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Exploring the Medication Rules and Mechanisms of Patent Application of Traditional Chinese Medicine Topical Ointment Against Gouty Arthritis Based on Data Mining and Network Pharmacology

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ABSTRACT

Background: Based on the patent database of the China National Intellectual Property Administration, to analyze the medication rule and mechanism of patent of Traditional Chinese Medicine （TCM） external ointment in the treatment of gouty arthritis (GA).

Methods: The database of patents for TCM external ointment on the treatment of GA were retrieved according to the inclusion and exclusion criteria. Patent set of TCM external ointment on the treatment of GA were constructed after deduplication through Microsoft Excel 2019. The frequency, properties, flavors, meridian tropism were further performed to screen the core external Chinese medicine datasets in the treatment of GA. SPSS software was used for statistical analysis, correlation analysis, and cluster analysis, etc. Exploring the therapeutic targets and related pathways of GA core prescriptions through network pharmacology, and evaluating the binding ability and stability between potential key targets and active ingredients through molecular docking.

Results: (1) General situation: There are 33 Chinese medicine prescription patents included in the treatment of GA, involving 226 kinds of TCM. (2) Usage frequency: There are 19 TCM with a usage frequency of more than 5 times, among which the top three are: myrrh (17 times, 51.52%), frankincense (15 times, 45.45%), and white atractylodes (15 times, 45.45%), as the core traditional Chinese medicines. (3) Properties of TCM: TCM that are cold, warm, hard, and sweet are commonly used, mainly in the liver meridian, while those that promote blood circulation and remove blood stasis are most commonly used. (4) Association analysis of TCM: The top 5 drug pairs with the highest correlation are myrrh frankincense, myrrh baizhi frankincense, myrrh rhubarb frankincense, myrrh angelica frankincense, and myrrh safflower frankincense baizhi. (5) Cluster analysis: Three clusters of TCM were obtained. (6) Network pharmacology: Core TCM contains 58 active ingredients, corresponding to 75 targets. After intersecting with 246 GAs, 10 common targets were obtained. Through PPI network topology analysis, the main targets of core TCM for treating GAs may be PTGS2, PGR, NCOA2, NR3C2, HSP90AA1, etc. GO and KEGG pathway enrichment analysis confirmed that the active ingredients of core TCM mainly act on related targets such as cAMP and interleukin-6, and treat GA through positive regulation of classical NF kappaB signalling transduction, positive regulation of RNA polymerase I transcription, positive regulation of phosphatidylinositol 3-kinase/protein kinase B signalling transduction and other signalling pathways; Molecular docking shows good binding ability between key active ingredients and core targets.

Conclusion: Through multidimensional data mining analysis, it has been confirmed that most of the TCM topical ointments used to treat GA have the characteristics of promoting blood circulation, removing blood stasis, clearing heat, and detoxifying. The core active ingredients of TCM, beta sitosterol, stigmasterol, and quercetin, mainly act on targets such as PTGS2 and PGR to treat GA.

INTRODUCTION

Gouty Arthritis (GA) is an inflammatory joint disease characterized by a significant increase in blood uric acid levels and the deposition of urate crystals in joints and surrounding tissues due to disorders in purine metabolism. The main clinical manifestations include joint swelling, pain, fever, and limited mobility. Its onset is related to various factors such as genetic factors, lifestyle, and environmental factors L W et al. 2021, X L et al. (2021). According to statistics from 2015, the global prevalence of gout ranged from 0.1% to 10% Kuo C F et al. (2015). A study showed that the overall standardized prevalence of gout in Chinese adults in 2019 was

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Key words: Gouty Arthritis; Patent Chinese medicine prescription ; External use of herbal medicines; Medication rule; Network pharmacology.

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3.2% M Z et al. (2021). The incidence rate of gout is increasing year by year. It is more common in men, and the disease is getting younger BRANCH C M A R. (2016). It is closely related to cardiovascular, cerebrovascular, kidney and other chronic diseases Bardin T et al. (2017). It affects the quality of life of patients, and brings heavy medical and economic burden to patients' families and society.

The main methods of modern medical treatment for GA are alkalinization of urine, reduction of uric acid production, and promotion of purine excretion. Traditional Chinese Medicine （TCM）believes that the onset of gout is caused by metabolic disorders in the spleen and kidneys, with internal generation of turbidity and toxins YH L et al. (2024). This is compounded by fatigue, overeating, and wind and cold, leading to obstruction of meridians and obstruction of qi and blood flow. In recent years, with the continuous progress in exploring the pathogenesis of GA, treatment strategies have become more precise and diversified. Traditional oral medication treatment often faces many challenges, such as systemic side effects and unstable therapeutic effects caused by individual differences. However, Chinese herbal topical ointments play an important role in reducing inflammation, relieving pain, and improving joint function due to the natural characteristics of their Chinese herbal ingredients and local administration methods. Mr. Wu Zun from the Qing Dynasty recorded it in Liye Pianwen: “the principle of external treatment, also known as the principle of internal treatment, the method of external treatment, also known as the method of internal treatment, and the difference between the above two lies in the different ways of drug administration” emphasizes the importance of external treatment in the treatment of surgical diseases LC L. (2005). The patent for topical TCM compound is derived from long-term clinical practice, which is often effective and highly reproducible. It plays an important role in the treatment of surgical diseases using TCM external treatment methods. They can not only directly act on the affected area, increase drug concentration, but also avoid metabolic losses and potential side effects caused by oral medication passing through the digestive system and blood circulation.

TCM patent formulas are the carriers of core technologies in the modern new drug research and development industry, and are the brilliant crystallization of clinical practice experience and scientific research. It has the significant characteristics of precise therapeutic effect and strong repeatability, and is the most direct form of transformation of scientific research achievements in TCM. It is also a key component of the traditional Chinese medicine market. This study uses data mining methods to summarize the medication rules of patent herbal plaster for GA treatment by retrieving the patent prescriptions of herbal plaster for external use for GA treatment in the China National Intellectual Property Administration of China HS W et al. (2022). Using network pharmacology methods to discover the core traditional Chinese medicine, main active ingredients, and corresponding targets for treating GA, predict important signaling pathways for treating GA, perform molecular docking analysis on the core targets and main active ingredients, provide reference for the selection of traditional Chinese medicine external treatment GA formulas, and also provide effective formula combinations and ideas for the development of GA new drugs.

MATERIALS AND METHODS

Data Sources

Log in to the China Patent Announcement Website of the China National Intellectual Property Administration（http://epub.sipo.gov.cn）In the advanced query interface, select both "Invention Authorization" and "Invention Publication", and search for "Gouty Arthritis", "Traditional Chinese Medicine", and "Gao" as keywords in the "Text" and "Abstract/Brief Explanation" items respectively. The search content will be unified, deduplicated, and filtered. The search time range is from the establishment of the patent database to August 2024.

Inclusion And Exclusion Criteria

Inclusion criteria: ① Patent prescriptions of TCM used to treat gouty arthritis; ② The patented prescription dosage form is an external ointment; ③ The prescription is complete and contains clear TCM components; ④ The patent name does not mention the topical ointment for gouty joints, but the details page clearly states the patent prescription for treating gouty joints.

Exclusion criteria: ① Patents in the food, beverage, and health categories; ② Patent for the combination of TCM and Western medicine③ Patent for internal use; ④ The patent contains extracts of TCM that cannot be clearly identified as their source; ⑤ The composition of patent prescriptions is unclear.

Data Processing

Data Entry and Standardization Processing

Manually input eligible patent prescriptions into Microsoft Excel2019, create data files, and have two people responsible for reviewing to ensure the accuracy

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of data entry. Referring to the "Chinese Pharmacopoeia (2020 Edition): Volume 1" COMMISSION C P. (2020). "Chinese Materia Medica" XM G. (2002). "Dictionary of Traditional Chinese Medicine" MEDICINE N U O T C. (2006). and "Chinese Materia Medica" MEDICINE E C O C M M O T S A O T C. (1999). standardize the names of TCM, such as standardizing "Shengdi" as "Shengdihuang", "Danggui Wei" as "Danggui", and "Seven Leaves and One Branch Flower" as "Chonglou".

Data Analysis

Microsoft Excel 2019 creates data files for statistical analysis of drug properties, taste, meridian tropism, and frequency. SPSS software was used for association rule analysis and cluster analysis of high-frequency drugs.

Network Pharmacology Analysis

Obtaining Core Active Ingredients and Targets of TCM

Using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), (http://tcmspw.com/tcmsp.php) Retrieve the active ingredients and corresponding targets of TCM with a medication frequency of ≥ 15 times, screen the active ingredients of the core drug group based on pharmacokinetic parameters such as oral bioavailability (0B) ≥ 30% and drug likeness (DL) ≥ 0.18, and obtain relevant target information. In the UniProt database (http://www. Uniprot. org/) will convert the target protein into a unified gene name.

Acquisition of Targets Related to Gouty Arthritis

Input "gouty arthritis" in Gene Cards (https://www.genecards.org) and OMIM (https://omim.org/) databases to search for disease targets related to gouty arthritis. Convert all target names into standard gene names through the Uni Port database(https://www.uniprot.org/). Import the target genes of drugs and diseases into Excel, map to obtain the common targets of drugs and diseases, and draw a Venn diagram through the online mapping website EVENN (http://www.ehbio.com/test/venn/#/).

Construction Of the Core Traditional Chinese Medicine - Active Ingredients - Gene Targets - Disease Network

The active ingredients of the core traditional Chinese medicine for treating GA and related targets obtained above were used to construct a traditional Chinese medicine - active ingredients - targets - disease targets network diagram through Cytoscape 3.10.2 software, to preliminarily study the pharmacological effects and action mechanisms of the core traditional Chinese medicine in treating GA.

Protein-Protein Interaction (Ppi) Network Construction

To study the interaction of target proteins and determine the core traditional Chinese medicine action target group, upload the above intersection targets to the String11.5 platform (https://cn.string-db.org/), and obtain the PPI network interaction diagram through online analysis. Screen key core targets according to the contribution value of the targets to the treatment of GA.

Gene Ontology (Go) Function and Kyoto Encyclopedia of Genes and Genomes (Kegg) Pathway Enrichment Analysis

Perform GO (gene ontology, GO) function and KEGG (Kyoto Encyclopedia of Genes and Genomes, KEGG) pathway enrichment analysis on common target genes, and use the DAVID database to analyze the GO function and KEGG pathway enrichment results. Among them, GO enrichment analysis includes three parts: biological process (BP), molecular function (MF), and cell component (CC). Draw GO and KEGG enrichment diagrams through the online drawing website of Microbial Letter (www.bio informatics.com.cn).

Component-Target Molecular Docking

Select the top two target genes ranked by degree value for molecular docking. Use Auto Dock Tools 1.5.6 for molecular docking, and use PyMOL 4.6.0 and Discovery studio 2019 software for visualization processing.

RESULTS

Data Retrieval Results

Results Of TCM Prescription Patent Retrieval

After retrieval, a total of 47 patents were obtained. After screening and deduplication, 33 patents were included in the analysis. All of them belong to TCM prescriptions for the treatment of GA with external ointments of TCM. The publication time of the 33 patents is from December 1993 to August 2024.

Statistical Analysis of Drug Frequency

The included patents involve 33prescriptions a and a total of 226 traditional Chinese medicines.

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The total frequency of use is 528 times. Among them, 41 traditional Chinese medicines have a frequency of use of ≥4 times.

The traditional Chinese medicines in the top 20 in terms of frequency of use in prescriptions are shown in Table 1.

Table 1: Frequency Distribution of High Frequency TCM

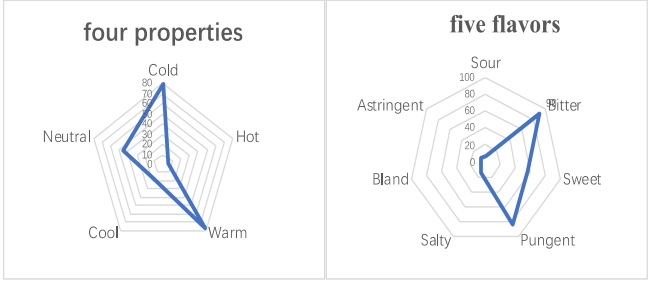
NO.	TCM	Frequency	proportion (%)	NO.	TCM	Frequency	proportion (%)
1	Myrrh	17	51.52	11	Clematis chinensis	7	21.21
2	Frankincense	15	45.45	12	Radix notoginseng	7	21.21
3	Radix angelicae	15	45.45	13	Lycopodium clavatum	7	21.21
4	Safflower	11	33.33	14	Musk	6	18.18
5	Radix aconiti	11	33.33	15	Radix Aconiti Kusnezoffii	6	18.18
6	Rhubarb	10	30.3	16	Semen strychni	6	18.18
7	Borneol	9	27.27	17	Paris polyphylla	6	18.18
8	Cortex phellodendri	9	27.27	18	Angelica pubescens	6	18.18
9	Chinses angelica	9	27.27	19	Ground beeltle	6	18.18
10	Dragon's blood	9	27.27	20	Notopterygium	5	15.15

Analysis Of Properties, Flavors, Meridian Tropism and Efficacy Of TCM

Conduct statistical analysis on the properties, flavors and meridian tropism of all TCM in the patent prescriptions. For TCM with multiple properties and flavors, all their properties and flavors are included in the statistics. Conduct statistics on properties, flavors and meridian tropism according to drug types and drug frequencies respectively. Among them, the analysis results according to drug types show that the properties of 226 TCM appear 226 times in total. Cold nature (80 times, 35.40%) and warm nature (77 times, 34.07%) are relatively common. The flavors appear 264 times in total. The flavors of bitterness (90 times, 34.09%), pungency (83 times, 31.44%) and sweetness (55 times, 21.21%) are relatively common (see Figure 1).

Figure 1: Frequency Distribution of TCM Propertie

(Calculated By Drug Type)



The analysis results according to drug frequencies show that the properties of 226 traditional Chinese medicines appear 528 times in total. Warm nature (231 times, 43.75%) and cold nature (163 times, 30.87%) are relatively common. The flavors appear 648 times in total. The flavors of pungency (236 times, 36.42%), bitterness (220 times, 33.95%) and sweetness (125 times, 19.29%) are relatively common (see Figure 2).

Figure 2: Frequency distribution of TCM properties Calculated by drug frequency)

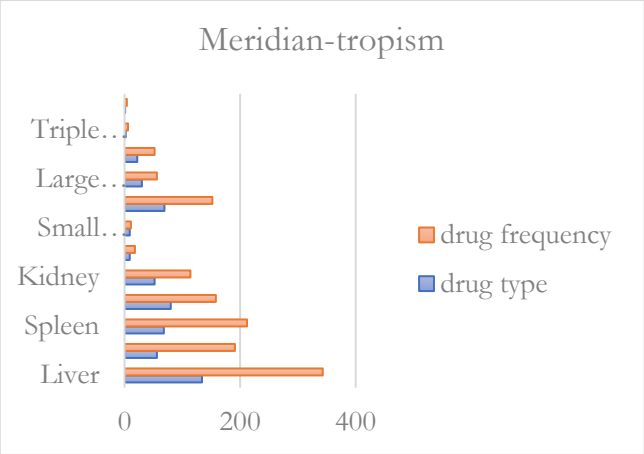


Conduct statistical analysis on the meridian tropism of all traditional Chinese medicines in the patent prescriptions. For traditional Chinese medicines with multiple meridian tropisms, all their meridian tropisms are included in the statistics. Conduct meridian tropism statistics according to drug types and drug frequencies respectively. Among them, the statistical results according to drug types show that the 226 traditional Chinese medicines appear 532 times in total in terms of meridian tropism, and the liver meridian (134 times, 25.19%) is the most common. The

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statistical results of drug occurrence frequencies show that the 226 traditional Chinese medicines appear 1317 times in total in terms of meridian tropism, and the liver meridian (343 times, 26.04%) is the most common. See Figure 3.

Figure 3: Frequency Distribution of TCM Meridian-Tropism



For the 41 traditional Chinese medicines with a usage frequency of ≥4 times, classify their efficacies according to "Traditional Chinese Materia Medica" XM G. (2002).

Statistical analysis found that the patent prescriptions for external ointments for treating GA are mainly blood-activating and stasis-eliminating drugs. See Table 2.

Association Analysis of Drug Compatibility

Based on the Apriori algorithm of IBM SPSS Modeler 18.0 software, in high-frequency drug pairs, the condition is set with a support degree of 10.0%, a confidence degree of 80.0%, and a maximum number of antecedents of 5. Conduct association rule analysis on TCM with a frequency of >5 times (a total of 37 flavors) and draw a network diagram (Figure 4).

Figure 4: Network diagram of association rules between high-frequency drugs and topical ointment of TCM for the treatment of GA

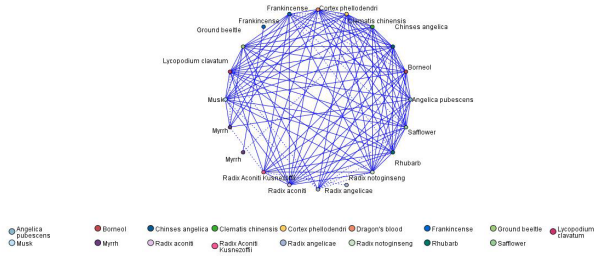


Table 2: TCM Categories in The Treatment of Gouty Arthritis with Topical Chinese Medicine Ointment

Classification	TCM	Frequency
Medicines for activating blood circulation and resolving stasis	Myrrh, Frankincense, Safflower, Dragon's blood, Semen strychni, Ground beeltle, Radix Curcuma, Corydalis yanhusuo, Achyranthes bidentata, Rhizoma chuanxiong	83
Medicines for relieving exterior syndromes	Radix angelicae, Notopterygium, Radices sileris, Fineleaf Schizonepeta herb, Asarum, Mint, Ginger	43
Medicines for expelling wind-dampness	Radix aconiti, Clematis chinensis, Lycopodium clavatum, Radix Aconiti Kusnezoffii, Angelica pubescens, Phryma leptostachya	41
Medicines for clearing away heat	Cortex phellodendri, Paris polyphylla, Gardenia jasminoides, Red Peony Root, Smilax glabra	29
Medicines for tonifying deficiency	Angelica sinensis, Dipsacus asperoides, Glycyrrhiza	17
Medicines for inducing resuscitation	Borneol, Musk	15
Purgative medicines	Rhubarb	10
Medicines for resolving phlegm, relieving cough and relieving asthma	Rhizome arisaematis, Sinapis alba	8
Medicines for promoting diuresis and draining dampness	Poria cocos, Polygonum cuspidatum	8

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Hemostatic medicines	Radix notoginseng	7
Medicines for expelling toxins, removing putrefaction and promoting tissue regeneration	Minium	5
Medicines for resolving dampness	Rhizoma Atractylodes	4

The thickness of the connecting lines indicates the degree of association. Screen out those with a frequency greater than 5 and a confidence degree greater than 90%, and obtain a total of 24 commonly used core drug pair combinations, including 4 drug pairs containing two drugs, 10 drug pairs containing three drugs, and 10 drug pairs containing four drugs (see Table 3).

Cluster Analysis

Use SPSS Statistics 24 to conduct cluster analysis on high-frequency traditional Chinese medicines (frequency > 5). Select the between-groups linkage and squared Euclidean distance as the clustering methods.

The above 19 traditional Chinese medicines can be clustered into three groups:

The first category: Myrrh, radix angelicae, and Frankincense.

The second category: Rhubarb, cortex phellodendri, Borneol, Dragon's blood, Chinses angelica, Radix aconiti, and Safflower.

The third category: Clematis chinensis, Lycopodium clavatum, Radix notoginseng, semen strychni, Radix Aconiti Kusnezoffii, Paris polyphylla, musk, Ground beeltle, and angelica pubescens.

Table 3: Association Rules of Core Drug Pairs in the Treatment of Gouty Arthritis with External Application of TCM Ointment

Consequent	Aforesaid	Support level	Confidence level
Myrrh	Frankincense	44.118	93.333
Radix aconiti	Radix Aconiti Kusnezoffii	17.647	100.0
Myrrh	Radix angelicae and Frankincense	26.471	100
Frankincense	Radix aconiti and Myrrh	23.529	100
Myrrh	Safflower and Frankincense	20.588	100
Frankincense	Chinses angelica and Myrrh	17.647	100
Frankincense	Rhubarb and Myrrh	17.647	100
Myrrh	Dragon's blood and Frankincense	17.647	100
Frankincense	Musk and Myrrh	14.706	100
Myrrh	Lycopodium clavatum and Frankincense	14.706	100
Frankincense	Ground beeltle and Myrrh	14.706	100
Myrrh	Borneol and Frankincense	14.706	100
Frankincense	Cortex phellodendri and Myrrh	14.706	100
Radix angelicae	Chinses angelica and Safflower	14.706	100
Frankincense	Dragon's blood and Radix aconiti	14.706	100
Myrrh	Dragon's blood and Radix aconiti	14.706	100
Frankincense	Radix aconiti and Radix angelicae	14.706	100
Myrrh	Radix aconiti and Radix angelicae	14.706	100
Radix aconiti	Radix Aconiti Kusnezoffii and Frankincense	11.765	100
Radix aconiti	Radix Aconiti Kusnezoffii and Myrrh	11.765	100
Frankincense	Radix Aconiti Kusnezoffii and Myrrh	11.765	100
Myrrh	Angelica pubescens and Dragon's blood	11.765	100
Frankincense	Angelica pubescens and Radix aconiti	11.765	100

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Myrrh	Angelica pubescens and Radix aconiti	11.765	100
Myrrh	Angelica pubescens and Frankincense	11.765	100
Safflower	Ground beeltle and Radix notoginseng	11.765	100
Frankincense	Ground beeltle and Radix aconiti	11.765	100
Myrrh	Ground beeltle and Radix aconiti	11.765	100
Safflower	Radix notoginseng and Borneol	11.765	100
Safflower	Radix notoginseng and Dragon's blood	11.765	100
Safflower	Radix notoginseng and Frankincense	11.765	100
Safflower	Radix notoginseng and Myrrh	11.765	100
Myrrh	Radix notoginseng and Frankincense	11.765	100
Radix angelicae	Cortex phellodendri and Safflower	11.765	100
Frankincense	Radix aconiti and Safflower	11.765	100
Myrrh	Radix aconiti and Safflower	11.765	100
Myrrh	Chinses angelica and Radix angelicae and Frankincense	14.706	100
Frankincense	Dragon's blood and Radix aconiti and Myrrh	14.706	100
Myrrh	Radix aconiti and Radix angelicae and Frankincense	14.706	100
Frankincense	Safflower and Radix angelicae and Myrrh	14.706	100
Radix aconiti	Radix Aconiti Kusnezoffii and Frankincense and Myrrh	11.765	100
Radix aconiti	Angelica pubescens and Frankincense and Myrrh	11.765	100
Frankincense	Ground beeltle and Radix aconiti and Myrrh	11.765	100
Frankincense	Ground beeltle and Safflower and Myrrh	11.765	100
Safflower	Radix notoginseng and Frankincense and Myrrh	11.765	100
Radix angelicae	Chinses angelica and Safflower and Frankincense	11.765	100
Radix angelicae	Chinses angelica and Safflower and Myrrh	11.765	100
Frankincense	Rhubarb and Radix angelicae and Myrrh	11.765	100
Myrrh	Radix aconiti and Safflower and Frankincense	11.765	100
Radix angelicae	Chinses angelica and Safflower and Frankincense and Myrrh	11.765	100

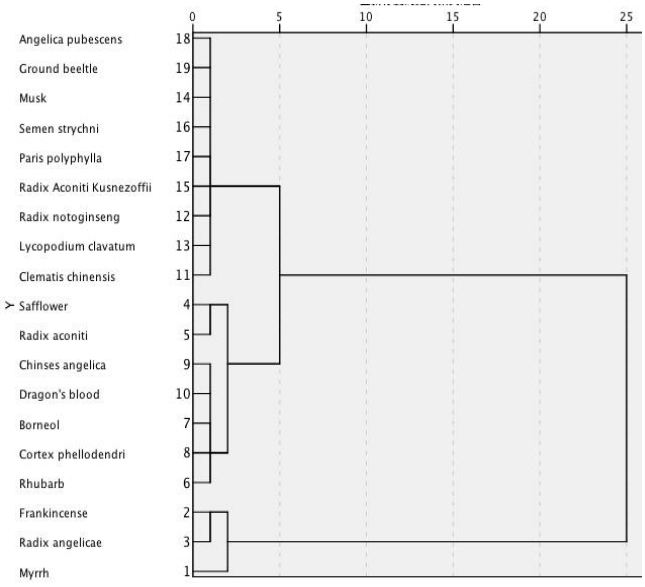
Acquisition of Active Ingredients of Core Traditional Chinese Medicines and Corresponding Targets.

According to the data mining results, the top three traditional Chinese medicines with the highest occurrence frequencies, namely myrrh, frankincense, and Angelica dahurica, were selected as core traditional Chinese medicines. From the TCMSP database, setting OB≥30% and DL≥0.18 as screening conditions, the core traditional Chinese medicines (myrrh, frankincense, and Angelica dahurica) have 45, 8, and 22 active ingredients respectively, totaling 75. After deduplication, there were a total of 58. Using the TCMSP and BATMAN-TCM databases, the potential target proteins corresponding to the 58 active ingredients were obtained. After correcting and deduplicating the target proteins in the Uniprot database, a total of 75 targets were screened out.

Screening of Key Targets of Gouty Arthritis Action Targets and Active Ingredients.

By searching for the disease keyword "Gouty arthritis" in the GeneCards database, 246 GA-related targets were collected.

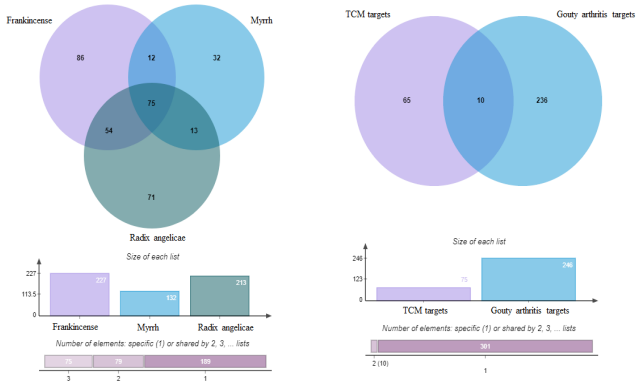
Figure 5: Dendrogram of Hierarchical Clustering for High Frequency TCM (N>5)



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Mapping TCM targets and disease targets and drawing a Venn diagram through an online drawing website yields 10 common drug-disease targets. (See Figure 6).

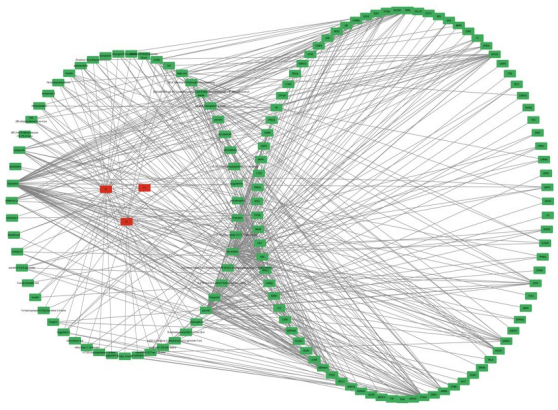
Figure 6: Venn diagram of the target of "myrrh frankincense baizhi" shares a common target with GA



Construction of Drug-Ingredient-Disease-Target Network

The common targets of drugs and diseases and the active ingredients of drugs were used to create a visualized network graph through Cytoscape 3.10.2 software. As can be seen from Figure 7, one chemical component corresponds to multiple intersection gene targets, and one intersection gene and target also correspond to multiple chemical components at the same time. Chemical components belong to different traditional Chinese medicines. This indicates that the core drug pair of "myrrh-frankincense- radix angelicae" took effect in the treatment of GA through multiple components, multiple targets, and multiple pathways. Among them, beta-sitosterol, stigmasterol, and quercetin in the graph were associated with more targets and can be seen as the main active ingredients for inhibiting GA inflammation.

Figure 7: TCM - component -disease-target network diagram



PPI Network Construction and Visual Analysis

The 10 common targets obtained after mapping the core drug targets and disease targets are used to initially construct a PPI network for the intersection genes through the String database. Select Homo sapiens as the species, set the minimum required connection score between targets to 0.9, and hide the disconnected nodes in the network to construct a PPI network. Import the data into Cytoscape 3.10.2 for visual analysis. According to the degree value from large to small, it is found that there is a relatively complex relationship among the top 12 targets. In the network, the degree value is one of the important topological parameters. The degree value of a node represents the number of nodes connected to the node in the network and is used to evaluate the importance of a certain component or target in the network Ge Q, et al. (2018). The larger the degree value, the more connected nodes there are, the closer the relationship between proteins, and the greater the regulatory role in the entire network. In this PPI network diagram, targets such as PTGS2, PGR, NCOA2, NR3C2, and HSP90AA1 rank high in degree, indicating that these targets play a crucial role.

Figure 8: PPI network diagram of core Chinese medicine target protein



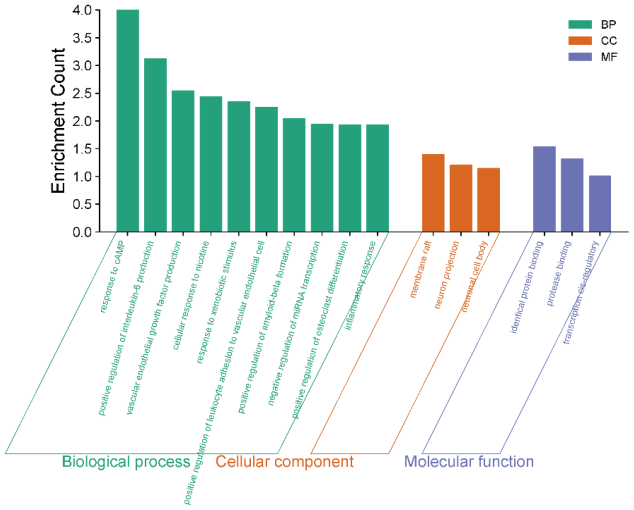
GO Enrichment and KEGG Signaling Pathway Analysis

Conduct GO and KEGG enrichment analysis on the intersection targets through the DAVID database. Select analysis items according to P≤0.01 and FDR≤0.05. The results of GO enrichment analysis include 38 items for biological process (BP), 4 items for cell component (CC), and 3 items for molecular function (MF). The results of KEGG signalling pathway analysis include a total of 37 pathways. BP mainly includes responses to cAMP, positive regulation of interleukin-6 production, production of vascular endothelial growth factor, cellular

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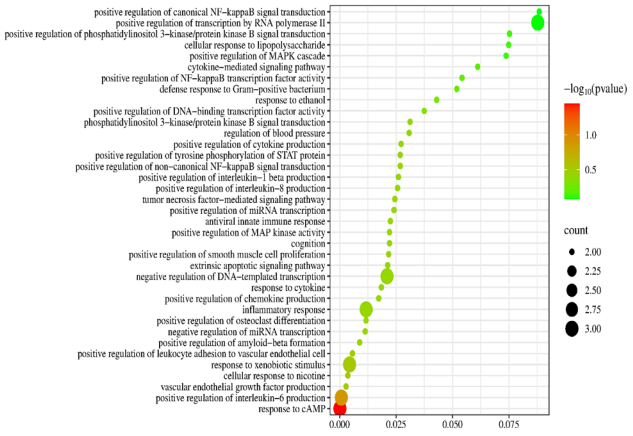
in terms of CC, it mainly involves membrane rafts, projection neurons, neuron cell bodies, etc.; in terms of MF, it mainly involves homotrimer binding, protease binding, cis-regulation, etc. Select the results of the top 10 sorted by P value for visualization and plotting, as shown in Figure 9.

Figure 9: GO enrichment analysis of TCM topical ointment in the treatment of GA



KEGG pathways are mainly enriched in positive regulation of classical NF-kappaB signal transduction, positive regulation of RNA polymerase I transcription, positive regulation of phosphatidylinositol 3-kinase/protein kinase B signal transduction (PI3K/Akt), cellular response to lipopolysaccharide, positive regulation of cytokine- mediated signal transduction of MAPK cascade, positive regulation of NF-kappaB transcription factor activity, etc. Select the top 20 key signalling pathways sorted by P value for visualization (Figure 10).

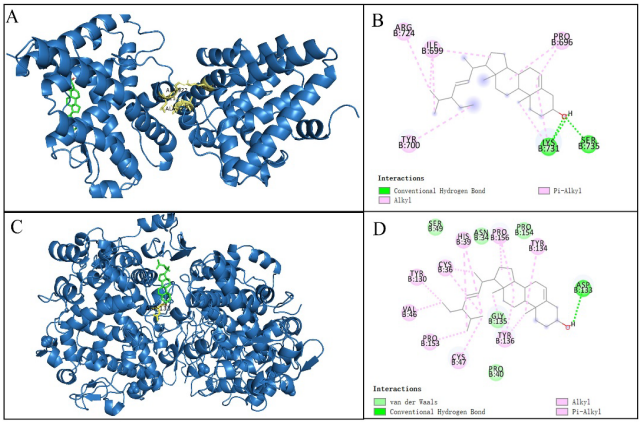
Figure 10: Top 20 KEGG pathways of enrichment analysis of treatment of GA with topical ointment of TCM



Molecular Docking Verification of Key Active Ingredients and Core Targets

Search the 3D chemical structure file of the predicted small molecule compound (ligand) in the PubChem (https://pubchem.ncbi.nlm.nih.gov/) database and save it in *mol2 format. The macromolecular crystal structures of target proteins such as PTGS2 and PGR are obtained from the RCSB PDB database and saved in *PDB format. Use PyMOL to perform "remove solvent" and "remove organic" processing on PDB protein molecules and save in *PDB format; then, use AutoDock Tools 1.5.6 software (The Scripps Research Institute, CA, USA) for pretreatment such as "delete water" and "add hydrogen", and save it in *pdbqt format. Afterwards, import the ligand molecule into the software for hydrogenation, detect the rotational bond to select the most suitable conformation, and save it in *pdbqt format. The docking steps are: "run AutoGrid", "set rigid filename", "search parameter: genetic algorithm", "docking parameter: default", "run AutoDock". In molecular docking, a binding energy <0 kcal/mol indicates that a small molecule compound can spontaneously bind to a macromolecular protein, and a binding energy less than -5 kcal/mol indicates that the two have a strong binding ability. The minimum docking binding energy is shown in Table 4. Finally, save the docking result as a *pdbqt format file, and import the molecular docking result with strong binding ability of the target protein and PTGS2 and PGR into PyMOL 4.6.0 and Discovery studio 2019 software for visual analysis. The results are shown in Figure 11.

Figure 11: Schematic diagram of docking results between active ingredients and PTGS2, PGR protein molecules



Note: (A) 3D schematic diagram of the docking between active ingredients and PGR protein; (B) 2D schematic diagram of docking between active ingredients and PGR protein; (C) 3D schematic diagram of the docking between active ingredients and PTGS2 protein; (D) 2D schematic diagram of docking between active ingredients and PTGS2 protein

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Table 4: Minimum binding energies of active ingredients and key targets

Target name	Binding energy（kcal/mol）		
	Quercetin	Beta-sitosterol	Stigmasterol
PTGS2(5F19)	-7.63	-8.04	-8.85
PGR(1TNF)	-6.76	-7.64	7.86

DISCUSSION

With the improvement of modern living standards, people's dietary structure has changed. Excessive intake of high-purine and high-cholesterol foods or heavy drinking, as well as changes in lifestyle and environmental factors can all increase the risk of gout. In recent 20 years, the incidence of gout in many countries has increased significantly Rai S K, et al. (2017), Kim J W, et al. (2017). Gout patients often have comorbidities such as hyperlipidemia, diabetes, and obesity Kim J W, et al. (2017), Elfishawi M M, et al. (2018). At present, the treatment methods of modern medicine mainly focus on controlling symptoms and reducing uric acid levels, but it is difficult to completely cure gouty arthritis. Once suffering from the disease, lifelong treatment and management are often required. Even under standardized treatment, some patients will still have gout attacks, especially under the inducements of unrestrained diet, fatigue, and trauma. Some patients also develop gout stones due to the long-term deposition of urate crystals in the surrounding bones, joints and soft tissues. It not only affects the local appearance but also has extremely strong destructive power and is easy to damage the bone and joint structure, leading to dysfunction and even loss Ran B, et al. (2017). If a patient has joint involvement symptoms, surgical removal of gout stones should be performed as soon as possible. This not only brings a greater economic burden to patients and their families but also seriously affects the patient's quality of life.

Traditional Chinese medicine has a long history in treating gouty arthritis. The earliest record can be traced back to "Supplementary Records of Famous Physicians" by Tao Hongjing: "It mainly treats all kinds of pathogenic winds. For those with gout in hundreds of joints, regardless of whether it is recent or long-standing." Traditional Chinese medicine believes that gout is mainly caused by the patient's inherent deficiency of the spleen and kidney, or excessive drinking and improper diet that leads to the dysfunction of the spleen and stomach in ascending the clear and descending the turbid. Or chronic illness that affects the kidney. Or the invasion of wind, cold, dampness and heat pathogens into the meridians, resulting in poor circulation of qi, blood, body fluids. Blood stasis occurs, and phlegm turbidity and stasis toxin combine and block the joints and tendons, making the tendons malnourished and joint movement unfavourable, thus triggering gout and causing joint pain, swelling and redness and heat GY Y, et al. (2021). Therefore, in the treatment of GA, traditional Chinese medicine treats both the symptoms and root causes according to the etiology and pathogenesis. At present, the classification in "Diagnostic and Therapeutic Standards for TCM Diseases and Syndromes" JX L, et al. (2018) is widely used, which are: damp-heat accumulation syndrome, stasis-heat obstruction syndrome, phlegm turbidity obstruction syndrome, and liver-kidney yin deficiency syndrome. In addition, Xu Lingtai's "Medical Records of Huixi" once recorded: "Generally speaking, for diseases of the nutrient-defense system and internal organs, taking medicine can reach the diseased area. Meridians, tendons and joints all belong to tangible entities. For decoctions and pills, if they are too mild, they cannot attack pathogenic factors. If they are too strong, they may damage the healthy qi. Medicines with thick qi and heavy potency must be used. Methods such as application, spreading, fumigation and steaming can penetrate deep into the diseased area and expel pathogenic factors." This fully shows that for diseases of meridians, tendons and joints, external treatment methods such as application, spreading, fumigation and steaming can penetrate deep into the diseased area and expel pathogenic factors FM J, et al. (2024) laying a foundation for the treatment of gouty arthritis with external ointments of traditional Chinese medicine. Moreover, the external treatment of GA with traditional Chinese medicine can not only act directly on the diseased area and increase the drug concentration but also avoid the metabolic loss and potential side effects caused by oral drugs passing through the digestive system and blood circulation, with high safety. This study mined and analyzed the patent prescription data of external ointments of traditional Chinese medicine for treating GA in the Chinese patent database and found that the patent prescriptions for treating GA are mainly composed of traditional Chinese medicines with the effects of promoting blood circulation and removing blood stasis,

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relieving exterior syndrome with pungent and warm herbs, expelling wind and removing dampness, clearing heat and detoxifying, and tonifying the liver and kidney, which are basically in line with the four major syndromes of traditional Chinese medicine in treating GA. "Liuyi Pianwen" clearly pointed out that external plasters should focus on promoting the circulation of qi and blood, believing that "when qi and blood circulate smoothly, the disease will heal by itself" SJ W. (2006). The book also discusses the significance of qi and blood circulation for external treatment methods in traditional Chinese medicine that is different from internal treatment methods, that is, "it should be known that for external treatment, the circulation of qi and blood is equivalent to tonification" SJ W. (2006). Traditional Chinese medicines for promoting blood circulation and removing blood stasis run through all stages of gout treatment. In the acute attack stage of gout, cooling blood and promoting blood circulation, removing blood stasis and dredging collaterals are indicated; in the intermittent remission stage, promoting blood circulation and removing blood stasis, tonifying deficiency and dredging collaterals are indicated; for those with obvious gout stones, breaking blood stasis and expelling stasis, and searching and dredging collaterals are indicated GY Y, et al. (2021), YY X, et al. (2015) .

Through the analysis of the medication rules of patent prescriptions for external ointments of traditional Chinese medicine for treating GA, it is found that the properties of traditional Chinese medicines for treating GA are mainly cold and warm in nature, bitter, pungent and sweet in flavour, and mainly acting on the liver meridian. Traditional Chinese medicines with high usage frequencies include myrrh, frankincense, Angelica dahurica, safflower, Aconitum carmichaelii, rhubarb, borneol, Phellodendron amurense, Angelica sinensis, dragon's blood, Clematis chinensis, Panax notoginseng, etc. Myrrh is neutral in nature, pungent and bitter in flavour, and has the effects of promoting blood circulation, dissipating blood stasis, relieving pain and promoting tissue regeneration; frankincense is warm in nature, pungent and bitter in flavour, and has the effects of promoting blood circulation, relieving pain and promoting tissue regeneration. Both have fragrant qi and are good at moving around. They both have the effects of promoting blood circulation, relieving pain, and promoting tissue regeneration. They are often used together. Frankincense is more inclined to promoting qi circulation and stretching tendons, while myrrh is more inclined to dissipating blood stasis. When the two are used together, qi and blood are treated simultaneously, and they jointly play the role of dredging meridians, promoting blood circulation and removing blood stasis, relieving pain and promoting tissue regeneration TM Z, et al. (2015). Angelica dahurica is pungent in flavour and warm in nature. It reaches the lung and stomach meridians. It is good at expelling wind and treating headache and facial pain; it can also aromatize turbidity, warm the middle-jiao and dispel cold. Angelica dahurica can also harmonize and benefit the blood vessels, expel wind and cold, remove dampness and dredge collaterals. It is widely used in treating pain caused by joint, muscle and soft tissue injuries XH W. (2000). Safflower is pungent in flavour and warm in nature. It can be used for promoting blood circulation and dredging meridians, removing blood stasis and relieving pain.

Aconitum carmichaelii is pungent and bitter in flavour and hot in nature. It has the effects of expelling wind and dampness, warming meridians and relieving pain. Modern pharmacology shows that it has obvious anti-inflammatory and analgesic effects and can quickly relieve the pain symptoms of gouty arthritis XT Y, et al. (2021). Rhubarb is bitter and cold in nature. It has the effects of clearing heat and promoting diuresis, cooling blood and detoxifying, and removing blood stasis and dredging collaterals. External application of rhubarb in the treatment of gouty arthritis can break up accumulated blood stasis, clear heat in the blood, and eliminate swelling and toxins on the skin. It can quickly relieve the acute symptoms of joint redness, swelling, heat and pain. Modern research has found that rhubarb has obvious anti-inflammatory effects. Emodin has a two-way regulatory effect on the immune function of the body X G, et al. (2017). Clinical external application in the treatment of gouty arthritis has remarkable curative effect BX H, et al. (2015). The above high-frequency traditional Chinese medicines all have the effects of promoting blood circulation and removing blood stasis, removing dampness and relieving pain, which are in line with traditional Chinese medicine theories and also prove the accuracy of drug selection in traditional Chinese medicine patents.

Through association analysis, it is found that the high-frequency drug pairs of traditional Chinese medicines in external ointments for treating GA mainly include frankincense-myrrh, Aconitum carmichaelii-Aconitum kusnezoffii-frankincense, frankincense-musk-myrrh, myrrh-borneol-frankincense, myrrh-Angelica sinensis-frankincense, myrrh-rhubarb-frankincense, myrrh-borneol-frankincense-Angelica dahurica, myrrh-Phellodendron amurense-frankincense-Angelica dahurica, etc. In the core drug combinations, frankincense and myrrh are a commonly used drug pair for promoting blood circulation and removing blood stasis. They are often used in combination. The volatile oils of both drugs can relieve pain and inflammation. External application has a promoting penetration effect and can accelerate the percutaneous absorption of drugs

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Wen W, et al. (2009). The core drug combinations obtained through association rule analysis in this study show the characteristics of mutual compatibility and application of exterior-releasing drugs, promoting blood circulation and removing blood stasis drugs, and regulating qi drugs. Among these drugs, whether they are exterior-releasing drugs or drugs for promoting blood circulation and regulating qi, they all show the characteristics of pungent fragrance and warmth-promoting. For example, the compatibility and application of frankincense-Angelica dahurica-myrrh, frankincense-Angelica dahurica-myrrh-Angelica sinensis, myrrh-rhubarb-frankincense, etc. Their effects are mainly promoting blood circulation and removing blood stasis, removing dampness and relieving pain, which are in line with the medication concept of external treatment methods in traditional Chinese medicine.

Through cluster analysis, it is found that traditional Chinese medicines in external ointments for treating GA can be clustered into three categories. The first category: frankincense, myrrh, and Angelica dahurica, mainly promoting blood circulation and removing blood stasis, and also having the effects of reducing swelling and relieving pain. The second category is divided into two parts. One part is pungent and hot substances represented by Aconitum carmichaelii, which can dispel cold and remove dampness and warm the meridians; the other part is cold and cool drugs represented by rhubarb and Phellodendron amurense, which have the effects of clearing heat, drying dampness and detoxifying. The combination of cold and heat can achieve the effects of removing dampness and dredging collaterals and relieving pain. The third category is represented by Clematis chinensis, Lycopodium japonicum, Panax notoginseng, Strychnos nux-vomica, Eupolyphaga sinensis, and Angelica pubescens, mainly focusing on dredging joints and relieving tendon contracture and joint stiffness. To explore the potential mechanism of action of external ointments of traditional Chinese medicine in treating GA, this study screened out three potential core traditional Chinese medicines for treating GA from traditional Chinese medicine compound patents through data mining, namely myrrh, frankincense, and Angelica dahurica. Using network pharmacology research, it is found that the main active ingredients of the above core traditional Chinese medicines are beta-sitosterol, stigmasterol, and quercetin. GO enrichment analysis found that the core traditional Chinese medicines mainly participate in processes such as the response to cAMP, positive regulation of interleukin-6 production, and production of vascular endothelial growth factor; KEGG pathway analysis found that in the treatment of GA, it mainly involves signal pathways such as positive regulation of classical NF-kappaB signal transduction, positive regulation of RNA polymerase I transcription, and PI3K/Akt, thereby playing roles in anti-inflammation, antibacterial, and promoting angiogenesis. Combined with the results of network pharmacology, it is speculated that the core targets for treating GA mainly include PTGS2, PGR, NCOA2, NR3C2, HSP90AA1, etc. Through molecular docking analysis and verification of the core action targets and their corresponding active ingredients of traditional Chinese medicine, it is found that the core targets can stably bind to the corresponding core active ingredients.

This study systematically analyzed and discussed the medication rules of patent external ointments of traditional Chinese medicine for treating GA by using data analysis technologies such as data mining and network pharmacology. It screened out the core drugs and main active ingredients for patent treatment of GA, as well as their corresponding key action targets. By using molecular docking, the binding affinity and stability between active ingredients and corresponding targets were explored. Through big data analysis, screening, discovery and verification of the key active ingredients and their potential mechanisms of action for patent treatment of GA were carried out. This lays a foundation for the targeted development of new Chinese patent medicine products for treating GA with clear mechanisms and rich dosage forms. However, this study only conducted research on the top-ranked active ingredients and corresponding targets. There are still many key ingredients and their involved targets and signal pathways that need further analysis and experimental verification. Relying solely on network pharmacology and molecular docking research has certain limitations. The further development of related new traditional Chinese medicine drugs still needs further laboratory and clinical verification. These deficiencies will be further improved in future studies.

CONCLUSION

This study excavated and analyzed patent prescriptions for the treatment of GA with topical Chinese medicine ointment, and identified the top three core Chinese medicines for GA treatment with patent prescriptions: Myrrh, Frankincense, and Radix angelicae; Using network pharmacology research, it was found that the main active ingredients of the core traditional Chinese medicine mentioned above are beta sitosterol, stigmasterol, and quercetin. It is further speculated that the core target for treating GA is PTGS2, PGR et al. have been validated through molecular docking analysis of their core targets and corresponding active ingredients in traditional Chinese medicine.

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The core targets can stably bind to the corresponding active ingredients.

DECLARATIONS

Data Availability Statement

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

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Author Contributions

Conception and design: RHJ. Development of methodology: LX. Acquisition of data (provided facilities, etc): LM, QXY, XM, YY, FK. Analysis and interpretation of data (e.g., statistical analysis): RHJ, XL. Writing, review, and/or revision of the manuscript: XL. Study supervision: XL.

Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could construed as a potential conflict of interest.

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