ORIGINAL RESEARCH

Network Pharmacology Analysis of Traditional Chinese Medicine for Treating Psoriasis: Identifying Core Components, Mechanisms, and Dosing Patterns

Shuai Yang, MBBS; Xuebing Hu, MBBS; Zizhang Wang, MBBS

ABSTRACT

Context • Psoriasis is a chronic, inflammation-mediated skin disease. The use of traditional Chinese medicine (TCM) in the treatment of psoriasis boasts a rich historical tradition. Researchers widely use network pharmacology to reveal the action mechanisms of TCM by establishing an interaction network—drug-component-target-disease.

Objective • The study aimed to use a network pharmacology approach to investigate the interaction between TCM and its targets in psoriasis, aiming to identify core drugs and mechanisms underlying TCM's treatment of common psoriasis and to create a new TCM formula.

Design • The research team performed a retrospective genetic study.

Setting • The study took place in the Dermatology Department at Beijing Wangfu Hospital of Integrative Medicine in Beijing, China.

Participants • Participants were patients that the dermatology clinic had diagnosed with common psoriasis between January 1, 2016 and January 1, 2019.

Outcome Measures • The research team: (1) calculated the frequency of each herb's occurrence; (2) identified the core drugs; (3) determined the core drugs' active ingredients and targets; (4) identified psoriasis' targets; (5) determined the target proteins; (6) identified the top-30, key signaling-set pathways; (7) identified the top 10 biological processes (BPs), cell components (CC), and molecular functions (MF); (8) screened the top-five major active ingredients; and (9) performed molecular docking.

Results • The research team: (1) based on 892 prescriptions from 95 patients, identified 161 herbal medicines, with Lonicerae Japonicae Flos, Herba Portulacae, Radix Gentianae, Bletilla striata, Raw Rehmanniae Radix, Dictamni Cortex, and Forsythia suspensa being core drugs; (2) found 58 active ingredients and 144 effective, target functional genes for the core drugs through network pharmacology screening, with 81 potential targets for psoriasis treatment; the core drugs for treatment may restore the keratin-forming cell function by inhibiting cancer-related pathways, the interleukin-17 (IL-17) signaling pathway, the tumor necrosis factor (TNF) signaling pathway, and the hypoxia-inducible factor-1 (HIF-1) signaling pathway; (3) using molecular docking, revealed high-affinity interactions between the active ingredients primuletin, luteolin, and wogonin and mitogen-activated protein kinase 8 (MAPK8), tumor protein 53 (TP53), and epidermal growth factor receptor (EGFR).

Conclusions • The new TCM formula to be used in the current research team's hospital may act on MAPK8, TP53, and EGFR targets through active ingredients such as primuletin, kaempferol, luteolin, wogonin, and β-sitosterol, which involve several signaling pathways, such as the cancer signaling, TNF signaling pathway, HIF-1 signaling pathway, and endocrine resistance. The research provides a theoretical foundation for the clinical use of the new TCM formula. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Psoriasis is a chronic, inflammation-mediated skin disease with a high prevalence in Asia.[1-3] Clinically, psoriasis vulgaris is the most common disease type, and high morbidity, recalcitrance, recurrence, and intractability characterize it, causing a long-term and substantial impact on patients' lives and psychological health.[3]

Psoriasis not only presents with skin-related symptoms but is also linked to an increased risk of comorbid conditions,[4] including psoriatic arthritis, cardiovascular disease, insulin resistance, and mental health disorders. These associated conditions impose a substantial burden on both patients and society.[5] The pathogenesis of psoriasis is presumably associated with the overactivation of adaptive immune system,[6] but the mechanism remains to be elucidated.

Pathogenic Factors

Psoriasis is related to T-cell-mediated inflammation, and the activation of T cells causes secretion of inflammatory factors that further promote the proliferation and migration of keratin-forming cells, thereby causing psoriasis' development. Currently, to treat psoriasis, most monoclonal antibody agents target the mechanism of psoriasis by blocking downstream inflammatory mediators such as tumor necrosis factor (TNF) and interleukin-17A (IL17A). Zhou et al found significantly elevated levels of expression of nuclear factor-kappa beta (NF-κB)in skin tissues and elevated interferon gamma (INF-γ) and IL-17 inflammatory factors in the serum of patients with psoriasis.[7]

Picciani et al and Furiati et al. in vitro cellular assays demonstrated that abnormal differentiation of T lymphocytes, especially type 1 T helper (Th1) and Th17 cells, and overproduction of pro-inflammatory factors—interleukins—

was closely associated with psoriatic disease manifestations, such as skin erythema, keratosis, and scaly skin.[8,9]

The cascade amplification effect of the interaction between T cells and human keratinocytes further aggravates the disease progression of psoriasis. IL-17 is an important factor involved in the pathogenesis of psoriasis, and helper T17 cells (Th17) mainly produce it, causing apoptosis by activating keratinocytes. IL-17A stimulates IL17 production through dendritic cells and fibroblasts, and IL17F induces IL6 production through keratinocytes.[10] IL17 also stimulates angiogenesis and endothelial cell proliferation through fibroblasts. AbuHilal et al found that inhibiting the IL17 signaling pathway can improve the therapeutic effects against psoriasis.[11]

Currently, a growing body of evidence supports the association of cancer with psoriasis. Several meta-analyses and retrospective studies have revealed a higher risk of cancer in patients with various psoriatic conditions compared to healthy participants, especially skin, lymphoma, colorectal, and lung cancers.[12-15] TNF from mononuclear macrophages is highly bioactive and the TNF/IL-23/IL17 axis regulates the skin's immune cells, which plays an important role in the pathogenesis of psoriasis and related psoriatic arthritis.[16]

Hypoxia-inducible factor-1 (HIF-1) is a heterodimeric transcription factor with elevated levels in the serum of psoriasis patients and promotes angiogenesis and skin inflammation.[17] Tang et al found that HIF1A might facilitate the glycolytic process in psoriasis vulgaris by increasing the expression of cluster of differentiation 147 (CD147) and glucose transporter protein type 1 (GLUT1).[18]

Several studies have reported that protein-expression levels of peroxisome proliferator activated receptor gamma (PPARγ) are closely associated with the incidence of psoriasis.[19-21] PPAR family members currently include three main isoforms, namely, alpha (α), delta (δ), and γ. PPARα is the target of a toll-like receptor signaling pathway that governs platelet and skin homeostasis. Platelets play an important part in immunological and inflammatory disorders.

Platelet aggregation increases in patients with psoriasis and stays active during the illness.[22] The recruitment of leukocytes to psoriatic lesions may involve platelet-derived inflammatory mediators, and activated platelets may induce the production of leukotrienes in areas of abnormal psoriatic skin damage with high levels of arachidonic acid lipoxygenase, resulting in neutrophil infiltration into psoriatic pustules and microabscesses.[23]

Active PPARs link the innate immune system to lipid-metabolism disorders. Xiao et al have found reduced levels of PPAR-gamma in the skin of patients with psoriasis.[24] Lima et al found that ligands of PPARα, such as oleic acid, can decrease skin-barrier development while restoring skin homeostasis, promoting differentiation and regulating epidermal apoptosis.[25] Wei et al found that the activation of c-JUN, a pathway closely associated with several autoimmune diseases, can stimulate the production of the inflammatory factor IL-6, which further exacerbates the inflammatory response.[26] Ehst et al found that growth factors and their receptors, such as Epidermal growth factor (EGF) and epidermal growth factor receptor (EGFR), are also inextricably associated with psoriasis.[27]

Treatment

Western medicine for psoriasis occurs through symptom alleviation, disease control, and relapse avoidance. Physicians commonly use methotrexate, retinoids, vitamin D3 derivatives, and hormones as medications. To treat psoriasis, currently, most monoclonal antibody agents target the mechanism that can block downstream inflammatory mediators, such as TNF and IL17A. In contrast to traditional Chinese medicine (TCM), Western medicine is linked to a high risk of adverse reactions, multiple contraindications, and significant medication-drug interactions, and it requires regular monitoring of the renal and hepatic functions during drug delivery.[28]

TCM serves as a complementary approach aimed at harmonizing the body's qi, enhancing immunity, and ameliorating clinical symptoms to improve cure rates. The use of TCM in the treatment of psoriasis boasts a rich historical tradition. That treatment features the advantages of evidence-based treatment, a customizable drug regimen, and low side effects.[29,30]

TCM has exhibited the ability to reduce the recurrence of psoriasis and yield long-lasting curative effects.[31,32]Coyle et al's qualitative study confirmed the safety and recurrence-preventing efficacy of TCM for psoriasis, although the field requires further clinical research.[33]

Potential Genetic Factors

Mitogen-activated protein kinase 8 (MAPK8). The main proteins that MAPK8 encodes are members of the MAP kinase and Jun N-terminal kinase (JNK) families. MAP kinases function as integration points for multiple biochemical signals that are involved in cell proliferation, differentiation, transcriptional regulation and development.[34] Excessive proliferation of psoriatic keratinocytes is closely associated with elevated levels of MAPK8 at a lesion site.[35]

Tumor protein 53 (TP53). In the cell cycle, p53 repairs a cell-cycle arrest in the G1 phase through the expression of p21 and also mediates cell death through the B-cell lymphoma 2 (Bcl-2)/ Bcl-2 associated X-protein (Bax) pathway.[36] Moorchung et al identified p53 as an important protein regulating the apoptotic process in psoriatic epidermal cells.[37] Zhang et al's prior clinical study using a UV light for psoriasis management found a significant decrease in p53 and forkhead box P3 (Foxp3) during treatment, and the researchers hypothesized that p53 is an essential protein for UV-induced Foxp3 transcription.[38]

Network pharmacology

Network pharmacology is an integrated approach based on pharmacology, network biology, systems biology, bioinformatics, and computational science. Researchers widely use it to reveal the action mechanisms of TCM by establishing an interaction network—drug-component-target-disease.

The integrity and systematic characteristics of TCM's network-pharmacology research strategy are in accordance with the principles of disease diagnosis and treatment as well as a feature of the synergistic effect of multiple components, approaches, and targets in TCM and its prescriptions.

Current Study

The current research team hypothesized that TCM exhibits unique characteristics and mechanisms of action in treating psoriasis, which network pharmacology analysis can elucidate. By establishing the drug-gene-target-disease interaction network, the team intended to gain insights into the dosing patterns and mechanisms of TCM-based treatment of psoriasis.

The current study intended to use a network pharmacology approach to investigate the interaction between TCM and its targets in psoriasis, aiming to identify core drugs and mechanisms underlying TCM's treatment of common psoriasis and to create a new TCM formula.

METHODS

Participants

The research team performed a retrospective genetic study, which took place in the Dermatology Department at Beijing Wangfu Hospital of Integrative Medicine in Beijing, China. Potential participants were patients at the dermatology clinic who had been diagnosed with common psoriasis between January 1, 2016 and January 1, 2019.

The study included potential participants if: (1) they had met the diagnostic criteria for common psoriasis as established in Psoriasis Area and Severity Index (PASI) [39] (2) they also had received a clear TCM diagnosis for common psoriasis, (3) their prescribed medications were for internal use, and (4) complete and comprehensive records of their herbal prescriptions were available for the specified time period.

The study excluded potential participants if: (1) the route of medication wasn't clearly written in the records and (2) the diagnosis included other diseases, and the hospital had prescribed drugs for those diseases.

Procedures

Evidence-based treatment. The outpatient treatment of psoriasis in the research team's dermatology clinic is evidence-based, and the medications used are consistent with the evidence-based characteristics and treatment ideas for each stage of psoriasis.[40]

Data collection. The research team selected the specific hospital for data collection based on its reputation, expertise in treating psoriasis, and accessibility to comprehensive prescription records, making it a suitable source. The team also carefully considered the timeframe for data collection, including data from three years to avoid the impact of the season in which the patient received treatment. All patients provided written informed consent, and we collected their data from their medical records. The data collection was carried out by one member of our research team. The study has been approved by the hospital's ethical committee, with an approval number of DYX-2016-021.

Standardization, data entry, and data mining of prescription medications. The process of standardizing, entering, and mining the data involved several key steps. First, the research team standardized drug names following the terminology outlined in the *Chinese Pharmacopoeia,* 2020 edition.[41] It's important to note that the study ignored the drugs' formulation methods, treating different formulations as the same Chinese medicine.

Second, the prescription data were entered into the TCM Heritage Assist Platform V2.5 (China Academy of Chinese Medical Science, Beijing, China to ensure data accuracy and reliability. Third, after establishing the database, the team used the Formulary Analysis feature within the platform's Data Analysis module for comprehensive data mining. The objectives of this analysis were to determine the frequency of medication usage, classify the efficacy of commonly used drugs, identify formula patterns, and pinpoint core drugs.

Network pharmacological analysis. The research team's network pharmacological analysis focused on identifying the core drugs and their composition. To achieve this, the team conducted an extensive search using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP),[42] Bioinformatics Annotation Database for Molecular Mechanism of Traditional Chinese Medicine (BATMAN-TCM),[43] DrugBank database,[44] and Encyclopedia of Traditional Chinese Medicine (ETCM)[45] The research team chose these databases based on the comprehensiveness of their drug information.

The team screened the core drugs using specific criteria, including an oral bioavailability (OB) of ≥30% and drug-likeness (DL) of ≥0.18, to select active ingredients and their corresponding target functional genes.

The OB criterion is significant because it reflects the fraction of the administered dose of a drug that reaches the bloodstream, making it available for interaction with the targeted proteins in the patients' body. By selecting drugs with an OB of ≥30%, the team ensured that the active compounds had a reasonable chance of reaching their intended biological targets.

DL is an essential parameter that assesses the chemical and pharmacological properties of a compound. A DL score of ≥0.18 indicates that the compound exhibits characteristics that are commonly associated with drug-like molecules. Choosing compounds with acceptable DL scores ensures that the core drugs are chemically suitable for further drug development.

Target functional genes. The selection of target functional genes is rooted in the understanding that psoriasis is a complex, multifactorial disease, with genetic and molecular underpinnings. Identifying genes associated with psoriasis helped the research team to pinpoint the biological factors that play a pivotal role in the disease's development and progression. Furthermore, the team employed the keyword psoriasis to search multiple databases, including GeneCards,[46] Online Mendelian Inheritance in Man (OMIM),[47] DrugBank, Therapeutic Target Database (TTD),[48]

and DisGeNET,[49] to identify genes associated with psoriasis. The team excluded genes with a GeneCards database score lower than one, due to their limited relevance. The team used the Search Tool for Retrieval of Interacting Genes/Proteins (STRING) database, version:12.0.[50]

Interaction analysis. The research team performed an interaction analysis using the STRING database to uncover potential associations among the identified target proteins. The STRING database is a valuable resource for exploring protein-protein interactions (PPIs), helping the team to understand the functional relationships between different proteins. The database plays a crucial role in building a network of interactions, which is essential for comprehending the complex molecular mechanisms underlying various diseases, including psoriasis.

Topological analysis. The team also conducted a topological analysis by importing the data into Cytoscape software (Institute of Systems Biology, Seattle, Washington, USA) the Gene Ontology (GO)[51,] and Kyoto Encyclopedia of Genes and Genomes (KEGG)[52] databases.

Network construction. Following the step above, the team constructed an "active ingredient-target functional gene-pathway" network and screened key active ingredients based on their degree value. Additionally, the team performed molecular docking for the top five key components in the network and the top five core targets in the protein-protein interaction (PPI) network.

The research team downloaded the core targets' protein structures from the Protein Data Bank database,[53] and processed the original ligands using the PyMOL 2.4.0 software (Schrödinger, New York, New York, USA), including dehydration, hydrogenation, and isolation. The team conducted molecular docking using AutoDock Vina software, version 1.1.2 (Scripps Research Institute, La Jolla, California, USA).

The choice of a molecular docking tool is crucial because it determines the results' accuracy and reliability. By using AutoDock Vina, the team aimed to provide robust and meaningful insights into the interactions between the selected core targets and the ligands derived from the active ingredients of the TCMs. This information is valuable for understanding the potential mechanisms of action and therapeutic effects of these TCM compounds in the context of psoriasis treatment.

AutoDock Vina provides binding affinity scores, which indicate the strength of the interactions between ligands and protein targets. These scores are essential in evaluating the potential of TCM compounds to bind to the core targets. Moreover, molecular docking reveals the binding sites on protein structures where ligands interact. This information is vital for understanding the specific mechanisms by which TCM compounds may modulate target proteins.

The results of molecular docking can rationalize the potential biological significance of the study's findings. They help interpret how the TCM compounds may influence the function of core targets, which is a key step in elucidating their therapeutic relevance in psoriasis treatment.

Outcome measures. The research team: (1) calculated the frequency of each herb's occurrence; (2) identified the core drugs; (3) determined the core drugs' active ingredients and targets; (4) identified psoriasis' targets; (5) determined the target proteins; (6) identified the top-30, key signaling-set pathways; (7) identified the top 10 biological processes (BPs), cell components (CC), and molecular functions (MF); (8) screened the top-five major active ingredients; and (9) performed molecular docking.

Outcome Measures

Frequency of medications. The research team calculated the frequency of each herb's occurrence (%) by dividing the frequency of each herb's occurrence by the total number of TCM prescriptions and then multiplying by 100%.

Core drugs. Heat-clearing and detoxifying medications are the most common in herbal combinations, often used in conjunction with heat-clearing and blood-cooling drugs, heat-clearing and damp-drying drugs, and astringent and hemostatic drugs. The research team determined that a drug was a core drug when the support number in the TCM Inheritance Support Platform was300. The "support number" refers to the support value in association rule mining. Specifically, a drug combination is considered a "core drug" when it appears in at least 300 prescriptions, indicating a minimum frequency of occurrence. This support number is a measure of how frequently the drug combination appears in the dataset, highlighting its significance in the context of prescription patterns. The confidence level was 0.6, indicating that when drug A appeared, a 60% chance existed of drug B also appearing. In this scenario, the "confidence level" of 0.6 signifies that there is a 60% probability that when drug A is present in a prescription, it is accompanied by the appearance of drug B. The confidence level is a measure used in association rule mining to indicate the reliability or strength of the relationship between two items, in this case, drugs A and B. A confidence level of 0.6 suggests a moderately strong association between the occurrences of these two drugs in prescriptions.

Core drugs' active ingredients and targets. The research team identified the core drug's active agreements and their targets.

Psoriasis disease targets. The research team used GeneCards, OMIM, DrugBank, TTD, and DisGeNET databases to identify targets.

Targets and Interactions Network. The research team imported the target genes into Cytoscape 3.9.3 for visualization and calculated the Degree (The degree of a node is the number of connections it has with other nodes. It represents how well-connected a node is within the network), Betweenness Centrality (Betweenness centrality measures the extent to which a node lies on the shortest paths between other nodes in the network. Nodes with high betweenness centrality play a critical role in connecting different parts of the network.), and Closeness Centrality (Closeness centrality measures how close a node is to all other nodes in the network. Nodes with high closeness centrality are positioned to quickly interact with

other nodes) of each node connected to the target protein, and the Closeness Centrality, the topological parameters of each node. The team selected the proteins as target proteins if their parameters were greater than the median.

Biological function process. The research team ranked the top 10 BP, CC, and MF entries according to the p.adjust value and the number of targets contained, the counted value. The team selected the top 10 BP, CC, and MF entries for bar graphs. The team based the top-30, key signaling-set pathways on the p.adjust value and the count value.

BP is mainly a response to nutrient levels, a cellular response to drugs, a cellular response to external stimulus, and a response to the metabolic processes of lipopolysaccharides and reactive oxygen species. CC is mainly a response to membrane raft, membrane microdomain, membrane region, transcription factor complex and ficolin-1-rich granule lumen. MF is mainly a response to nuclear receptor activity, transcription factor activity, direct ligand-regulated sequence–specific DNA binding, steroid hormone receptor activity, RNA polymerase II transcription factor binding, and RNA polymerase II basal transcription factor binding.

Core pathway screening. The research team screened the top five major active ingredients according to the magnitude of the degree values, from largest to smallest.

Molecular docking. To verify the accuracy of the network-analysis results, the research team used the top-5 core targets from the analysis of the PPI network neutrality value as receptors and employed the main active ingredients as ligands for molecular docking validation using Vina software. The lower the binding energy value, the more stable the binding conformation.

RESULTS: DATA MINING

Participants

Figure 1 A shows that the study included 95 participants, comprising 58 males (61%) and 37 females (39%). Figures 1 B is a histogram of the age distribution—aged 0-9 y, 4 participants (4.21%); aged 10-19 y, 3 participants (3.16%); aged 20-29 y, 23 participants (24.21%); aged 30-39 y, 28 participants(29.48%); aged 40-49 y, 8 participants (8.42%); aged 50-59 y, 14 participants (14.73%); aged 60-69 y, 10 participants (10.53%); aged 70-79 y, 4 participants (4.21%); and aged 70-79 y, 1 participant (1.05%).

Figure 1C shows a violin plot of gender by age group; Figure 1D shows a pie chart of the age distribution; and Figure 1E depicts the gender distribution by age group. The oldest participant was 82 years old, and the youngest was 7 years. Figure 1 C shows that male patients had a mean age of 39.0 ± 2.53 y, while female patients had a mean age of 40.7 ± 3.14 y(data not shown), with $P = .1398$.

Frequency of Medications

Among the 892 prescriptions in the database, the study identified 161 types of TCM herbs, with a combined frequency of 13 188 administrations (Table 1). When arranged in descending order of frequency of use, 23 Chinese medicinal herbs had usage rates exceeding 20%, totaling 9267 administrations, which accounted for 70.3% of the total frequency. They included: (1) Lonicerae Japonicae Flos—837 (93.83%), (2) Herba Portulacae—791 (88.68%), (3) Radix Gentianae—595 (66.70%),(4) Bletilla striata—595 (66.70%),(5) Rehmanniae Radix—572 (64.13%),(6) Dictamni Cortex—560 (62.78%), (7) Forsythia suspensa—537 (60.20%), (8) Cornu Bubali—509 (57.06%), (9) Radix Arnebiae/Radix Lithospermi—486 (54.48%), (10) Oldenlandia diffusa—380 (42.60%), (11) Curcumae Radix—336 (37.67%), (12) Dandelion—329 (36.88%), (13) Isatis root—314 (35.20%), (14) Scutellariae Radix—299 (33.52%), (15) Tetrapanacis

Figure 1. Participants' Demographics. The figure shows: (1) a pie chart of the gender distribution (Figure 1A), (2) a histogram of the age distribution (Figure 1B), (3) a violin plot of gender by age (Figure 1C), (4) a pie chart of the age distribution (Figure 1D), and (5) a gender distribution by age group (Figure 1E).

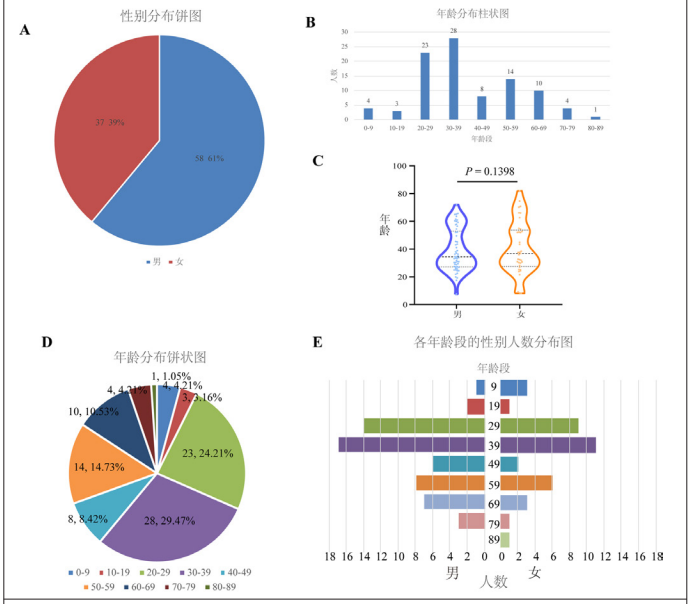
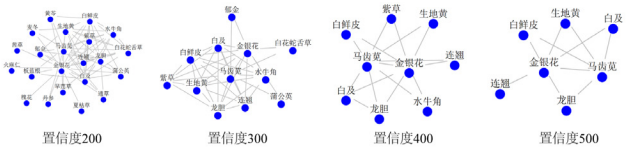


Table 1. Traditional Chinese Medicines Used With a Frequency of Over 20%

Herb	Use n (%)
Lonicerae Japonicae Flos	837 (93.83)
Herba Portulacae	791 (88.68)
Radix Gentianae	595 (66.70)
Bletilla striata	595 (66.70)
Rehmanniae Radix	572 (64.13)
Dictamni Cortex	560 (62.78)
Forsythia suspensa	537 (60.20)
Cornu Bubali	509 (57.06)
Radix Arnebiae/Radix Lithospermi	486 (54.48)
Oldenlandia diffusa	380 (42.60)
Curcumae Radix	336 (37.67)
Dandelion	329 (36.88)
Isatis root	314 (35.20)
Scutellariae Radix	299 (33.52)
Tetrapanacis Medulla	294 (32.96)
Herba Ecliptae	283 (31.73)
Ophiopogonis Radix	263 (29.48)
Sophorae Flos	242 (27.13)
Salviae Miltiorrhizae Radix et Rhizoma	229 (25.67)
Rubiae Radix et Rhizoma	214 (23.99)
Fructus Cannabis	212 (23.77)
Prunellae Spica	206 (23.09)
Phellodendri Chinensis Cortex	184 (20.63)

Figure 2. Network Diagram of TCM Association Rules Under Different Support Numbers



Abbreviations: TCM, traditional Chinese medicine

Figure 3. Venn Diagram of Target Intersection of Core Drug and Psoriasis

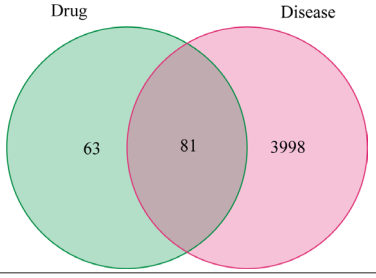


Figure 4. PPI Network Diagram of Intersection Targets

Abbreviations: PPI, protein-protein interaction

Medulla—294 (32.96%), (16) Herba Ecliptae—283 (31.73%), (17) Ophiopogonis Radix—263 (29.48%), (18) Sophorae Flos—242 (27.13%), (19) Salviae Miltiorrhizae Radix et Rhizoma—229 (25.67%), (20) Rubiae Radix et Rhizoma—214 (23.99%), (21) Fructus Cannabis—212 (23.77%), (22) Prunellae Spica—206 (23.09%), (32) Phellodendri Chinensis Cortex—184 (20.63%).

Core Drugs

Figure 2 illustrates the outcomes when support was set at 200, 300, 400, and 500. Under the condition of 500 support, the network diagram included seven herbs: Lonicerae Japonicae Flos, Herba Portulacae, Radix Gentianae, Bletilla striata, Raw Rehmanniae Radix, Dictamni Cortex, and Forsythia suspensa. The frequency analysis above showed that participants used all seven herbal medicines more than 500 times.

The analysis of the dosing pattern revealed that the drug combinations of the seven herbs ranked as follows (data not shown): (1) Lonicerae Japonicae Flos + Herba Portulacae (756), (2) Lonicerae Japonicae Flos + Bletilla striata (577), (3) Radix Gentianae + Lonicerae Japonicae Flos (562), (4) Radix Gentianae + Herba Portulacae (542), (5) Herba Portulaca + Bletilla striata (541), (6) Lonicerae Japonicae Flos + Sheng Rehmanniae Radix (537), (7) Lonicerae Japonicae Flos + Herba Portulacae + Bletilla striata (530), (8) Dictamni Cortex + Lonicerae Japonicae Flos (528), (9) Lonicerae Japonicae Flos + Forsythia suspensa (525), (10) Radix Gentianae + Lonicerae Japonicae Flos + Herba Portulacae (514), (11) Dictamni Cortex + Herba Portulacae (510), and (12) Herba Portulacae + Rehmanniae Radix (506).

The top drug combinations with the highest confidence ranking (data not shown), all belonged to the above seven drugs, including, in descending order, Forsythia suspensa, Herba Portulacae, Rehmanniae Radix→ Lonicerae Japonicae Flos, Dictamni Cortex, Herba Portulacae, Bletilla striata→ Lonicerae Japonicae Flos, Forsythia suspensa, and Rehmanniae Radix→ Lonicerae Japonicae Flos. The core-drug combinations thus were Forsythia suspensa + Herba Portulacae + Rehmanniae Radix, Lonicerae Japonicae Flos + Dictamni Cortex + Herba Portulacae + Bletilla striata, Lonicerae Japonicae Flos + Forsythia suspensa + Rehmanniae Radix, and Lonicerae Japonicae Flos.

RESULTS: NETWORK PHARMACOLOGY

Core Drug's Active Ingredients and Targets

The database search yielded 236 active ingredients from Lonicerae Japonicae Flos, 150 from Forsythia suspensa, 63 from Radix Gentianae, 54 from Herba Portulacae, 36 from Bletilla striata, 76 from Rehmanniae Radix, and 63 from Dictamni Cortex. The removal of duplicate molecules provided 58 active-pharmaceutical-ingredient molecules. The research team converted this collection of 58 active-ingredient compounds from the TCMSP database to UniProt gene-symbol names and removed duplicate targets, yielding 144 active, target functional genes.

Psoriatic Disease Targets

GeneCards, OMIM, DrugBank, TTD, and DisGeNET databases yielded 4079, 190, one, 119, and 1308 psoriasis-related genes, respectively. The removal of duplicates provided 4078 unique, psoriasis-related genes.

Targets and Interactions Network

Figure 3 shows that 81 genes intersect both the 144 target functional genes and the 4078 psoriasis-related genes, accounting for 56.25% of the total drug targets. The PPI network analysis of those intersecting functional genes showed a total of 80 nodes and 745 edges, with an average node degree of 18.6 (Figure 4).

Figure 5. Network Interaction Diagram for Core Target Proteins

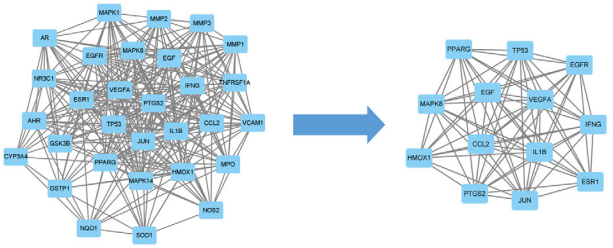
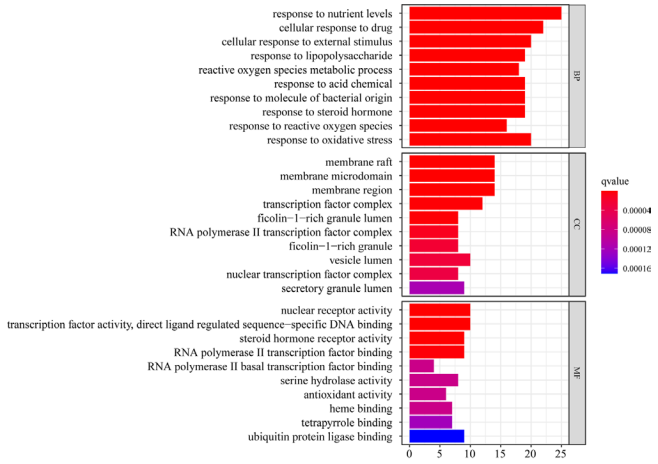


Figure 6. Bar Chart of GO Enrichment Analysis (BP, CC, MF)



Abbreviations: BP, biological process; CC, cell component; GO, gene ontology; MF, molecular function

Figure 5 shows the 13 key target proteins: (1) MAPK8, (2)TP53, (3) interferon gamma (IFNG), (4) epidermal growth factor receptor (EGFR), (5) prostaglandin-endoperoxide synthase 2 (PTGS2), (6) C-C motif chemokine ligand 2 (CCL2), (7) epidermal growth factor (EGF), (8) peroxisome proliferator activated receptor gamma (PPARG), (9) JUN, (10) interleukin 1 beta (IL1B), (11) estrogen receptor 1 (ESR1), (12) heme oxygenase 1 (HMOX1), and (13) vascular endothelial growth factor A(VEGFA).

Biological Functional Process

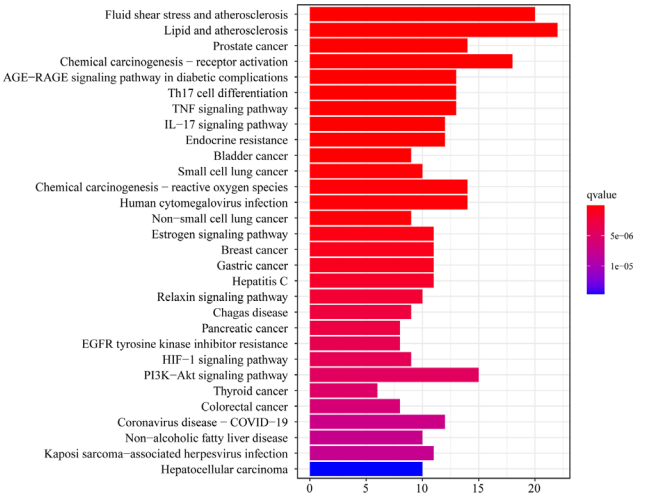
The GO functional enrichment included 1394 BPs, 30 CCs, and 96 MFs. Figure 6 shows the bar graphs for the top 10 BP, CC, and MF entries.

The KEGG pathway enrichment revealed 135 pathways. Figure 7 shows the top-30, key signaling-set pathways. Significant pathways include fluid shear stress and atherosclerosis, lipids and atherosclerosis, prostate cancer, chemical carcinogenesis-receptor activation, the advanced glycation end products (AGE)-receptor for advanced glycation end product (RAGE) signaling pathway in diabetic complications, T helper 17 (Th17) cell differentiation, the TNF signaling pathway, the IL-17 signaling pathway, and endocrine resistance.

Core Pathway Screening

Figure 8 shows the network diagram based on 144 target functional genes and their corresponding 58 active drug ingredients and 81 intersecting target genes. Table 2 shows that the top five major active ingredients, from largest to smallest, were primuletin (degree 56), kaempferol (degree 32), luteolin (degree 30), wogonin (degree 24), and β-sitosterol (degree 22).

Figure 7. Bar Chart of KEGG Pathway Enrichment Analysis



Abbreviations: KEGG, Kyoto Encyclopedia of Genes and Genomes

Figure 8. Network Interaction Mapping of Component-Target-Pathway

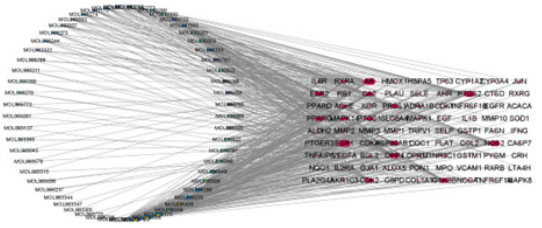


Table 2. Node Degree of Main Active Component

MOL ID	Molecular Name	Degree
MOL000098	Primuletin	56
MOL000422	Kaempferol	32
MOL00000	Luteolin	30
MOL000173	Wogonin	24
MOL000358	Beta-sitosterol	22

Table 3. Molecular Docking Results

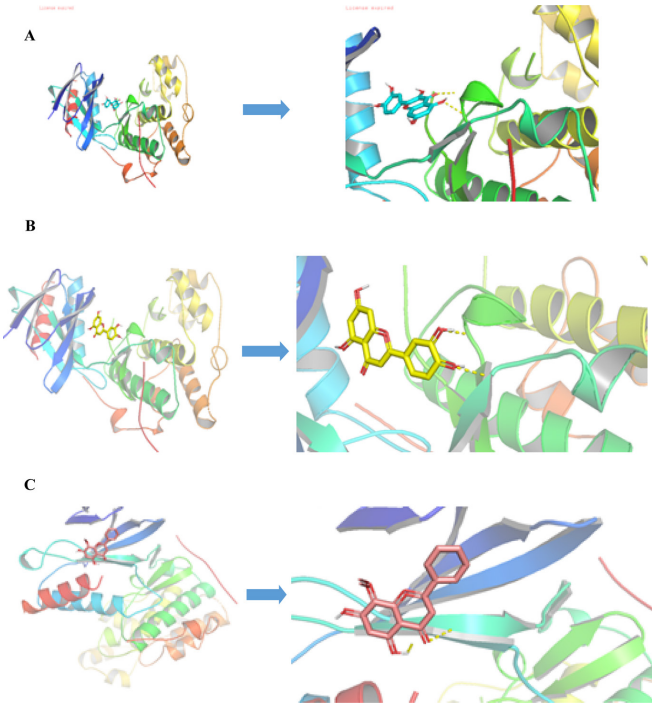
	Combined Energy		
Active Ingredients	MAPK8	TP53	EGFR
Primuletin	-7.4	-6.3	-8.5
Kaempferol	-6.0	-5.9	-8.1
Luteolin	-7.8	-6.2	-8.4
Wogonin	-6.6	-5.8	-8.0
β-sitosterol	-5.8	-6.4	-6.2

Abbreviations: EGFR, epidermal growth factor receptor; MAPK8, mitogen-activated protein kinase 8; TP53, tumor protein 53

Molecular Docking

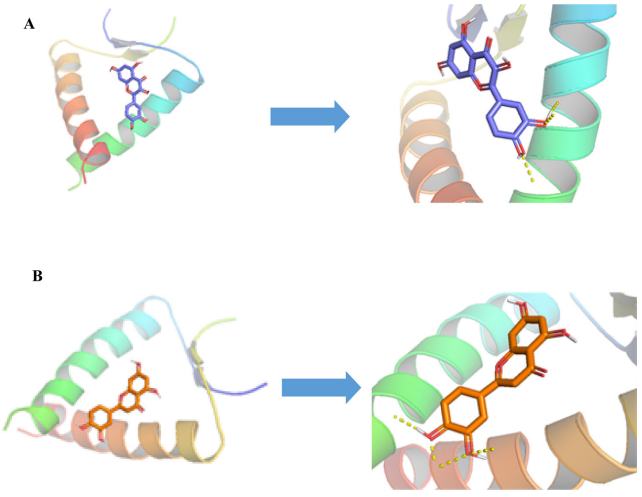
Table 3 shows that the binding energy to MAPK8, TP53, and EGFR: (1)of primuletin was -7.4, -6.3, and -8.5, respectively; (2) of kaempferol was -6.0, -5.9, and -8.1, respectively; (3) of luteolin was -7.8, -6.2, and -8.4, respectively; (4) of wogonin was -6.6, -5.8, -8.0, respectively; and (5) of β-sitosterol was -5.8, -6.4, and -6.2, respectively. A binding energy of ≤-6.0kcal/mol suggests a strong binding ability for the receptor to the ligand.

Figure 9. Main Active Components Docking With the MAPK8 Molecule. The figure shows: (1) primuletin and MAPK8 (Figure 9A), luteolin and MAPK8 (Figure 9B), and (3) wogonin and MAPK8 (Figure 9C).



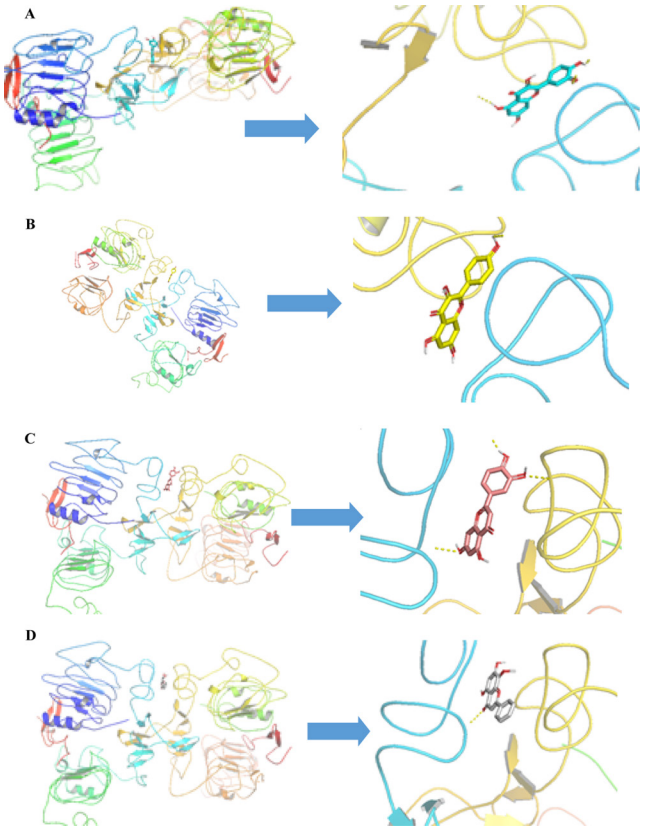
Abbreviations: MAPK8, mitogen-activated protein kinase 8

Figure 10. Main Active Components Docking With TP53 Molecule. The figure shows: (1) primuletin and TP53 (Figure 10A) and (2) luteolin and TP53 (Figure 10B).



Abbreviations: TP53, tumor protein 53

Figure 11. Main Active Components Docking With EGFR Molecule. The figure shows: (1) primuletin and EGFR (Figure 11A), (2) kaempferol and EGFR (Figure 11B), (3) luteolin and EGFR (Figure 11C), and wogonin and EGFR (Figure 11D).



Abbreviations: EGFR, epidermal growth factor receptor

Figures 9, 10, and 11 show the main active components docking with the MAPK8, TP53, andEGFR molecules, respectively.

DISCUSSION

The top 10 commonly used herbs for the treatment of psoriasis in the current research team's dermatology outpatient clinics, by frequency of use, were Lonicerae Japonicae Flos, Herba Portulacae, Radix Gentianae, Bletilla striata, Rehmanniae Radix, Dictamni Cortex, Forsythia suspensa, Cornu Bubali, Radix arnebiae/ Radix Lithospermi, and Oldenlandia diffusa. Based on the current study's association-rule algorithm, the research team identified the commonly used drug combinations: Lonicerae Japonicae Flos + Herba Portulacae, Lonicerae Japonicae Flos + Bletilla striata, Radix Gentianae + Lonicerae Japonicae Flos, Radix Gentianae + Herba Portulacae, Herba Portulaca + Bletilla striata, Lonicerae Japonicae Flos + Sheng Rehmanniae Radix, Lonicerae Japonicae Flos + Herba Portulacae + Bletilla striata, Dictamni Cortex + Lonicerae Japonicae Flos, Lonicerae Japonicae Flos + Forsythia suspensa, Radix Gentianae + Lonicerae Japonicae Flos + Herba Portulacae, Dictamni Cortex + Herba Portulacae, andHerba Portulacae + Rehmanniae Radix.

In a new network pharmacology approach to investigate the interaction between drug and target, the research team envisaged that medications can rebalance the biological network to investigate the effect of TCMS on the treatment of psoriasis. The network pharmacology analysis screened 58 active ingredients for a new in-hospital herbal formula and 81 potential targets for the treatment of psoriasis. The

topological analysis showed that the main components were primuletin, kaempferol, luteolin, wogonin, and β-sitosterol.

Several previous studies found that primuletin and luteolin could inhibit the activation of the NF-κB pathway; reduce serum TNF-α, IL-6, and IL-17 levels; and significantly decrease the psoriasis area and severity index (PASI) score of imiquimod (IMQ)-induced psoriasis in mouse model.[54-56] In addition, Sundarrajan et al found that primuletin can significantly decrease the level of tyrosine kinase expression in "high sensitivity of human epidermal keratinocytes" (HaCaT) cells,[57] and Lv et al found that luteolin can promote the expression of heat shock protein 90 (HSP90) in HaCaT cells, decrease the ratio of Th1/Th2 and Th17/Treg in immune cells of psoriatic mice, and suppress the increase of Th1 and Th17 in peripheral blood.[58]

Furthermore, the current study's potential target PPI network and topology analysis showed that the hospital's core prescription was available for psoriasis management by acting on core targets such as MAPK8, IFNG, TPP53, EGFR, PTGS2, CCL2, EGF, PPARG, JUN, IL1B, ESR1, HMOX1 and VEGFA. The current study's GO functional enrichment analysis and KEGG pathway enrichment analysis showed that the pathways related to the hospital's new TCM formula for psoriasis mainly involved pathways of cancer, including multisystem and multi-organ cancers, the TNF signaling pathway, and the HIF-1 signaling pathway.

The current research team hypothesizes that the core prescription for the treatment of psoriasis in the hospital may provide substantial therapeutic benefits for psoriasis management by inhibiting cancer-related pathways, the IL17 signaling pathway, the TNF signaling pathway, and the HIF-1 signaling pathway, thereby restoring the function of keratin-forming cells.

Among the EGFR target proteins, primuletin shows the lowest free energy of binding to that protein,-8.5kcal-mol-1, together with three hydrogen bonds, suggesting that primuletin may affect the new formula's function by competitively inhibiting the binding of the docking pocket to the target receptor EGFR, and could play an important role in the treatment from core prescriptions, thereby enhancing the reliability of target prediction.

However, the current study still had some limitations. First, the study heavily relied on web-based databases, such as TCMSP, BATMAN-TCM, DrugBank, and ETCM. While these databases offer valuable information, they have inherent limitations, including potential data gaps and lack of updates. The research team could further enhance the depth of the research by incorporating data from recent literature, which may provide insights into additional biological targets related to the study. The research team recommends that future investigations remain attentive to the latest scientific developments and include more comprehensive sources.

The study used disease databases such as GeneCards, OMIM, DrugBank, TTD, and DisGeNET to identify potential targets. However, the current study didn't explicitly address the specificity of differential genes concerning comparisons with healthy individuals. Future research should include a more comprehensive analysis, including differential gene expression in various conditions, to provide a broader context for the findings.

Moreover, the current research team performed molecular docking to evaluate the binding affinity of compounds, which provided valuable insights. However, it's important to note that future studies should validate molecular-docking results experimentally to confirm their biological relevance. The current research team recommends that future studies incorporate experimental validation to strengthen the credibility of the predictions.

Above all, to substantiate the current study's computational findings, future research should prioritize experimental validation of the interactions between active ingredients, targets, and associated pathways. Continuous monitoring of the latest scientific literature and emerging databases can ensure that the research remains up to date and provides a more comprehensive understanding of the topic. Expanding the scope to include differential gene expression and targets related to a wider range of diseases can enhance the breadth and applicability of the study's findings. In addition to molecular docking, future studies should verify the effects of active ingredients through a series of in-vivo and in-vitro experiments, providing a more holistic view of their mechanisms of action.

The current study contributes to a comprehensive understanding of psoriasis' pathogenesis and offers potential treatment strategies. The clinical significance of the research lies in its ability to inform the development of novel therapeutic approaches that could complement or enhance existing treatments for psoriasis. The current study's findings highlight TCM' promise in managing psoriasis, and future clinical studies may further explore its practical application in psoriasis treatment.

CONCLUSIONS

The new TCM formula to be used in the current research team's hospital may act on MAPK8, TP53, and EGFR targets through active ingredients such as primuletin, kaempferol, luteolin, wogonin, and β-sitosterol, which involve several signaling pathways, such as the cancer signaling pathway, TNF signaling pathway, HIF-1 signaling pathway, and endocrine resistance. The research provides a theoretical foundation for the clinical use of the new TCM formula.

AUTHORS' DISCLOSURE STATEMENT

The authors declare that they conducted the research in the absence of any commercial or financial relationships that could constitute a potential conflict of interest.

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