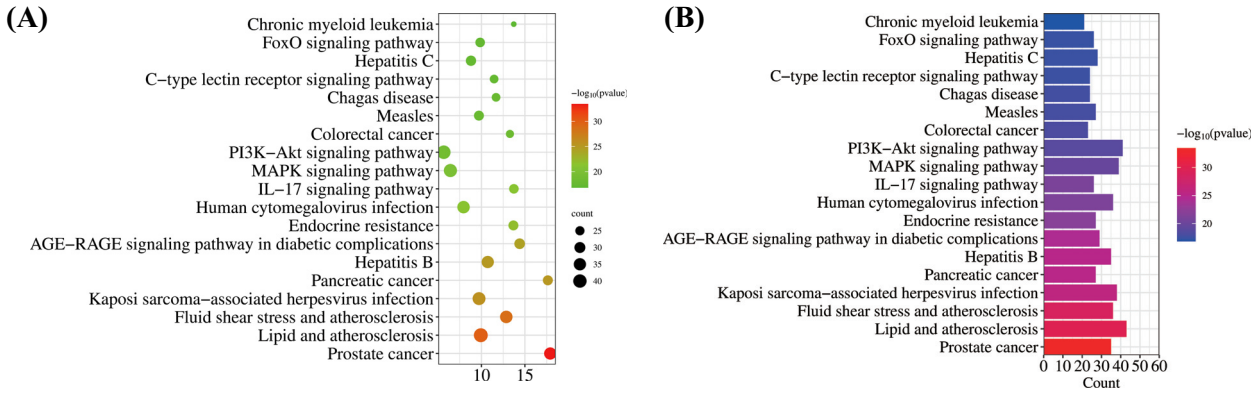
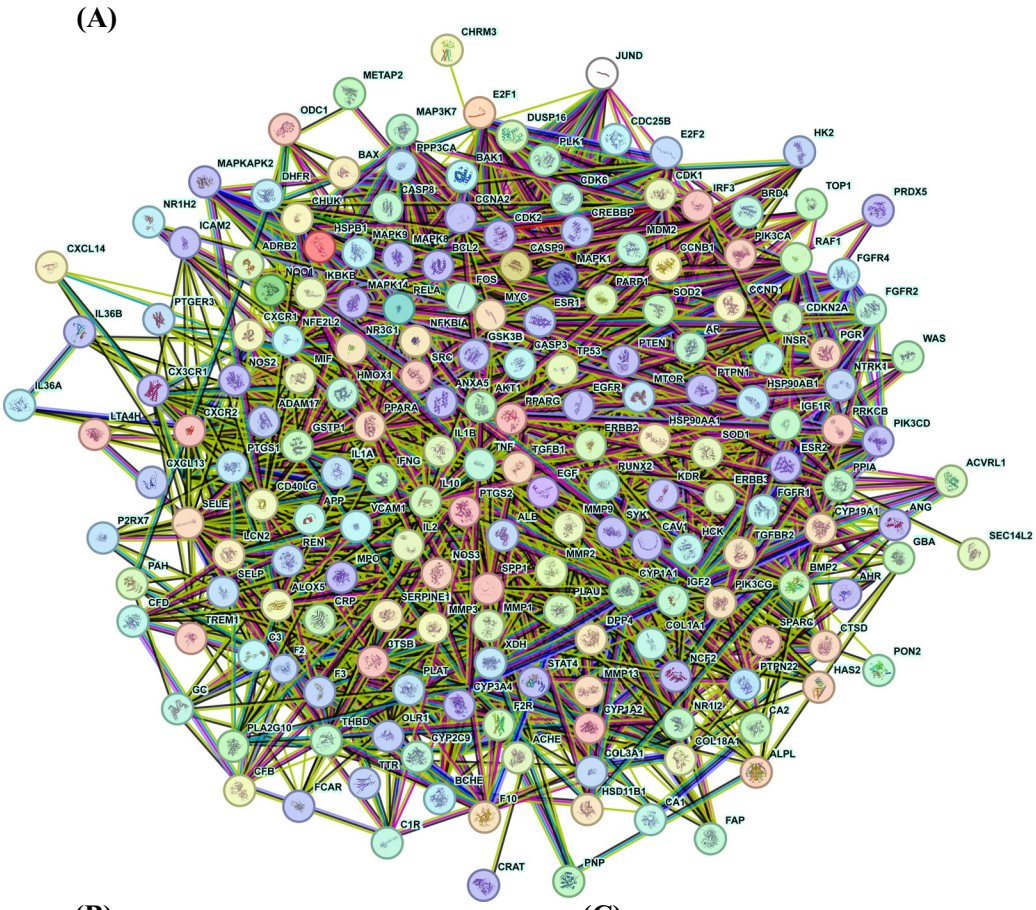


Fig. (4). KEGG enrichment results of potential therapeutic targets. (**A**) Bubble plot of KEGG signaling pathway; (**B**) Column plot of KEGG signaling pathway. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

pathway, IL-17 signaling pathway, and AGE-RAGE signaling pathway. These results provided some very important information for revealing the molecular mechanism of *R. molle* for treating RA.

3.4. Protein-protein Interaction (PPI) Network

The PPI network of potential therapeutic targets for RA with *R. molle* was obtained through the string platform, as shown in Fig. (**5A**). After removing irrelevant nodes, the PPI network had a total of 188 nodes and 4135 edges. The top ten Hub targets (TNF, AKT1, ALB, IL1B, TP53, EGFR, CASP3, MMP9, PTGS2, BCL2) were selected with comprehensive scores by importing the data of the PPI network into the CytoHub plugin of Cytoscape 3.9.1 software. These 10 target proteins are core targets, which have been confirmed to be closely related to inflammatory responses in the previous research. The names and comprehensive scores of 10 core targets are shown in Figs. (**5B**, **C**). The color of the nodes represents the connectivity value of the target and the color from light yellow to deep red indicates a higher target connectivity value. The results showed that the target TNF and AKT1 are at the core position of the network. The



Rank	Target	Score
1	TNF	146
2	AKT1	140
3	ALB	132
4	IL1B	131
5	TP53	130
6	EGFR	115
7	CASP3	114
7	MMP9	114
9	PTGS2	109
10	BCL2	108

Fig. (5). PPI network of potential therapeutic targets. (**A**) Protein-protein interaction diagram; (**B**) 10 core target interaction diagram; (**C**) Comprehensive score of core targets. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

network nodes corresponding to targets such as IL-1β (IL1B), ALB, and TP53 are darker in color, indicating their crucial regulatory role in the PPI network.

3.5. Molecular Docking Validation

Through statistics, among the 19 drug active components, Rm8 contains 8 core targets: TNF, AKT1, IL-1β, TP53, CASP3, MMP9, PTGS2 and BCL2; Rm9 contains 5 core targets: TNF, AKT1, CASP3, PTGS2, BCL2; Rm3 contains ALB and EGFR; Rm12 contains ALB and EGFR. The remaining components contain one or none of the 10 core targets. So, Rm3, Rm8, Rm9, and Rm12 are predicted to be the key active components of *R. molle* for RA. The molecular docking between 4 key active components and their corre-

sponding core targets were respectively simulated, and their minimum docking energies were recorded, as shown in Table **2**.

Table 2. Results of molecular docking.

Target Protein	Binding Energy / kcal·mol^{-1}			
	Rm3	Rm8	Rm9	Rm12
TNF	-	-3.74	-4.18	-
AKT1	-	-4.43	-4.31	-
ALB	-5.88	-	-	-5.19
IL1β	-	-4.25	-	-
TP53	-	-4.38	-	-
EGFR	-5.79	-	-	-5.54
CASP3	-	-4.35	-4.67	-
MMP9	-	-4.69	-	-
PTGS2	-	-4.02	-5.41	-
BCL2	-	-4.03	-2.31	-
Average avlue	-5.835	-4.236	-4.176	-5.365

Molecular docking can predict the binding mode and estimate the binding strength, that is, the size of binding energy or affinity. In general, binding energy less than 0 indicates that ligand and receptor can spontaneously bind, and the more stable the binding conformation is, the lower the required binding energy is [37]. The binding energy is less than -5 kcal·mol^{-1}, which indicates that the ligand has a strong binding activity with the receptor [30]. In our study, the binding energy of 4 drug active components docking with their core targets is less than 0. Rm3 has the lowest binding energy with the target protein ALB, which is -5.88 kcal·mol^{-1}. The average minimum docking energies of Rm3, Rm8, Rm9, and Rm12 with their core targets are -5.835, -4.236, -4.176, and -5.365 kcal·mol^{-1}, respectively. This indicates that 4 drug active components in *R. molle* have a good binding effect with the targets related to RA disease. Especially for Rm3 and Rm12, the average minimum docking energy between them and the core target is less than -5 kcal·mol^{-1}, which indicated a more strong binding activity. The model with the lowest binding energy between each active component and the core target is shown in Fig (**6**).

4. DISCUSSION

In this study, 4 key active components of *R. molle* for the treatment of RA were identified through network pharmacology and molecular docking. Quercetin (Rm8) is a polyhydroxyl flavonoid compound with various biological activities. It can clear out free radicals, complex or capture free radicals to avoid the body's lipid peroxidation [38-40]. Rm8 can also inhibit inflammation and neurotoxicity caused by microglia activation by reducing the expression of TNF-α, IL-1β, and IL-6 [41]. Kaempferol (Rm9) is a common flavonoid compound, which has a good inhibitory effect on lung cancer, cervical cancer, and glioblastoma. It improves cognitive dysfunction through antioxidant, anti-inflammatory, anti-apoptotic, and anti-acetylcholinesterase effects [42]. Rm9 can also inhibit the proliferation of RA synovial fibroblastoid cells, induce apoptosis, and reduce inflammation [43]. Rhodojaponin III (Rm3) and rhodojaponin VI (Rm12) are diterpenoids in *R. molle*, and are the main components of diterpenoids [25]. He (2021) found that diterpenoid fraction in *R. molle* significantly inhibited the abnormal proliferation of T and B lymphocytes and remarkably reduced the levels of pro-inflammatory cytokines IL-6, IL-1β, and TNF-α [35]. Li (2015) found that Rm3 and Rm12 are more potent than morphine for both acute and inflammatory pain models [34]. According to molecular docking results, the docking binding energy between Rm3 or Rm12 and the core targets is smaller than that of Rm8 or Rm9. It is speculated that the efficacy of them in treating RA would be better. These results suggest that Rm3 and Rm12 in *R. molle* may be active components with high content and more effective anti-RA effects, which are worth further study and exploitation.

Based on PPI network analysis, TNF, AKT1, ALB, IL-1β, TP53, EGFR, CASP3, MMP9, PTGS2 and BCL2 were identified as core targets. Many studies have shown that they were closely related to the occurrence of RA. For example, TNF is a tumor necrosis factor, divided into TNF-α and TNF-β, which can directly kill tumor cells without obvious toxicity to normal cells. TNF-α participates in inflammatory and immune responses, leading to abnormal apoptosis of chondrocytes and rupturing of cartilage tissue [44]. In addition to being a tumor suppressor, TP53 is also an inflammatory suppressor. It involves multiple cellular biological processes and is closely related to autoimmune diseases [21]. IL-1β (Interleukin-1β) is an important proinflammatory cytokine in the human body. Studies have shown that the expression of IL-1β is abnormally increased in the synovial fluid of middle-aged and elderly patients with knee osteoarthritis [45], and it can also cause the release of other proinflammatory factors and inflammatory pain. CASP3, a member of the cysteine protease family, plays a key role in apoptotic pathways through the cleavage of several key cellular proteins [46]. Besides, other core targets also play important roles in biological processes related to inflammation, apoptosis, immunity, or cancer.

The results of GO and KEGG analyses in the present study showed that the biological effects of *R. molle* in treating RA mainly involved biological processes such as response to lipopolysaccharides, cell apoptosis, and inflammatory response. The treatment process may have a role in signal pathways of cancer, C-type lectin receptor, human T-cell leukemia virus I infection, PI3K-Akt, MAPK and IL-17. C-type lectin is a superfamily of proteins containing calcium ion (Ca^{2+}) dependent sugar recognition domains. It is an important pattern-recognition receptor in the innate immune system [47]. Adult T-cell leukemia (ATL) is a special type of malignant clonal proliferative disease of the lymphatic system that occurs in adults and is directly related to human T-cell leukemia virus I (HTLV I) infection [48]. IL-17 is a specific effector from Th17 cells, which facilitates the production of inflammatory factors such as IL-6 and IL-1β

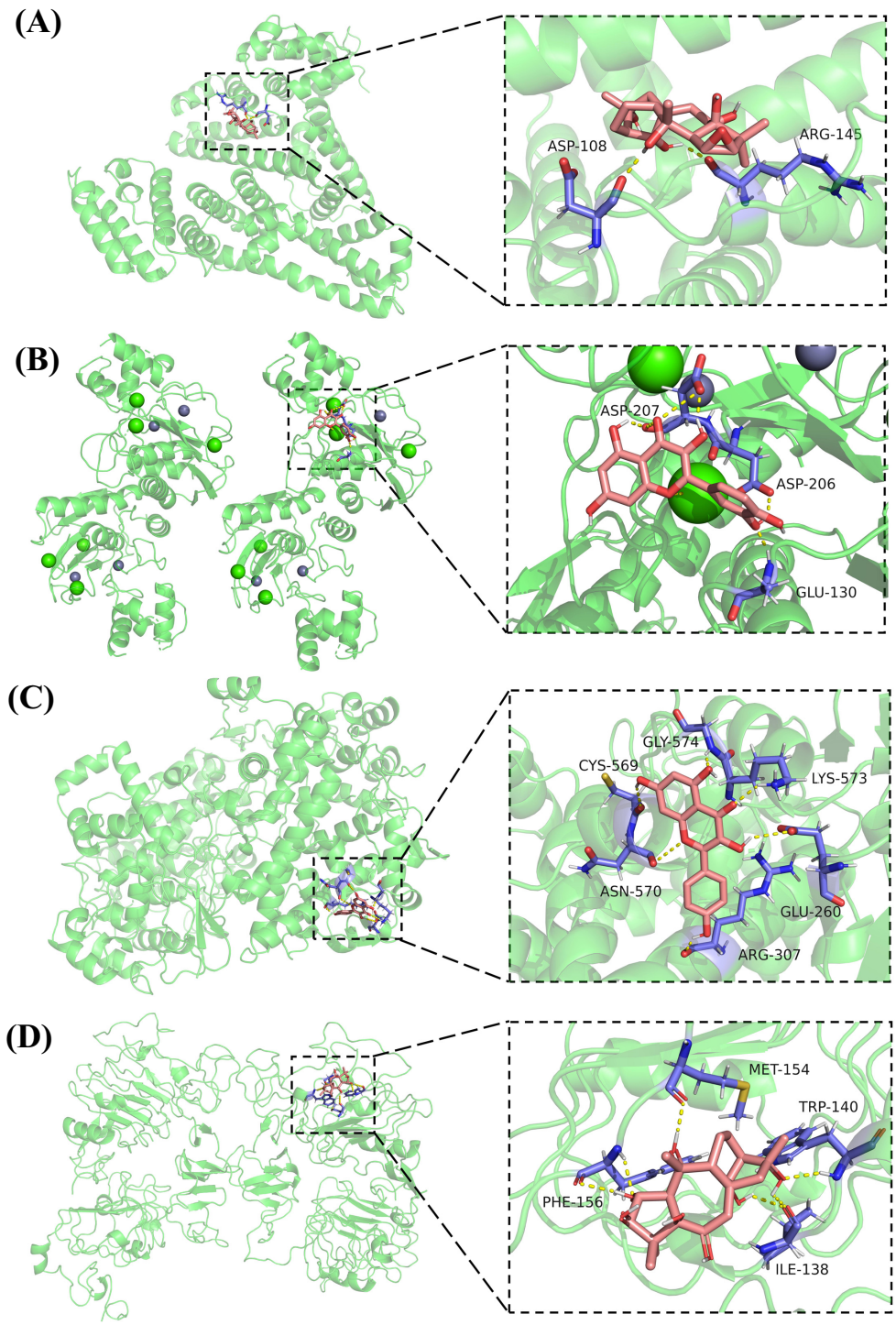


Fig. (6). The optimal molecular docking model of (**A**) rhodojaponin III and ALB; (**B**) quercetin and MMP9; (**C**) kaempferol and PTGS2; (**D**) rhodojaponin VI and EGFR. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

through the recruitment, mobilization, and activation of macrophages and neutrophils, mediating inflammatory invasion and tissue damage [49]. This further indicates that RA is an autoimmune disease. Perhaps due to excessive autoimmune function, T cells undergo malignant proliferation, damaging the patient's own organs and systems. This also led to other accompanying diseases one after another, ultimately causing serious harm to the patients' entire body.

In summary, the use of *R. molle* for RA could be mainly linked to its anti-inflammatory and antioxidant properties. Its multiple active compounds aim for multiple targets, which are mapped to different pathways embodied in the complex integrated network mechanisms of multi-component, multi-targeted, and multichannel regulated treatment of RA. The key active components in *R. molle*, rhodojaponin III, quercetin, kaempferol, rhodojaponin VI, may be linked tightly with

core target proteins such as TNF, AKT1, IL-1β, and ALB. Then, multiple signaling pathways that relate to inflammation, apoptosis, immunity, and cancer will be regulated. The release of inflammatory factors will be reduced and the joint pain in patients will be alleviated. During these processes, *R. molle* plays a therapeutic role in RA.

CONCLUSION

In this study, 19 drug-active compounds in *R. molle* were screened for network pharmacology analysis. Through potential therapeutic target prediction, interaction network and molecular docking analysis, 4 key drug active compounds (rhodojaponin III, quercetin, kaempferol, rhodojaponin VI) for RA treatment and 10 core target proteins (TNF, AKT1, ALB, IL-1β, TP53, EGFR, CASP3, MMP9, PTGS2, BCL2) were identified. The potential effects and molecular mechanisms of key drug active compounds in *R. molle* for RA mainly involved signaling pathways related to inflammation, human T-cell leukemia virus type I infection, PI3K-Akt, and IL-17. These results would provide scientific evidence for the study of the pathogenesis of RA and the development of drugs for treating RA.

AUTHORS' CONTRIBUTIONS

Xiangdong Luo designed the study and directed the experiment. Xianxian Zhao and Yu Shen performed the research and analyzed the data, as well as wrote the manuscript. Yongchun Huang participated in the data analysis together. Xinyuan Li participated in experimental assistance. Liangfang Dai participated in the revision of the manuscript. All authors read and approved the final manuscript.

LIST OF ABBREVIATIONS

RA	=	Rheumatoid Arthritis
iNOS	=	Nitric Oxide Synthase
PGE2	=	Prostaglandin E2
NSAID	=	Non-Steroidal Anti-Inflammatory Drugs
DMARD	=	Disease Improving Anti-Rheumatic Drugs

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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