A Network Pharmacology Study on Active Components and Targets of Citri Reticulatae Pericarpium for Treating Keloids

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Abstract [**Objectives**] To investigate the mechanisms and pharmacologic effects of Citri Reticulatae Pericarpium against keloids by network pharmacology systematically. [**Methods**] TCMSP, Uniprot and BATMAN-TCM databases were used to obtain the active constituents and targets of Citri Reticulatae Pericarpium. "Keloid" was used as key word to search for related therapeutic targets from Drug Bank, OMIM, TTD, and GEO databases. The Chinese medicine compound-target network was constructed by Cytoscape software. Besides, gene ontology (GO) and Kyoto Encyclopedia of genes and genome enrichment analysis were also performed. Afterward, Discovery Studio software was used to assess the interaction of key components and genes. [**Results**] Five active components of Citri Reticulatae Pericarpium, 773 compound targets and 676 keloid treatment targets were obtained in the databases. After the intersection, there are 47 targets of Citri Reticulatae Pericarpium for treating keloids. Hub genes were identified such as *MMP9*, *IL6*, *TNF*, *TP53*, and *VEGFA*, which were enriched in tumor necrosis factor-α, nuclear factor kappa-B, and other signaling pathways. The molecular docking stimulation confirmed the interaction between the *MMP9* and three components of Citri Reticulatae Pericarpium. [**Conclusions**] Citri Reticulatae Pericarpium may play an important role in treating keloids through modulating genes and signaling pathways. The present study sheds light on the mechanisms of active compounds of Citri Reticulatae Pericarpium for the treatment of keloids.

Key words Network pharmacology, Keloids, Citri Reticulatae Pericarpium

1 Introduction

Keloids are abnormal, persistent, hard, and tough scar tissue that occurs during skin injury healing[1]. It is a common clinical skin fibrotic disease known for the deposition of the extracellular matrix and excessive fibroblasts proliferation[2]. It can happen after any type of dermal trauma, resulting in an exophytic protuberant growth that spreads into the surrounding normal skin beyond the initial injury site[3-4]. The keloid tissue is often recurrent and refractory since the persistent invasive growth of keloid fibroblasts (KFs)[1]. Keloids have been seen in people of various ethnicities, but were found to be more common in people with deeper pigmentations, including blacks, Hispanics, and Chinese (4.5% to 16%), with a male-to-female ratio of equal[5]. Most keloid occurs between the ages of 10 and 30[6]. Therapies for keloids include surgery, radiotherapy, antimetabolic agents, and compression but with unsatisfying results and a high recurrence rate[7].

Traditional Chinese medicine (TCM) or natural products are widely used in the prevention and treatment of a wide range of diseases with great efficacy, minimal side effects, and nearly no resistance[8-9]. TCM also has the most abundant bioactive compounds and pharmaceutical components, making it ideal for medication development[10]. It is believed that keloid is a disease caused by deficiency of positive qi, stagnation of qi, phlegm, siltation of blood, *etc*[11]. Treatment methods such as moving qi, and removing dampness and phlegm were eligible[12].

Citri Reticulatae Pericarpium (Chenpi) is the dried mature peel of *Citrus reticulata* Blanco (Rutaceae) with function of invigorating spleen qi, eliminating dampness and phlegm. It has a long history of medicinal use in TCM. Its main drug active component is flavonoids (hesperidin, Chenpi multi-methoxy flavonoids, nobiletin), volatile oil (limonene), alkaloi (synephrine) ingredients[13]. Zeng[14] *et al.* discovered the modulatory effects of Nobiletin, the flavonoid active component in Citri Reticulatae Pericarpium, was able to inhibit the formation and development of proliferative scarring through three aspects: inhibition of fibroblast proliferation, promotion of fibroblast apoptosis and inhibition of fibroblast migration. It was found that Nobiletin and polymethoxyflavonoid extracts had an effect on the production of both IF-6 and IF-1β, which played an important role in the formation of the keloids[15]. However, there were no network pharmacology-based analysis of the effective components of Citri Reticulatae Pericarpium in the treatment of keloids and its mechanism of action.

The goal of this study was to screen the bioactive components of Citri Reticulatae Pericarpium and identify the targets that contribute to its therapeutic impact on of keloids using network pharmacology.

2 Data and methods

2.1 Identification of bioactive ingredients and corresponding targets for Citri Reticulatae Pericarpium Fig. 1 depicts the workflow and databases used in this study. The Traditional Chinese Medicine Systems Pharmacology database (TCMSP, http://lsp.nwu.edu.cn/tcmsp.php) is a systematic pharmacology resource[16] that provides information on the absorption, distribution, metabolism, and excretion (ADME) properties of TCMs or compounds, such as oral bioavailability (*OB*), drug-likeness (*DL*), and blood-brain barrier properties (BBB)[17-18]. According to the TCMSP platform, the bioactive ingredients of Citri Reticulatae Pericarpium were obtained. The rate and extent to which

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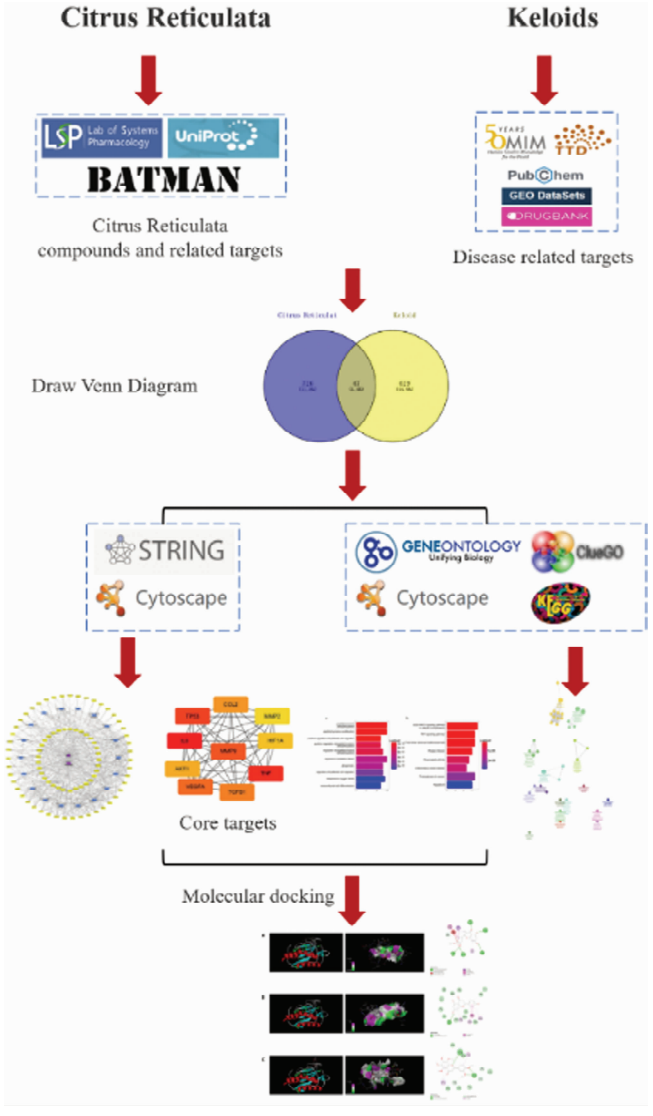
a medicine is absorbed into the blood circulation is referred to as oral bioavailability. Druglike features describe the nature of a drug with a given functional group or physical traits that are the same or similar. Based on $OB \geqslant 30\%$ and $DL \geqslant 0.18$, bioactive ingredients were obtained. The targets of Citri Reticulatae Pericarpium were screened from three databases, including TCMSP, Uniprot and BATMAN-TCM. The Universal Protein Resource (UniProt, https://www.uniprot.org/) is a well-known protein database[19] which includes information on protein functional Gene Ontology (GO) annotations, species names and classification, subcellular localization, protein processing modifications, expression, *etc*. A Bioinformatics Analysis Tool for Molecular mechANism of Traditional Chinese Medicine (BATMAN-TCM, http://bionet.ncpsb.org/batman-tcm/) is the Chinese medicine's first online bioinformatics tool designed specifically to analyze molecular mechanisms. Using BATMAN-TCM, each query TCM component is predicted to have potentially useful targets, which are then functionally analysed, including Gene Ontology term, KEGG pathway and OMIM/TTD disease enrichment analysis. Pathways/disease associations with TCM components will be shown, as well as biological pathways with prominent TCM targets. Putative targets of Citri Reticulatae Pericarpium were also predicted by Swiss Target Prediction.

2.2 Identification of potential therapeutic targets of keloids We searched therapeutic gene targets with "keloid" as a search term in Drug Bank, OMIM and TTD database. Drug Bank (https://go.drugbank.com/) database is a bioinformatics and cheminformatics database, which can get drug interactions, pharmacology, chemical structures, targets, metabolism, *etc*. OMIM (https://omim.org/) is a database of genetic conditions in humans. The purpose of this database is to investigate the relationship between human genetic variation and phenotypic differences and it can be consulted for any genetic disease, trait, or gene. TTD (http://db.idrblab.net/ttd/) contains information on known and researched therapeutic proteins and nucleic acids, target diseases, and signaling pathways and the corresponding drugs for each target. We also searched for studies focusing on identifying differentially expressed genes (DEGs) in keloids compared with normal skin in Nation Center for Biotechnology Information (NCBI, https://www.ncbi.nlm.nih.gov/), gene expression omnibus (GEO) database. The DEGs were added to the potential therapeutic targets of keloids for more thorough results. The targets of Citri Reticulatae Pericarpium and therapeutic gene targets of keloids were imported into VENNY 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/index.html). The overlapping targets of Citri Reticulatae Pericarpium and therapeutic gene targets of keloids were shown using Venn diagram with VENNY 2.1.0.

2.3 Construction of the PPI network In the STRING database (http://string-db.org/), interactions between proteins and proteins can be analyzed. Accordingly, we limited the species to "Homo sapiens", and we set the minimum interaction value to medium confidence (0.400), then hide a single target and leave the rest of the parameters at their default settings. Consequently, the PPI network with potential therapeutic targets of keloids was obtained and visualized in the STRING database.



Note: TCMSP: Traditional Chinese Medicine Systems Pharmacology database and analysis platform. UniProt: The Universal Protein Resource. BATMAN-TCM: A Bioinformatics Analysis Tool for Molecular mechANism of Traditional Chinese Medicine. NCBI GEO: Nation Center for Biotechnology Information gene expression omnibus. GO: gene ontology. KEGG: Kyoto encyclopedia of genes and genome.

Fig. 1 Detailed design and workflow

2.4 Construction of active component-predictive target network and hub gene analysis The visualization software Cytoscape 3.7.1 enables a more intuitive analysis of the mechanism of action of drugs in treating diseases. In our study, nodes in different shapes represent the ingredients, potential target of the Citri Reticulatae Pericarpium or related functions. The edges represent the relationship. Using the cytoHubba function of the Cytoscape software, significant targets and subnetworks were detected from the network. The cytoHubba assigns a value to each gene by a topological network algorithm to sort and discover its key genes and

sub-networks.

2.5 GO and KEGG analysis Clue GO is a plug-in for Cytoscape that visualizes the biological terms for large clusters of genes in functionally grouped networks. ClueGO analyzes a single cluster and compares multiple clusters (gene lists). From the used ontology sources, terms are selected according to different filter criteria. Related terms with similar related genes have been merged to reduce redundancy. The ClueGO network is constructed from the kappa statistic and reflects the relationship between terms based on the similarity of related genes. ClueGO also visualizes terms and pathways from other enrichment analyses as functional grouping networks. GO analysis is widely used to annotate gene functions, including molecular functions, cellular components, and biological processes. KEGG is used to systematically study the pathway information of genes. GO analysis divides the gene function into three components: cellular component (CC), molecular function (MF), and biological process (BP). Using GO analysis, we can obtain what the target gene is mainly related to at the CC, MF and BP levels. KEGG treats gene information and expression as a complete network, organically combines genomic information and functional information, systematically analyzes gene function, computerizes known biological processes in cells, and standardizes existing gene function interpretations.

2.6 Molecular docking simulation The chemical structures of main components of Citri Reticulatae Pericarpium were downloaded from Pubchem (https://pubchem.ncbi.nlm.nih.gov/). We identified the Protein Data Bank (PDB)-ID of the most correlated and biological meaningful target gene-encoded protein from Protein Data Bank (PDB) database. The interactions between the ingredients and target protein were analyzed in Discovery studio software (version 4.5.0, Biovea Inc., Omaha, NE, USA). In short, active ingredients were processed with "Prepare Ligands" while the target proteins with "Prepare Protein" after removing water molecules. Then, molecular docking was stimulated with "LibDock" and illustrated. The LibDockScore between the target protein and the ligand means the activity level of the interaction.

3 Results and analysis

3.1 Bioactive ingredients and targets collection Five bioactive components of Citri Reticulatae Pericarpium were obtained following the aforementioned method from TCMSP database (Table 1). There were 88, 164 and 1 885 treatment targets of Citri Reticulatae Pericarpium were obtained from the TCMSP, Uniprot and BATMAN-TCM databases separately. After excluding duplicate values, the remaining 773 treatment targets of Citri Reticulatae Pericarpium were obtained.

According to DrugBank, OMIM and TTD, 8 441 and 1 targets of keloid were obtained severely. We retrieved three studies from the GEO database which focused on the therapeutic targets of keloids[20-22] (search inception 2021/08/01). We obtained the DEGs provided in the papers or the supplementary files of these studies and gained 152 genes as the treatment targets of keloid. Moreover, we also included the 102 DEGs in keloids based on our previous study[23]. There were 676 unique putative treatment targets of keloid obtained in total. After the intersection, 47 overlapping treatment targets of Citri Reticulatae Pericarpium for keloid were collected, as presented in Fig. 2.

Table 1 Information of 5 bioactive compounds in Citri Reticulatae Pericarpium

Mol ID	Molecule Name	*OB*//%	Caco-2	*DL*	*HL*
MOL000359	sitosterol	36.91	1.32	0.75	5.37
MOL004328	naringenin	59.29	0.28	0.21	16.98
MOL005100	5, 7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one	47.74	0.28	0.27	16.51
MOL005815	Citromitin	86.90	0.88	0.51	15.62
MOL005828	nobiletin	61.67	1.05	0.52	16.20

Note: Mol: molecular; *OB*: oral bioavailability; Caco-2: Caco-2 permeability; *DL*: drug-likeness; *HL*: half-life.

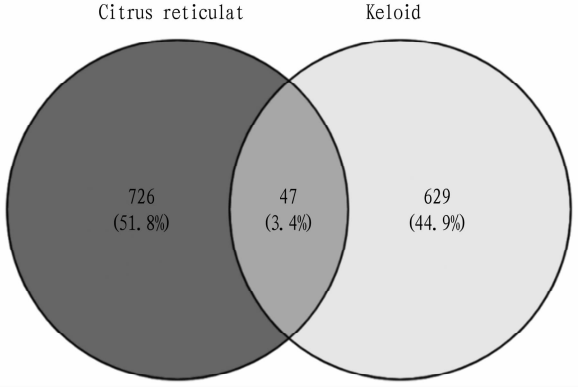


Fig. 2 Venn diagram of Citri Reticulatae Pericarpium targets and keloid treatment targets

3.2 Protein-protein interaction (PPI) analysis and compound-target network For PPI network analysis, the 47 overlapping treatment targets were analyzed in the STRING database and then illustrated (Fig. 3). The mean node degree of freedom was 13.070, and the mean aggregation coefficient was 0.681.

We constructed the compound-target interaction network with Cytoscape 3.7.1 software. There were 100 nodes in the network, including 33 bio-active molecules, 47 common target genes, 1 drug, 1 disease and 18 gene functions, as shown in Fig. 4. In the network, the three bio-active molecules with the highest degree values were naringenin, lauric Acid and Thymol. The three genes with the highest degree values were FAS, TNF and TGFB1.

3.3 Key targets analysis With the cytoHubba plugin in Cytoscape, we identified the top 10 gene targets of Citri Reticulatae Pericarpium in treating keloid (Fig. 5). For each targeted gene, the degree of color represents the importance of gene: the darker the more important. As shown in Fig. 5, target genes including *MMP9*, *IL6*, *TNF* and *TP53* may be an important regulator in the treatment of keloids.

3.4 GO enrichment and KEGG enrichment The results of the enrichment by ClueGO were shown in Fig. 6, with each circle representing a pathway. Pathways such as regulation of glomerulus development, fibroblast growth factor receptor signaling pathway involved in mammary gland specification and positive regulation of

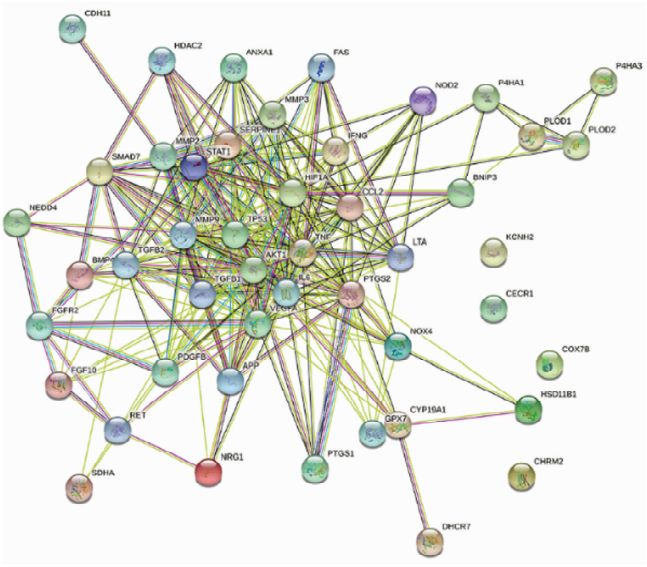
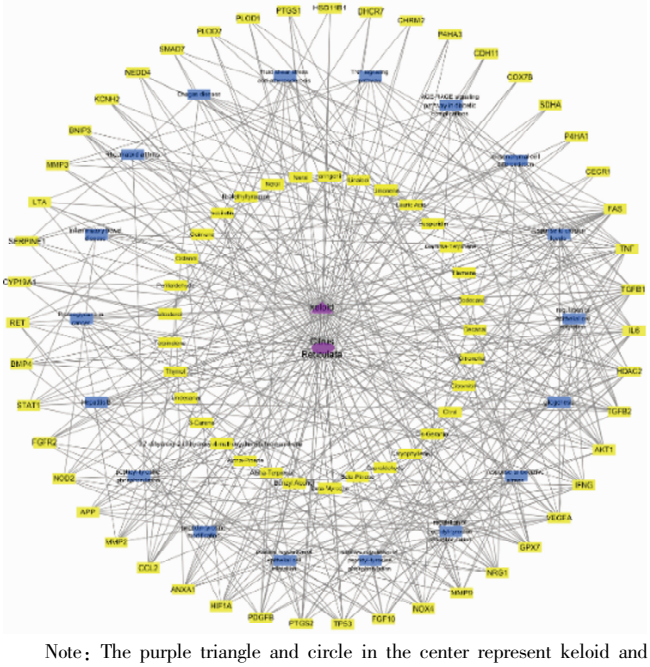


Fig. 3 PPI network of overlapping targets of Citri Reticulatae Pericarpium targets and keloid treatment targets



Note: The purple triangle and circle in the center represent keloid and Citri Reticulatae Pericarpium. The yellow, blue, and green oblong separately represent target genes, function, and compounds.

Fig. 4 Drug-disease-target-function network

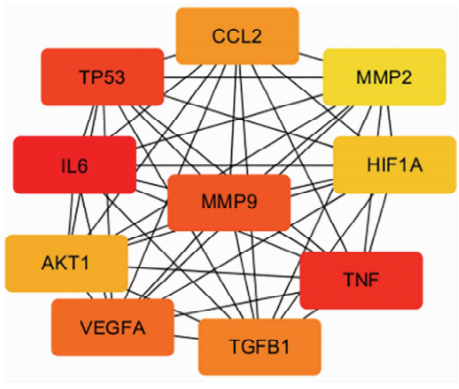


Fig. 5 CytoHubba results of overlapping targets of Citri Reticulatae Pericarpium targets and keloid treatment targets

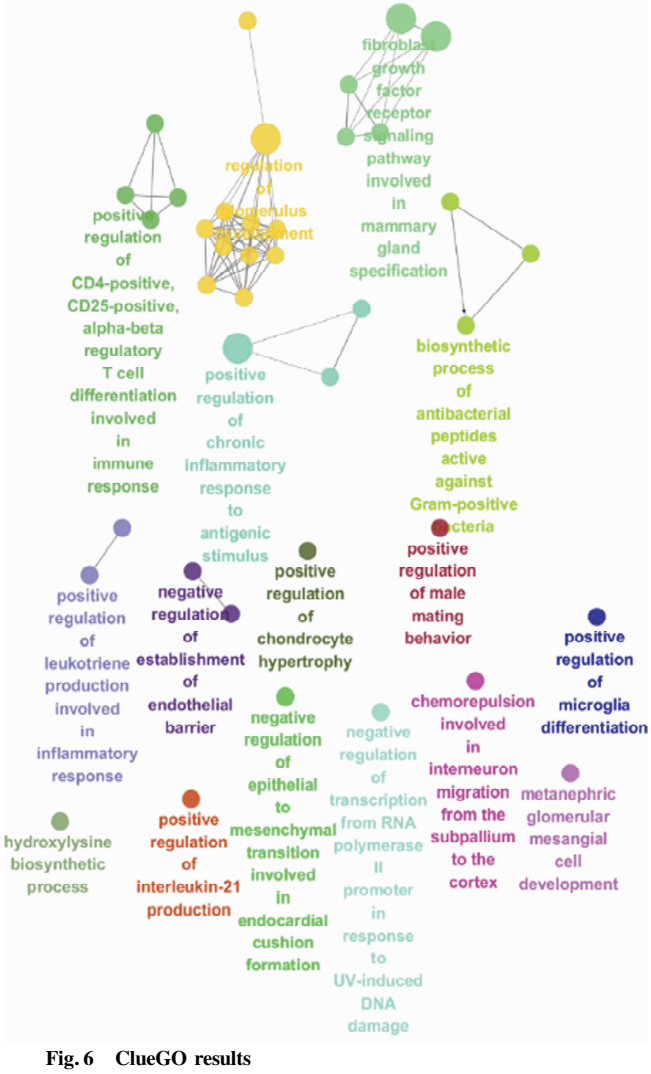
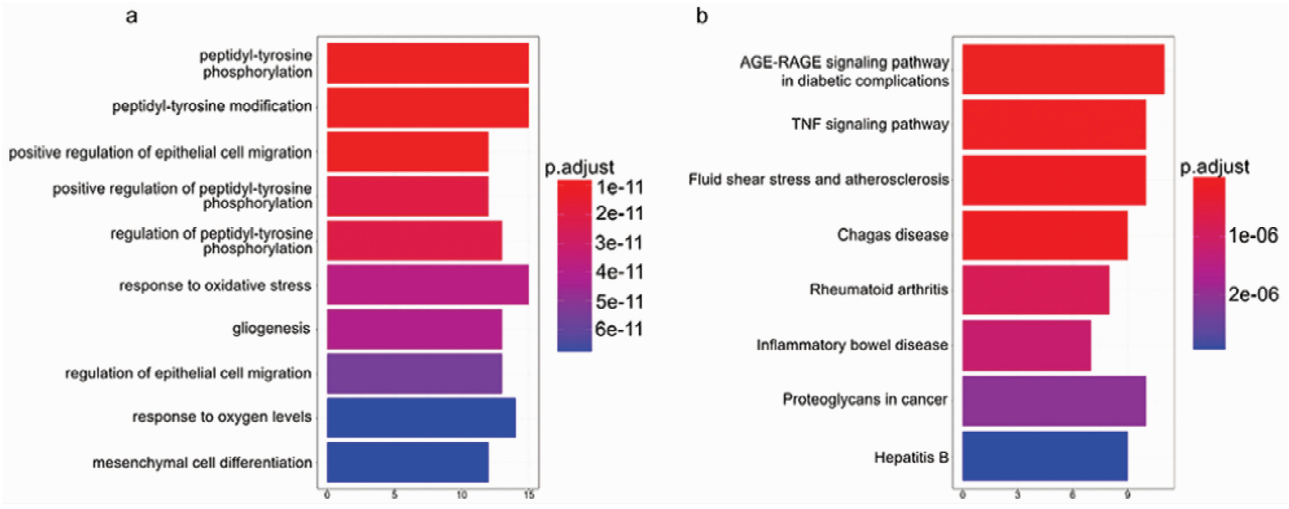


Fig. 6 ClueGO results

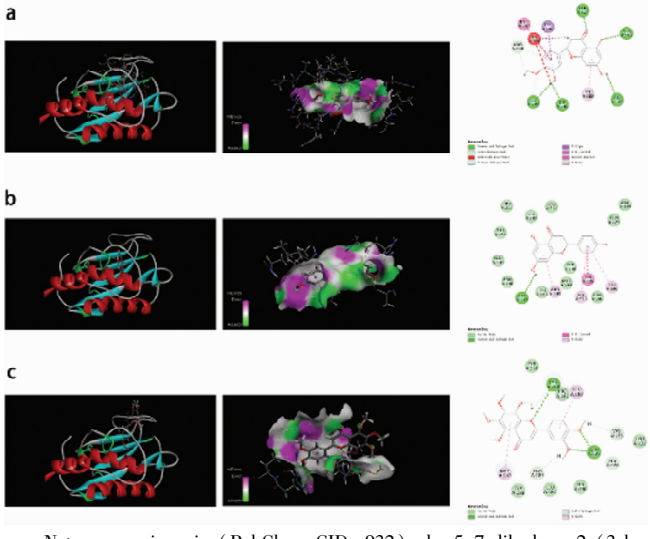
inflammatory response to antigenic stimulus were enriched. GO enrichment analysis of 47 target genes was performed as well. The top 10 significantly enriched terms were illustrated in Fig. 7a. We obtained 8 pathways in the KEGG enrichment analysis results (Fig. 7b).

3.5 Molecular docking results and analysis The MMP9 genes showed strong interactions with functional pathways and three components of Citri Reticulatae Pericarpium. Thus, we illustrated the interaction between the MMP9 protein with these three components as shown in Fig. 8. The Libdock scores of naringenin (PubChem CID: 932), 5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)chroman-4-one (PubChem CID: 676152) and nobiletin (PubChem CID: 72344) were 141.079, 154.408, and 47.661 8, respectively. This result revealed that the 5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one could be the most promising component of Citri Reticulatae Pericarpium for treating keloids targeting MMP9.



Note: a: GO: molecular function categories; b: KEGG signaling pathways.

Fig. 7 Enrichment analysis results of overlapping targets of Citri Reticulatae Pericarpium targets and keloid treatment targets



Note: a: naringenin (PubChem CID: 932); b: 5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one (PubChem CID: 676152); c: nobiletin (PubChem CID: 72344).

Fig. 8 Molecular docking results for the active compounds of Citri Reticulatae Pericarpium with *MMP9* gene

4 Discussion

In this study, we constructed a component-target network for the treatment of keloids with Citri Reticulatae Pericarpium by a network pharmacology approach and analyzed its possible mechanisms of action. After screening the active ingredients of Citri Reticulatae Pericarpium according to *OB* and *DL*, five active ingredients were obtained: sitosterol, naringenin, 5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl) chroman-4-one, citromitin and nobiletin; which were matched to 773 drug targets. After taking the intersection of Citri Reticulatae Pericarpium targets and keloid targets, 47 targets were obtained. Core targets such as MMP9, TNF, IL6, TP53, VEGFA, TGFβ1, CCL2, AKT1, HIF1A and MMP2 were underlined. The signaling pathways involved are the AGE-RAGE signaling pathway in diabetic complications, and TNF signaling pathway, *etc.*

Hypoxia-inducible factor-1A (HIF1A) is an important effector molecule in the hypoxic tissue microenvironment and is highly expressed in the hypoxic environment[24]. It has been found that the overexpression of the HIF1A in keloids can promote vascular endothelial growth factor (VEGF), angiogenesis, and inflammatory factors[24]. Simonart *et al.* [25] showed that HIF1A is positively correlated with interleukin-6 (IL-6) and inflammatory response in keloids tissue. Si *et al.* [26] found that HIF1A expression was higher in keloids tissue vascular cells than in normal skin tissue. In our study, hub genes were also found to be involved in the HIF-1 signaling pathway, which could be one of the important pathways of Citri Reticulatae Pericarpium for the treatment of keloids.

Extracellular matrix (glycoproteins and water) and increased deposition of collagen make up the majority of the keloid[27-28]. Various modulators, such as pre- and posttranscriptional modulators, as well as growth factors, take part in the keloids' abnormal growth[29]. Transforming growth factor and platelet-derived growth factor are vital in wound healing because they modulate fibroblast function[30]. The excessive proliferation of keloid fibroblasts and the excessive deposition of extracellular matrix (ECM) are required for the formation of keloids These processes could be summarized as the dysregulation of the fibroblast growth[31]. It is noted that transforming growth factor-β1 (TGFβ1) is an important factor in promoting ECM accumulation, which can promote type I collagen production in fibroblasts in keloid tissue. While matrix metalloproteinase (MMP) can degrade excessive ECM, thus maintaining the dynamic balance of ECM[32]. Tao Zhang *et al.* [33] showed that TGFβ1 expression was up-regulated in the cytoplasm of fibroblasts in proliferative scar tissue, which in turn promoted scar proliferation. In our study, the key genes obtained by network pharmacological analysis included Hub genes such as *TGFβ1* and *MMP-9*. The results of the enrichment analysis of GO and KEGG pathways also involved pathways such as mesenchymal cell differentiation and gliogenesis, which showed that Citri Reticulatae Pericarpium was found to be significant in controlling keloid fibroblast proliferation and ECM homeostasis.

It has been suggested that keloid is a chronic inflammatory response[34]. And the increased levels of pro-inflammatory factors such as HIF1A and IL-6 in keloids tissues can lead to abnormal differentiation and over-proliferation of cells, further aggravating the keloids and forming a vicious cycle[35]. Chen *et al.* [36] used cDNA microarray to discover that the expression of pro-inflammatory factors such as interleukin-1β(IL-1β), TNF-α and IL-6 was elevated in keloid fibroblasts. Various cytokines, including interleukin IL-6, interleukin-8 (IL-8), and interleukin-10 (IL-10), have been implicated in the pathogenesis of keloids[37]. It was shown that the inflammatory response was milder in well-healed scar tissue and suppression of the inflammatory response during trauma healing could reduce scar formation[38]. In the present study, we found that the TNF signaling pathway and other inflammatory pathways are involved in the treatment of keloids by Citri Reticulatae Pericarpium, with core targets including IL6, TNF, and HIF1A, which is consistent with the reviewed literature results.

5 Conclusions

In this paper, network pharmacology was used to explore the active compounds, potential targets and mechanisms of Citri Reticulatae Pericarpium in treating keloids. The results showed that the identified ingredients of Citri Reticulatae Pericarpium may play important roles in biological processes by modulating the *MMP9* genes and TNF-α, NF-κB signaling pathways. More importantly, our research provides valuable evidence for further investigation of Citri Reticulatae Pericarpium for treating keloids.

In this study, the active compounds, possible targets, and mechanisms of Citri Reticulatae Pericarpium in treating keloids were investigated using network pharmacology. The findings revealed that identified components of Citri Reticulatae Pericarpium could modulate key gene targets such as MMP9 and TNF-α, NF-B signaling pathways. More importantly, our findings add to the growing evidence supporting the application of Citri Reticulatae Pericarpium in the treatment of keloids.

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(From page 23)

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