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Exploration of action mechanisms of Resina Draconis (*Daemonorops draco* Bl.) against pain by network pharmacology and molecular docking analysis

Wen-Jie Lai[1], Chu-Yun Zhao[1], Shu-Zhen Lin[2], Hui Peng[2], Si-Ni Chen[2], Qing-Feng Liang[3], Shu-Mei Wang[1,3*], Dan Tang[2,3*]

[1]School of Pharmacy, Guangdong Pharmaceutical University, Guangzhou 510006, China. [2]School of Traditional Chinese Medicine, Guangdong Pharmaceutical University, Guangzhou 510006, China. [3]Key Laboratory of Digital Quality Evaluation of Chinese Materia Medica of State Administration of TCM and Engineering Technology Research Center for Chinese Materia Medica Quality of Guangdong Province, Guangdong Pharmaceutical University, Guangzhou 510006, China.

[*]**Corresponding to:** Dan Tang, School of Traditional Chinese Medicine, Guangdong Pharmaceutical University, No. 280, East Outer Ring Road, Panyu District, Guangzhou 510006, China. E-mail: tdpharm@126.com. Shu-Mei Wang, School of Pharmacy, Guangdong Pharmaceutical University, No. 280, East Outer Ring Road, Panyu District, Guangzhou 510006, China. E-mail: gdpuwsm@126.com.

Author contributions

Wen-Jie Lai was responsible for investigation, visualization, writing-original draft preparation methodology. Chu-Yun Zhao was responsible for investigation, visualization, data curation. Shu-Zhen Lin was responsible for formal analysis. Hui Peng was responsible for software. Si-Ni Chen was responsible for writing-reviewing and editing. Qing-Feng Liang was responsible for resources. Shu-Mei Wang was responsible for conceptualization, funding acquisition. Dan Tang was responsible for conceptualization, funding acquisition, writing-reviewing and editing.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

BP, biological processes; CC, cellular components; GO, gene ontology; ISAP, International Association for the Study of Pain. KEGG, Kyoto Encyclopedia of Genes and Genome; MF, molecular function; PPI, protein-protein interaction; TCM, Traditional Chinese medicine; ALB, albumin; TNF, tumor necrosis factor; AKT1, RAC-alpha serine/threonine-protein kinase 1; EGFR, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; SDF, structure data file; HPLC-DAD-ESI-TOF-MS, high-performance liquid chromatography coupled to electrospray time-of-flight mass spectrometry.

Peer review information

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Citation

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Abstract

Background: Resina Draconis is a traditional Chinese medicine mainly used to treat pain. However, the pharmacological mechanisms and chemical composition of Resina Draconis are not clear yet. **Methods:** In this study, based on the 21 main active components of Resina Draconis previously analyzed by our group, the potential action targets of the active components were predicted and screened out by using the databases such as Swiss Target Prediction and Pharmapper. The genes corresponding to the related targets were retrieved by UniProt and GeneCards, and then the "component-target" network model was established using Cytoscape 3.9.1 software. The protein-protein interaction network was constructed by using STRING database for analysis. The STRING database was used for enrichment analysis of gene ontology and Kyoto Encyclopedia of Genes and Genome pathways to explore the underlying action mechanisms. **Result:** A total of 21 main analgesic active components of Resina Draconis and 77 intersecting targets of Resina Draconis and pain were screened out. PPI network analysis indicated that such targets as albumin (ALB), tumor necrosis factor (TNF), RAC-alpha serine /threonine-protein kinase 1 (AKT1) and epidermal growth factor receptor (EGFR) might be the core targets of analgesia. Through gene ontology enrichment analysis, a total of 169 gene ontology entries were obtained ($P < 0.01$), including 111 biological processes, 31 molecular functions and 27 cellular components. Through enrichment analysis of KEGG pathways, a total of 112 ($P < 0.01$) signaling pathways were screened. **Conclusion:** Dracaenogenins A, Resveratrol and 7,4′-dihydroxyflavone in Resina Draconis may be the main material basis for analgesia, which can interact with multiple targets such as AlB, AKT1, TNF, and EGFR, and exerts analgesic effect through signaling pathways such as mitogen-activated protein kinase (MAPK) signaling pathway, PI3K-Akt signaling pathway, and Rap1 signaling pathway.

Keywords: Resina Draconis; pain; network pharmacology; molecular docking

Highlights

1. The pharmacological mechanisms of Resina Draconis in the treatment of pain were firstly explored by network pharmacology and molecular docking.
2. Resina Draconis exerts analgesic effect through MAPK, PI3K-Akt, and Rap1 signaling pathway.

Background

In 2020, the International Association for the Study of Pain (IASP) redefined pain, which states, "pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [1]. Pain is divided into 3 types: Chronic pain, acute pain, and unspecified pain. Generally, different types of chronic pain have different rates, which is related to a variety of factors, such as regional factors, socioeconomic factors, living habits, etc. Chronic pain is a major public health problem that affects 30%–40% of the population, that is, about 1 in every 3 people suffers from it [2]. The pathogenesis of pain is exceedingly complex. At present, western medicine is the main treatment for pain, especially antidepressants and antiepileptic drugs have the advantage of exact curative effect and quick effect. However, pain belongs to chronic pain, which often has a long course of the disease. During treatment, certain drug dependence and adverse drug reactions may occur, and the disease is prone to relapse after drug withdrawal, and the overall safety and effectiveness are still controversial, so pain is limited in its application. At present, more and more neurologists choose to treat pain with traditional Chinese medicine. The treatment of pain in TCM has a long history, including plant drugs, mineral drugs, animal drugs, Chinese herbal compounds and other traditional Chinese non-drug therapies [3–4].

Resina Draconis, also known as "Dragon's Blood", is a red resin extracted from the lipid-containing wood of *Dracaena cochinchinensis* (Lour. S.C. Chen), a plant of Liliaceae. Resina Draconis is known as the "sacred medicine for promoting blood circulation", because it has the remarkable effects of promoting blood circulation to remove blood stasis, and relieving swelling and pain, which is in line with the key pathogenesis of pain in traditional Chinese medicines, and its effect on chronic pain is remarkable [5]. Now, Resina Draconis has also been developed into a variety of marked medicines, such as Resina Draconis Capsule, Longxue Tongluo Capsule, Sanjie Zhentong Capsule, etc., which are widely used in clinical practice for pain treatment. Some previous studies on the analgesic pharmacological activities have been reported, however, considering the complex chemical composition of Resina Draconis such as homoisoflavones, dihydrochalcones, and stilbenes, the effective components and the underlying mechanisms of the Resina Draconis with analgesic effects are still need to be further excavated [6–8].

In this study, the pharmacological mechanisms of Resina Draconis in the treatment of pain were firstly studied by network pharmacology and molecular docking. Our previous research has revealed that there are 21 main chemical components in Resina Draconis [5]. In order to explore the analgesic mechanism of Resina Draconis, we intended to use the network pharmacology method to construct a "drug-target-disease" network based on the previous research, and explored the potential mechanisms of Resina Draconis in analgesia through network analysis, GO and KEGG analysis, to provide a scientific reference for clinical treatment and drug development [9].

Data and methods

Collection of active ingredients of Resina Draconis

Based on our preliminary work, 21 chemical components of Resina Draconis were collected, and the basic information of each chemical component was further searched in the PubChem database, the names of the chemical components were unified, and the PubChem ID and 2D structure diagram of each component were downloaded and saved [5].

Prediction of potential action targets of Resina Draconis

The obtained 2D structure diagram of chemical components was uploaded to Pharmmapper in SDF format (http://www.lilab-ecust.cn/pharmmapper/), Swiss TargetPrediction (http://www.swisstargetprediction.ch/) and other databases, and further in the UniProt (https://www.uniprot.org/) database for annotation and confirmation of target genes [10–14].

Screening of pain-related targets

With "pain" and "ache" as search keywords, disease targets related to pain were retrieved in the Gene Cards (https://www.genecards.org/) database [15]. Duplicate targets were combined and eliminated using the Uniprot database (https://www.uniprot.org/) . The inquired target protein was converted into the corresponding Gene symbol.

Screening of Resina Draconis intervention pain targets

The collected potential targets of the analgesic active components of Resina Draconis and pain-related disease targets were uploaded to Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/index.html), a Venn Diagram online mapping software, to obtain the intersection targets of the potential targets of the active components and the disease targets.

Construction of "drug-active ingredient-target" network diagram

The active ingredient target of Resina Draconis was introduced into Cytoscape 3.9.1 (http://www.cytoscape.org/) to construct the visual network diagram of "Resina Draconis-active ingredient-target".

Construction of protein-protein interaction (PPI) network diagram

The obtained target genes were uploaded to an online STRING 11.5 database, limiting the species to human, setting a confidence protein parameter score value > 0.400, obtaining corresponding protein interaction information, and analyzing the target proteins according to the results.

GO enrichment analysis and KEGG pathway enrichment analysis

GO and KEGG pathway enrichment assays are commonly used analytical methods to elucidate the roles of target proteins of compounds in signaling pathways and gene functions. The intersecting targets collected in item 1.4 were imported into DAVID database and the species was defined as human. The threshold was set as $P < 0.01$ for GO biological process enrichment analysis and KEGG signaling pathway enrichment analysis. The results were then visualized by online mapping website BioInformatics (http://www.bioinformatics.com.cn/).

Docking of Resina Draconis active components with potential target molecules

In order to better illustrate the binding between the potential analgesic targets of the active ingredients of Resina Draconis and the corresponding active ingredients, the core targets with the highest median value in the PPI network were molecularly docked with their corresponding active ingredients. The structure data file (SDF) format of the active components collected in "1.1" was selected and imported into Chemdraw 3D software for structural optimization, to obtain the mol2 format of the lowest energy conformation of the active component molecules, and exported to pdbqt format by AutoDockTools software. The 3D structure of the core target protein was downloaded from the PDB database (http://www.wwpdb.org/) and stored in pdb format, and the preprocessing of the protein receptor molecule was performed using PyMOL and AutoDockTools software [16]. The pre-processed active components and potential targets were imported into docking software AutoDockTools for molecular docking, and the results were saved in pdbqt format. Molecular docking result files were converted into pdb format with

the help of PyMOL software which was used for visual analysis.

Results

Collection of main chemical components from Resina Draconis

A total of 21 main compounds with various structures were tentatively identified and characterized in Resina Draconis by high-performance liquid chromatography coupled to electrospray time-of-flight mass spectrometry (HPLC-DAD-ESI-TOF-MS) technique in our previous research [5]. Thus, in this study, the 21 main compounds were selected for further network pharmacology analysis. The compound names and molecular structure diagrams of the 21 compounds were listed through the PubChem database and relevant literature (Table 1).

Prediction of potential targets of main components of Resina Draconis

The 21 main compounds were uploaded to the Pharmmapper and Swiss TargetPrediction databases for potential target prediction. The predicted targets were aggregated and deduplicated for each compound in both platforms, then were checked and corrected by UniProt online platform. Eventually, a total of 804 potential targets were obtained.

Screening of pain-related targets

A total of 1,202 disease targets related to pain were obtained by retrieving the Genecard database, which was mapped with the potential targets in item "2.2". Through online Venn diagram drawing, a total of 77 related targets that were possible to intervene in pain were finally obtained, as shown in Figure 1.

Network construction and analysis of analgesic active ingredients of Resina Draconis

The analgesic active components of Resina Draconis were imported into Cytoscape3.9.1 software to construct a visual network diagram of "Resina Draconis-active components-target", as shown in Figure 2. Meanwhile, network topology analysis was performed, as shown in Table 2.

Table 1 Main chemical ingredient in Resina Draconis

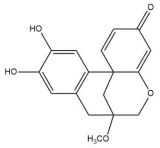
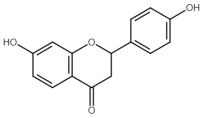
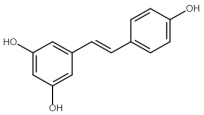
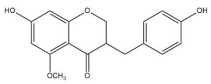
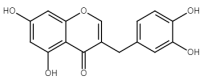
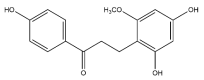
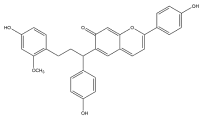
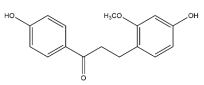
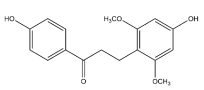
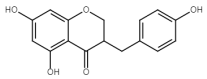
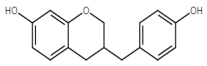
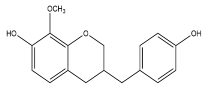
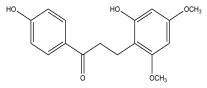
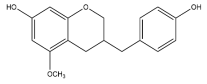
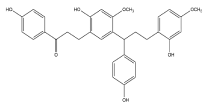
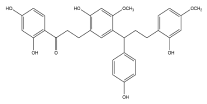
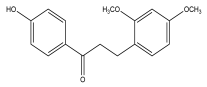
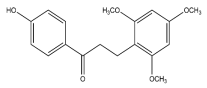
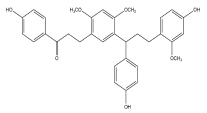
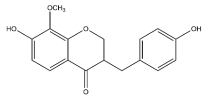
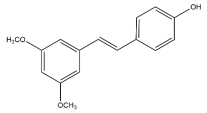
No.	Compound name	Structure diagram
1	10,11-dihydroxy-7- methoxydracaenone C	
2	7,4′-dihydroxyflavone	
3	Resveratrol	
4	7,4′-dihydroxy-5-methoxyhomoisoflavanone	
5	5,7,3′,4′-tetrahydroxyhomoisoflavone	
6	Loureirin D	
7	Dracaenogenins A	
8	Loureirin C	
9	4,4′-dihydroxy-2,6-dimethoxydihydrochalcone	

Table 1 Main chemical ingredient in Resina Draconis (*continued*)

No.	Compound name	Structure diagram
10	5,7,4'-trihydroxyhomoisoflavanone	
11	7,4′-dihydroxyhomoisoflavan	
12	7,4′-dihydroxy-8-methoxyhomoisoflavan	
13	2,4′-dihydroxy-4,6-dimethoxydihydrochalcone	
14	7,4′-dihydroxy-5-methoxyhomoisoflavan	
15	Cinnabarone	
16	Hydroxyl cinnabarone	
17	Loureirin A	
18	Loureirin B	
19	Cochinchinenin B	
20	7,4′-dihydroxy-8-methoxyhomoisoflavanone	
21	Pterostilbene	

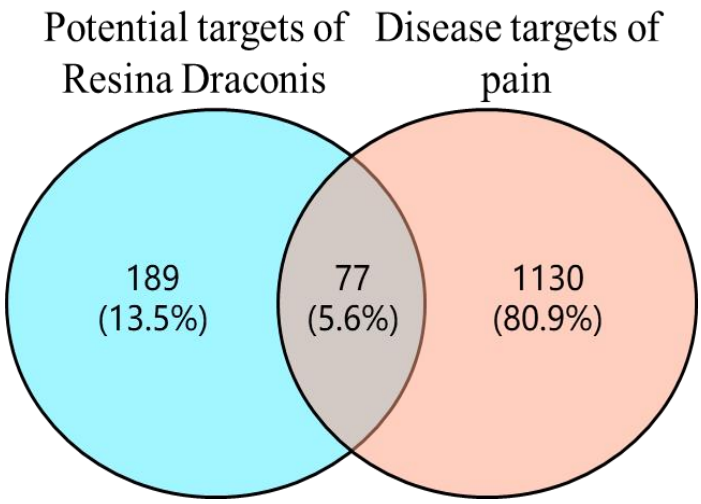


Figure 1 Venn diagram for mutual map of potential targets and pain gene. The common target for drug and disease by Venn diagrams. Each circle represents the marked database, the sum of the numbers in them is the total number of targets in the database, and the number in the intersection of the two circles represents the number of targets shared by the two parts.

Table 2 Information for active components of Resina Draconis

Compound name	Node degree	Median centrality
7,4′-dihydroxy-8-methoxyhomoisoflavanone	16	0.0772
Cinnabarone	16	0.1066
Loureirin A	15	0.0440
7,4′-dihydroxy-8-methoxyhomoisoflavan	15	0.0725
Resveratrol	15	0.1134
7,4′-dihydroxyflavone	15	0.0814
5,7,3′,4′-tetrahydroxyhomoisoflavone	14	0.1243
7,4′-dihydroxyhomoisoflavan	14	0.1291
7,4′-dihydroxy-5-methoxyhomoisoflavan	14	0.0566
Pterostilbene	14	0.0812
Loureirin B	14	0.0698
5,7,4′-trihydroxyhomoisoflavanone	13	0.0646
2,4′-dihydroxy-4,6-dimethoxydihydrochalcone	13	0.0267
Dracaenogenins A	12	0.0634
7,4′-dihydroxy-5-methoxyhomoisoflavanone	12	0.0534
Loureirin D	12	0.0264
Hydroxyl cinnabarone	12	0.0745
Cochinchinenin B	11	0.0410
4,4′-dihydroxy-2,6-dimethoxydihydrochalcone	11	0.0219
Loureirin C	10	0.0292
10,11-dihydroxy-7- methoxydracaenone C	9	0.0723

In the network, nodes represent the information of compounds, and edges represent the “active ingredient-target” interaction. Ellipse was used as medicinal material, and the rectangle was used as an action target.

Construction and analysis of PPI network diagram

The 77 common potential targets were uploaded to the STRING database, and protein interaction data were obtained after the operation. Network topology analysis was performed using the Analyzer Network function in Cytoscape3.9.1, and the core target interaction network diagram was drawn, as shown in Figure 3. The depth and size of the color indicate how important the node is in the network. In this figure, 772 sides of protein interaction were generated by the interaction of intersecting targets. It was speculated that four core targets with node degree value ≥ 48, namely, ALB (degree value = 60), TNF (degree value = 53), AKT1 (degree value = 53) and EGFR (degree value = 48), might be the key targets for analgesia.

GO enrichment analysis and KEGG pathway enrichment analysis

GO enrichment analysis of component-disease intersection target gene GO enrichment analysis was performed on 77 intersecting targets using the DAVID database, and a total of 169 GO entries ($P \leq 0.01$) were obtained, including 111 biological processes (BP). It mainly involves heterologous xenobiotic stimulation, signal transduction, and positive regulation of gene expression. There are 27 cellular components (CC), mainly including the plasma membrane, cytoplasm and integral component of membrane; 31 molecular

function (MF), mainly involving protein binding, identical protein binding, and ATP binding. The histogram was drawn based on the first 10 results (Figure 4).

Enrichment of KEGG pathway of component-disease intersection target gene The enrichment analysis of KEGG pathways was performed on 77 intersecting targets using DAVID database, and 112 related pathways with $P < 0.01$ were finally enriched. These include Endocrine resistance, MAPK signaling pathway, PI3K/Akt signaling pathway, and Pap1 signaling pathway. The top 20 signaling pathways were selected for the above results and the bubble diagram was drawn (Figure 5), where the X axis represents the percentage of genes, the Y axis represents the name of the signaling pathway, the bubble area represents the number of enriched genes, and the bubble color represents the size of *P*-value.

Docking of active ingredients with potential target protein molecules 21 active ingredients were screened out by reverse screening of ALB, ATK1, TNF and EGFR for molecular docking. The selected target information and molecular docking results are shown in Figure 6. It is generally believed that the lower the energy when the protein receptor binds to the molecular ligand, the more stable the conformation is, and the greater the possibility of interaction is. Molecular docking results showed that most ingredients and proteins have the strong binding ability, and the molecular docking visualization analysis was carried out with the help of Pymol software (Figure 7).

Discussion

Resina Draconis is a traditional Chinese medicine that has a variety of pharmacological effects, such as promoting blood circulation, removing blood stasis, analgesia, anti-inflammatory, and hemostasis. In recent years, some studies have found that the total flavonoids of Resina Draconis have a good analgesic effect, which often occurs simultaneously with antibacterial and anti-inflammatory effects [17, 18].

Its effect on chronic pain is remarkable, however, the effective components and mechanisms are unclear yet. Therefore, based on network pharmacology and molecular docking technology, this study screened out the main active components and potential targets of analgesia of Resina Draconis, and explored its possible analgesic mechanism.

In this study, potential targets were retrieved through 21 components of Resina Draconis, including ALB, ATK1, TNF, EGFR, SRC, CASP3, JUN, PTGS2, etc. ALB, also known as negative acute response protein, is the most abundant protein in plasma in the human body. It is commonly used in systemic inflammatory response syndrome (SIRS) and sepsis by reducing oxidative stress and improving cellular oxidative state thereby playing an important role in anti-inflammation. Studies have shown that supplementing exogenous ALB to SIRS patients can effectively improve the prognosis of patients [19]. AKT1 plays a key role in regulating cell proliferation and growth, resisting apoptosis, and promoting angiogenesis, and its mechanism may be related to the activation of PI3K-AKT signaling pathway, up-regulation of VEGF expression, and inhibition of cellular inflammatory response [20]. Pro-inflammatory factor (TNF-α) is the

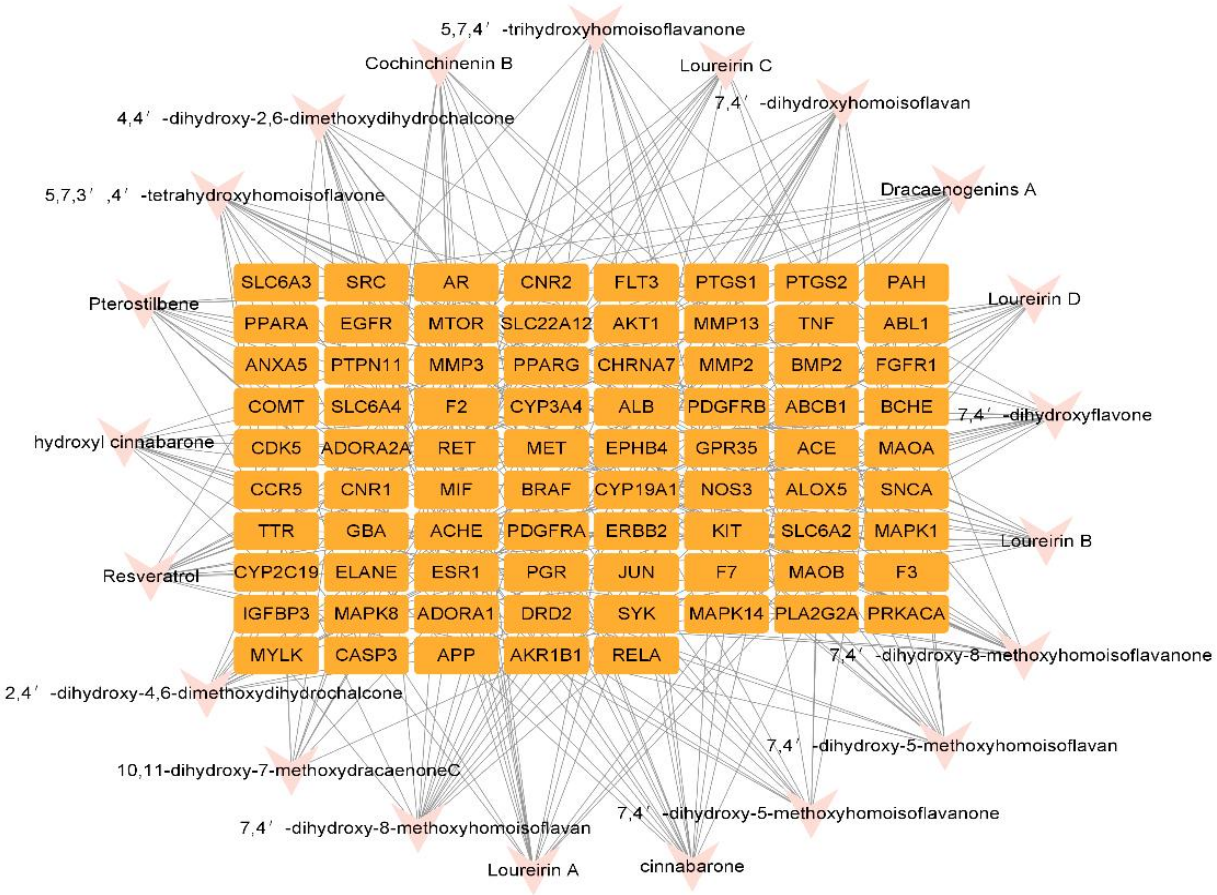


Figure 2 Diagram of components-target network. The network of Components-Target. Pink V represent key compounds in Resina Draconis; orange triangle represent common targets of drug and pain disease.

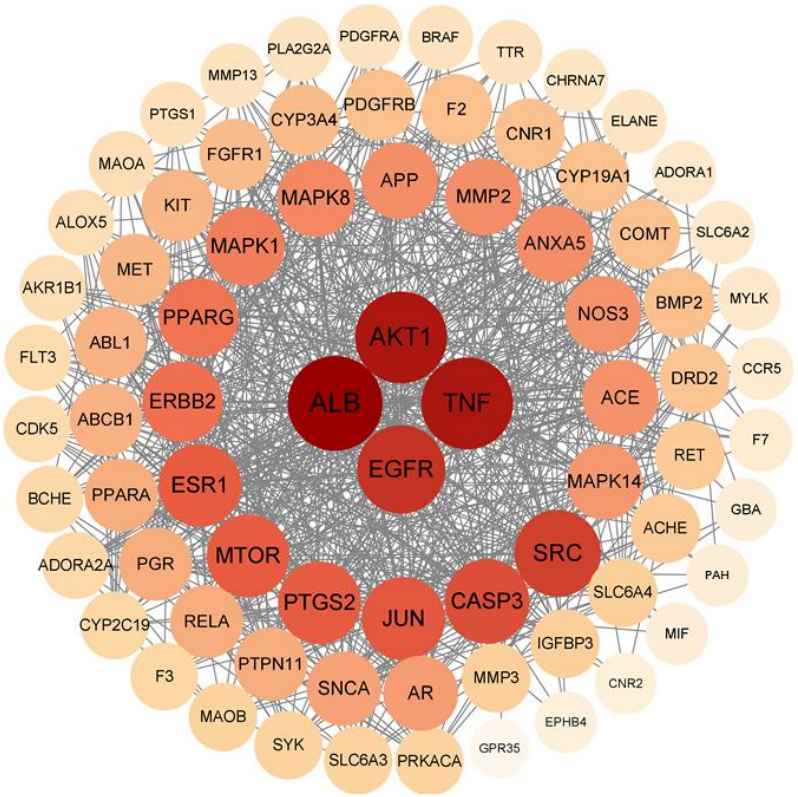


Figure 3 PPI interaction network. The common target PPI network for drug and disease. Each small circle represents a protein, and their interconnected lines represent interactions between them. PPI, protein-protein interaction.

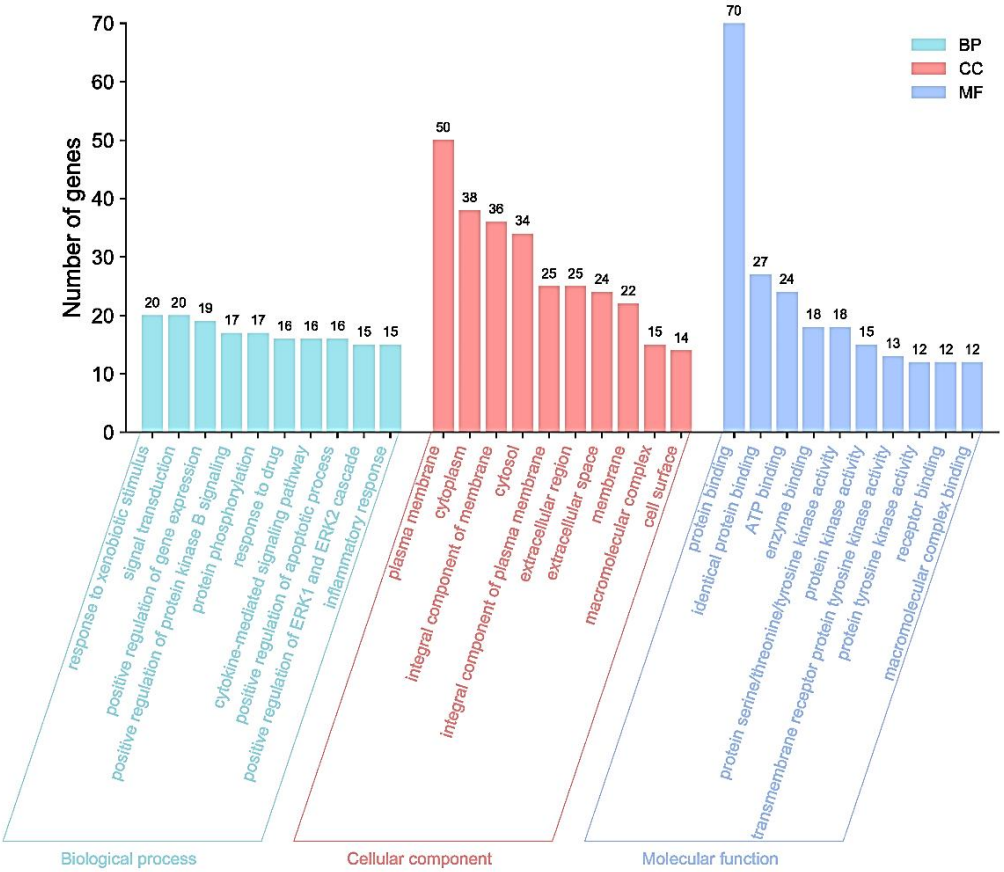


Figure 4 GO enrichment analysis of intersection targets. GO enrichment analysis, including biological process, molecular function and cellular component. BP, biological processes; CC, cellular components; MF, molecular function.

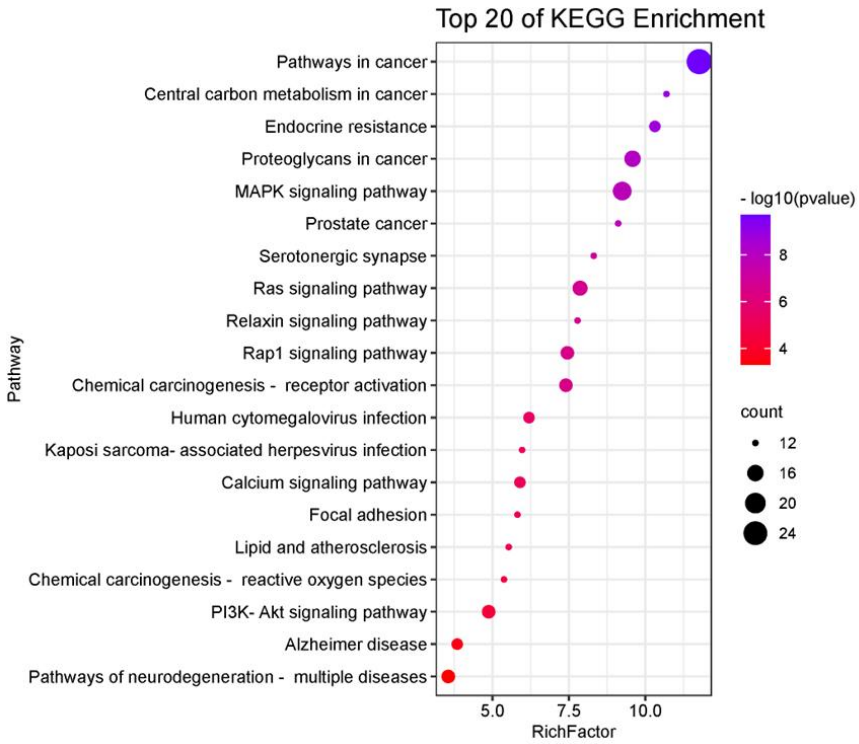


Figure 5 Analysis of KEGG pathway enrichment at intersecting targets. Enrichment analysis of GO pathways. The abscissa represents the proportion of the target, and the ordinate represents the ID of the enriched word. The ordinate refers to the number of genes involved in each pixel. Colors ranging from red to blue represent q-values from small to large, which means that the depth of the color is proportional to the degree of enrichment. KEGG, Kyoto Encyclopedia of Genes and Genome; GO, gene ontology.

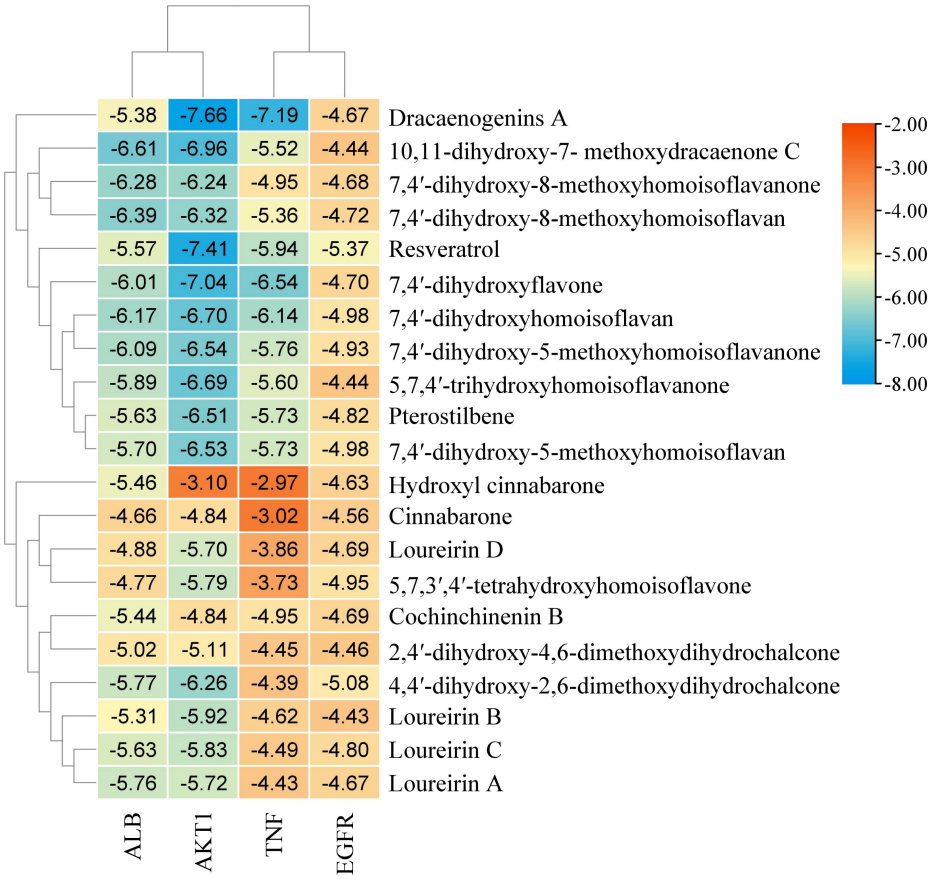


Figure 6 Molecular docking heat-map. The difference in color indicates the difference in binding energy. The lines represent the clustering relationship between the components of Resina Draconis and the disease targets.

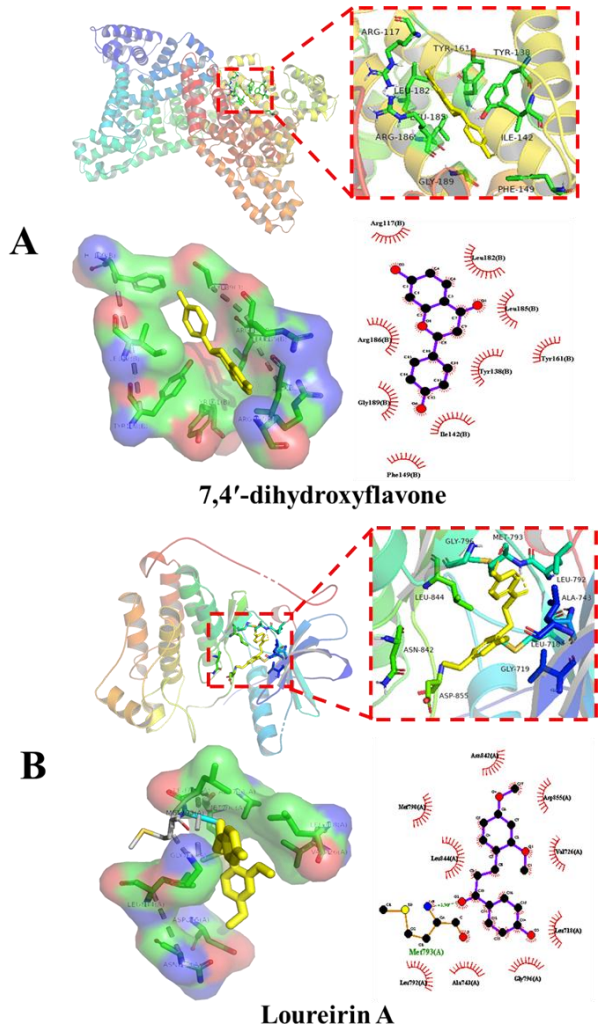


Figure 7 Diagram of molecular docking. (A) Docking diagram of AKT1 target and Resina Draconis 7,4'-dihydroxyflavone. (B) Docking diagram of AKT1 target and Resina Draconis Loureirin A. On top is the overall graph of the docking results and some details of the docking result. Below are 3D and 2D diagrams of the docking result are shown.

earliest and most important inflammatory mediator in the process of the inflammatory response, which can activate neutrophils and lymphocytes, increase the permeability of vascular endothelial cells, and regulate the metabolic activities of other tissues and promote the synthesis and release of other cytokines. The synthesis and release of cytokines can promote inflammatory pain by mediating inflammation [21]. Epidermal growth factor receptor (EGFR) can promote the proliferation and differentiation of epithelial cells and play an important regulatory role in airway inflammation [22].

GO functional enrichment analysis showed Resina Draconis's main involvement in response to xenobiotic stimulus, signal transduction, positive regulation of gene expression, cellular components with the plasma membrane, cytoplasm, an integral component of membrane, protein binding, identical protein binding, ATP binding, etc. play analgesic and anti-inflammatory effects. The results of KEGG pathway enrichment analysis showed that Resina Draconis can act on Endocrine resistance, MAPK signaling pathway, PI3K-Akt signaling pathway, and Rap1 signaling pathway, and other signaling pathways which play important roles in its anti-inflammatory and analgesic effect. The p38 mitogen-activated protein kinase in the MAPK signal transduction pathway mainly mediates inflammation and apoptosis-related pathways, inhibits the release of the inflammatory factor TNF-α, and then triggers an inflammatory cascade. By mediating central sensitization processes, it exerts analgesic effect. The PI3K-AKT signaling pathway is an important intracellular signaling pathway that can regulate various cellular functions including metabolism, growth, proliferation, survival, transcription, and protein synthesis. After being activated, PI3K-Akt signaling pathway can cause phosphorylation of Akt to promote cell proliferation, inhibit apoptosis, and increase the expression of inflammatory factors [23].

Furthermore, the results of network pharmacology were further validated by molecular docking. The results of molecular docking show that there are binding sites between the core targets of ALB, AKT1, TNF, and EGFR and their corresponding compounds, with the lowest binding energy ranging from –7.66 to –2.97 kJ/mol. Conjugation and other intermolecular binding forces further verify that they are potential active ingredients for analgesia.

In summary, the action mechanisms of the main active components of Resina Draconis are explored in this study by network pharmacology, indicating that the analgesic effects of Resina Draconis have the characteristics of multi-component, multi-target, multi-path, and multi-mechanism, which would provide a reference for further study on analgesic effects of Resina Draconis.

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