 DOI: 10.19600/j.cnki.issn2152 - 3924.2026.05.003

A Network Pharmacology Study of a Traditional Chinese Medicine Formula for Qingxuan Zhiyang Foot Spray

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Abstract [**Objectives**] To systematically screen the core active components, action targets, and signaling pathways of Qingxuan Zhiyang Foot Spray (Phellodendri Chinensis Cortex, Stemonae Radix, Sophorae Flavescentis Radix, Dictamni Cortex, Pseudolaricis Cortex, Kochiae Fructus, and Senecionis Scandentis Herba) based on network pharmacology, and to elucidate its molecular mechanism in the external treatment of tinea pedis and superficial skin fungal infections. [**Methods**] Potential active components and targets of the seven medicinal herbs were screened using the TCMSP database combined with physicochemical criteria for transdermal penetration of external preparations. Disease targets for tinea pedis, athlete's foot, and superficial skin fungal infections were retrieved from the GeneCards database. Drug-disease overlapping targets were obtained using the Venny tool. A protein-protein interaction (PPI) network was constructed using the String database. A visualized "Chinese herbal medicine-active component-target" interaction network was constructed using Cytoscape 3.10.1, followed by topological analysis. GO functional enrichment and KEGG pathway enrichment were performed using the DAVID database, and the enrichment results were visualized using bubble plots and bar charts. [**Results**] A total of 132 active components, 418 drug targets, 452 disease targets, and 96 core overlapping targets were obtained. The PPI network revealed TNF, IL6, IL1B, AKT1, TP53, JUN, and PTGS2 as hub proteins. The core pharmacologically active substances were quercetin, luteolin, berberine, matrine, stemonine, and pseudolaric acid B. GO enrichment was mainly concentrated in processes such as inflammatory response, apoptosis, and keratinocyte proliferation. KEGG enrichment revealed that the PI3K-Akt, AGE-RAGE, MAPK, TNF, IL-17, and C-type lectin receptor signaling pathways were the core regulatory pathways. [**Conclusions**] Through the multi-component transdermal targeted action, this spray regulates targets and pathways related to inflammation, innate antifungal immunity, and skin barrier repair, thereby achieving the triple efficacy of bacteriostasis, anti-inflammatory and antipruritic effects, and barrier repair. This study reveals the molecular mechanism of "multi-component synergy and multi-pathway coordination" underlying the external treatment of superficial fungal infections with Chinese herbal compound formulas.

Key words Traditional Chinese Medicine Formula for foot spray, Network pharmacology, Tinea pedis, Superficial skin fungal infection, Protein-protein interaction (PPI), Enrichment analysis

1 Introduction

Tinea pedis, clinically commonly known as athlete's foot, is the most common superficial skin fungal infectious disease in dermatology, with a persistently high global incidence. The disease is mainly caused by the invasion of the foot epidermal stratum corneum by keratinophilic dermatophytes such as *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*[1]. Fungi use foot keratin as a nutrient source for persistent colonization and proliferation, disrupting the normal structural organization of the skin. The typical clinical manifestations include vesicles, maceration and whitening, erosion and exudation, hyperkeratosis, desquamation and fissuring, and intractable pruritus. The condition is protracted and difficult to cure, with a high recurrence rate and strong contact transmissibility[2]. If not properly intervened over the long term, it can lead to secondary bacterial infections, lymphangitis, erysipelas, cellulitis, and other complications, severely affecting the patient's foot function and quality of daily life, while also posing a hidden risk of public health transmission.

In traditional Chinese medicine, tinea pedis is classified under the disease categories of "jiao shi qi (foot dampness), chou tian luo (fetid snail), and e zhang feng (goose-foot wind)". Physicians of past dynasties have elaborated in detail on its etiology and pathogenesis, and the core pathogenesis is attributed to endogenous damp-heat pouring downward to the foot, combined with external contraction of insect toxins, with damp-heat and insect toxins accumulating in the skin and causing failure of skin nourishment[3]. The foot is located in the lower energizer of the human body, where dampness readily accumulates and yang qi is difficult to reach. A habitual diet of spicy and greasy foods and dysfunction of the spleen and stomach in transportation and transformation lead to endogenous damp-heat. In addition, excessive sweating and dampness of the foot and the enclosed, non-breathable environment of shoes and socks, together with external contraction of wind-dampness and insect toxins, result in the combination of internal and external pathogenic factors. Damp-heat stagnates in the skin, and insect toxins erode the skin and flesh, thereby causing itching, vesicles, erosion, desquamation, hyperkeratosis, and other symptoms[4]. The disease is located in the skin of the foot and is associated with the transportation and transformation functions of the spleen and stomach and water-dampness metabolism. Its pathogenesis is mainly characterized by damp-heat, insect toxins, and stasis[5]. The core treatment principles are clearing heat and drying dampness, killing insects and detoxifying, dispelling wind and relieving itching, draining dampness and promoting sore healing, and repairing the skin[6-7]. External therapy in TCM is the preferred treatment for tinea, following the principle that "the rationale for external therapy is the same as that for internal thera-

Received: August 3, 2026 Accepted: September 16, 2026

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py". The medicinals act directly on the affected skin, reaching the diseased site and exerting immediate effects, Qingxuan Zhiyang Foot Spray is a purely herbal external spray formulation, scientifically composed of seven classic anti-tinea Chinese medicinal herbs: Phellodendri Chinensis Cortex, Stemonae Radix, Sophorae Flavescentis Radix, Dictamni Cortex, Pseudolaricis Cortex, Kochiae Fructus, and Senecionis Scandentis Herba. The formula is rigorously designed, with a well-structured sovereign-minister-assistant-envoy compatibility that precisely addresses the core pathogenesis of tinea pedis. The sovereign medicinals are Sophorae Flavescentis Radix and Phellodendri Chinensis Cortex, both of which are bitter and cold in nature with descending properties and enter the kidney, bladder, and spleen meridians. They are highly effective in clearing damp-heat from the lower energizer, drying dampness, and detoxifying, while also exhibiting broad-spectrum insecticidal and antibacterial activities, thereby directly targeting the fundamental etiology of tinea pedis—damp-heat and insect toxins[8-9]. The minister medicinals include Stemonae Radix and Dictamni Cortex. Stemonae Radix is specifically effective in killing insects, relieving itching, relaxing tension, and dispelling wind, and is indicated for various insect-related skin pruritus, thereby alleviating intractable foot pruritus. Dictamni Cortex functions to clear heat, dispel wind, dry dampness, detoxify, and free the joints, and serves as a key medicinal for stubborn skin tinea and damp-sore pruritus; it assists the sovereign medicinals in reinforcing the actions of clearing heat, drying dampness, dispelling wind, and relieving itching[10-11]. The assistant medicinals include Pseudolaricis Cortex and Kochiae Fructus. Pseudolaricis Cortex is a specific and highly effective TCM agent for tinea, with potent insecticidal, antibacterial, dampness-drying, and antipruritic effects, specifically targeting skin tinea toxins. Kochiae Fructus clears heat, drains dampness, dispels wind, and relieves itching, and can guide damp-heat from the lower energizer outward, such that once dampness is resolved, tinea resolves naturally, thereby addressing both the manifestations and the underlying cause[12-14]. The envoy medicinal is Senecionis Scandentis Herba, which clears heat, detoxifies, cools blood, promotes sore healing, reduces swelling, and relieves pain. It concurrently addresses inflammatory repair following foot vesicles, erosion, and skin breakage, harmonizes the properties of all medicinals in the formula, and guides the medicinals to act directly on the foot lesions[15]. The formula as a whole achieves a balanced compatibility of cold and warm properties, with simultaneous attention to drying dampness and dispelling wind, and parallel actions of killing insects and protecting the skin. It eliminates pathogenic factors without damaging healthy qi, and comprehensively aligns with the pathogenesis of tinea pedis, which is characterized by "damp-heat pouring downward and insect toxins accumulating in the skin". Clinically, it is widely used as an adjunctive treatment for tinea pedis, athlete's foot, and various superficial skin fungal infections, and possesses the application advantages of mild onset, high safety, good patient compliance, and low susceptibility to drug resistance.

At present, the molecular network underlying the antifungal action of this compound external preparation remains to be systematically deciphered, with insufficient bioinformatics evidence. In this study, network pharmacology approaches were applied to construct a visualized traditional Chinese medicine-active component-target interaction network and a protein-protein interaction (PPI) network. By integrating GO and KEGG enrichment profiles, we systematically elucidated the integrated regulatory mechanism by which this foot spray acts against superficial skin fungal infections, thereby furnishing molecular biological evidence to support formulation process optimization, quality standard development, and clinical translation.

2 Data and methods

2.1 Screening of active components and action targets of traditional Chinese medicine All chemical components of Phellodendri Chinensis Cortex, Stemonae Radix, Sophorae Flavescentis Radix, Dictamni Cortex, Pseudolaricis Cortex, Kochiae Fructus, and Senecionis Scandentis Herba were retrieved from the TCMSP database. Based on the transdermal penetration properties of the external spray, the following screening criteria were established: $DL \geqslant 0.18$, $MW \leqslant 500$, and AlogP 2-3, so as to identify active components amenable to stratum corneum penetration. Components absent from TCMSP were supplemented via Chinese- and English-language pharmacological literature. The targets corresponding to all identified components were then mapped in the Uniprot database and standardized to official human gene symbols. Following deduplication, a consolidated target set of the active components was obtained.

2.2 Acquisition of disease targets Disease-related targets were retrieved from the GeneCards database using the English search terms tinea pedis, athlete's foot, and superficial cutaneous fungal infection. The obtained targets were then aggregated, deduplicated, and mapped in the Uniprot database to official human gene symbols, generating a comprehensive disease-related target library.

2.3 Screening and visualization of overlapping targets The intersection between drug targets and disease targets was determined using the Venny 2.1 online tool, and the resulting overlapping targets were regarded as the potential core targets of the compound formula against tinea pedis.

2.4 PPI network construction The intersecting targets were submitted to the String database, with the species restricted to Homo sapiens and a confidence threshold of 0.4. The interaction data were then exported, and core hub targets were identified based on node degree and betweenness centrality.

2.5 Construction of the traditional Chinese medicine-active component-target network A visualized interaction network

was plotted using Cytoscape 3.10.1. The nodes were classified into three categories: red diamond-shaped nodes represented the seven Chinese medicinal herbs, yellow diamond-shaped nodes represented active components, and blue circular nodes represented target genes, while edges represented interactions. The topological parameter Degree was used to screen key medicinal herbs, core active components, and core targets in the network.

2.6 GO and KEGG enrichment analysis The intersecting targets were imported into the DAVID database, with $P<0.05$ set as the screening threshold. GO functional enrichment (BP, biological process; CC, cellular component; MF, molecular function) and KEGG signaling pathway enrichment were performed separately. Bar charts were used to visualize the top-ranked GO enrichment terms, and bubble plots were used to visualize the KEGG pathway enrichment results.

3 Results and analysis

3.1 Results of the traditional Chinese medicine-active component-target network analysis This formulation comprises seven traditional Chinese medicinal herbs; a total of 85 chemical compounds were identified from these herbs, which mapped to 249 molecular targets. By searching the Genecards database using the English search terms "tinea pedis", "athlete's foot", and "superficial cutaneous fungal infection", 906 targets associated with foot disorders were retrieved; further analysis using Venny identified 96 overlapping targets, as shown in Fig. 1.

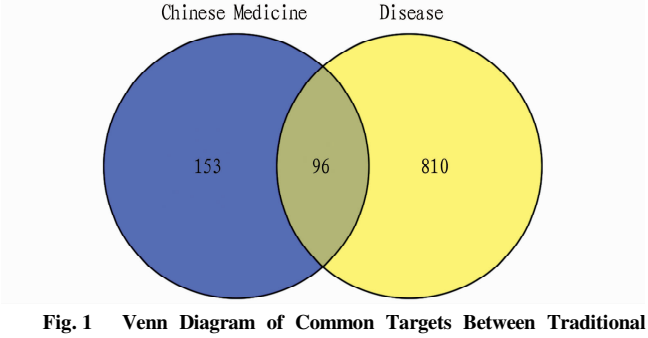


Fig. 1 Venn Diagram of Common Targets Between Traditional Chinese Medicine Compositions (Blue) and diseases (yellow)

The traditional Chinese medicine-active component-target network contained 152 nodes and 372 interaction edges: red diamond-shaped nodes represented the seven Chinese medicinal herbs (Phellodendri Chinensis Cortex, Stemonae Radix, Sophorae Flavescentis Radix, Dictamni Cortex, Pseudolaricis Cortex, Kochiae Fructus, and Senecionis Scandentis Herba); yellow diamond-shaped nodes represented the screened small-molecule active components; and blue circular nodes represented the disease intersecting targets.

Topological analysis showed that the top 6 core active components by degree value were Quercetin, Luteolin, berberine, matrine, stemonine, and pseudolaric acid B. These components connected the largest number of targets and were the core substances underlying the pharmacological efficacy of the compound formula. PTGS2, TNF, IL6, JUN, AKT1, and TP53 were the targets connected to the largest number of active components in the network and served as the core hub genes of drug action (Table 1). From the edge distribution, the active components of the seven Chinese medicinal herbs highly shared downstream disease targets, reflecting the compatibility advantage of the compound formula in "multi-component synergistic action on the same target" (Fig. 2).

Table 1 Key nodes and their topological characteristics in the active component-target network of the compound formula

No.	Node name	Node type	Degree	Betweenness Centrality
1	Quercetin	Compound	78	0.508 350 746
2	luteolin	Compound	41	0.148 099 558
3	PTGS2	Target	38	0.329 417 422
4	formononetin	Compound	36	0.061 022 239
5	Kaempferol	Compound	29	0.102 450 176
6	wogonin	Compound	27	0.085 057 837
7	apigenin	Compound	25	0.047 737 457
8	Stemonae Radix	Plant	16	0.088 908 135
9	PIK3CG	Target	15	0.053 549 683
10	PPARG	Target	13	0.027 450 235
11	DPP4	Target	12	0.0347 034 12
12	ESR1	Target	12	0.007 256 875
13	Sophorae Flavescentis Radix	Plant	12	0.014 437 145
14	NOS2	Target	10	0.008 073 077
15	Amurensin	Compound	10	0.013 617 794
16	CDK2	Target	9	0.004 224 774
17	Calycosin	Compound	9	0.010 188 653
18	NR3C1	Target	8	0.007 251 688
19	JUN	Target	7	0.012 842 799
20	GSK3B	Target	7	0.001 461 161
21	CASP3	Target	6	0.010 214 371
22	MAPK14	Target	6	0.001 032 942
23	Coniferin	Compound	6	0.006 977 167
24	kushenin	Compound	6	0.003 018 415
25	Glyceollin	Compound	6	0.002 776 405
26	sesamin	Compound	6	0.040 068 142
27	(±)-lyoniresinol	Compound	6	0.005 798 064
28	Phellodendri Chinrnsis Cortex	Plant	6	0.002 025 958
29	TNF	Target	5	0.005 336 048
30	CASP9	Target	5	0.007 379 640
31	AKT1	Target	5	0.005 336 048
32	RELA	Target	5	0.005 336 048
33	LACTB	Target	5	9.15E-04
34	CCND1	Target	5	0.014 492 093
35	F2	Target	5	0.008 757 795
36	Senecionis Scandentis Hebra	Plant	5	0.019 545 638
37	oleanolic acid	Compound	5	0.004 515 117
38	Kochiae Fructus	Plant	5	0.004 812 051
39	Dictamni Cortex	Plant	5	0.006 181 866
40	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one	Compound	5	0.003 846 450

3.2 PPI network results A total of 96 intersecting targets were identified and submitted to String for PPI network construction. After removal of isolated nodes, 92 protein nodes and 864 interaction edges were retained. The node circle size and color intensity were positively correlated with the Degree value, with larger and darker nodes denoting proteins occupying a more central regulatory position in the interaction network (Fig. 3). Topological analysis revealed the top 10 hub targets: TNF, IL6, IL1B, AKT1, TP53, JUN, PTGS2, EGFR, MAPK8, and BCL2. These proteins collectively formed a tightly regulated network and were primarily engaged in inflammatory cascades, fungal pattern recognition, apoptosis, skin cell proliferation, and oxidative stress modulation, thereby representing the core molecular foundation through which the compound formula ameliorates foot tinea lesions, suppresses fungal growth, and alleviates pruritus.

3.3 GO functional enrichment analysis results The GO enrichment bar chart is divided into three modules: biological process (BP, green), cellular component (CC, orange), and molecular function (MF, purple). The x-axis represents the enrichment terms, and the y-axis represents the number of enriched targets (Fig. 4). Biological process (BP): The top-ranked terms by number of enriched targets included RNA polymerase II-mediated transcriptional regulation, positive and negative regulation of gene expression, regulation of apoptosis, and inflammatory response, among other pathological changes. Cellular component (CC): The targets were mainly distributed in the cytoplasm, cytosol, nucleus, extracellular region, and plasma membrane, suggesting that the active components of the drug can penetrate the cell membrane and enter intracellular compartments and organelles such as mitochondria to regulate signal transduction, which is consistent with the dosage form characteristics of an external spray that exerts its effects through transdermal penetration into cells. Molecular function (MF): The enriched terms were predominantly protein binding, identical protein binding, enzyme activity, protein kinase activity, DNA binding, and metal ion binding. This indicates that the core targets are mostly kinases, transcription factors, and cytokine-binding proteins, which can mediate the activation and inhibition of multiple inflammatory and immune signaling pathways.

3.4 KEGG pathway enrichment bubble plot In the KEGG bubble plot, the y-axis represents pathway names, and the x-axis represents the Count of enriched targets (number of targets). The bubble color from blue to red represents increasing Pvalue, indicating higher pathway significance (Fig. 5). The top 8 core pathways ranked by enrichment significance and target count were: AGE-RAGE signaling pathway, PI3K-Akt signaling pathway, MAPK signaling pathway, IL-17 signaling pathway, TNF signaling pathway, C-type lectin receptor signaling pathway, NOD-like receptor signaling pathway, and Toll-like receptor signaling pathway. In addition, pathways related to inflammation and immunity, such as apoptosis, Th17 cell differentiation, chemokine, and NF-κB, were also enriched. According to pathway function, these pathways can be classified into three major categories: C-type lectin, NOD-like, and Toll-like receptor pathways are responsible for skin cell recognition of fungal pathogens and belong to the fungal recognition and innate immunity module; TNF, MAPK, IL-17, and NF-κB are core inflammatory pathways and belong to the inflammation and pruritus regulation module; PI3K-Akt and AGE-RAGE pathways regulate keratinocyte proliferation, skin barrier repair, and oxidative stress damage, and belong to the skin barrier repair module. The pathways are interconnected, forming a complete regulatory network of "fungal recognition-inflammation inhibition-barrier repair".

4 Discussion

4.1 The traditional Chinese medicine-component-target network diagram reveals the multi-component synergistic action characteristics of the compound formula The visualized traditional Chinese medicine – active component – target network intuitively demonstrates that this Chinese herbal formula does not rely on a single "core pharmacodynamic substance," but rather depends on small-molecule active substances released from multiple medicinal herbs such as Phellodendri Chinensis Cortex, Sophorae Flavescentis Radix, and Stemonae Radix (quercetin, luteolin, berberine, matrine, pseudolaric acid B, *etc.*) to share the regulation of key targets such as TNF, IL6, and PTGS2, thereby achieving additive synergy of multiple components. Quercetin and luteolin are broad-spectrum active flavonoids shared by the seven Chinese medicinal herbs and possess dual antifungal and anti-inflammatory activities[16-17]; berberine (from Phellodendri Chinensis Cortex) and matrine (from Sophorae Flavescentis Radix) disrupt the cell membrane of Trichophyton rubrum and inhibit fungal nucleic acid synthesis[18-19]; stemonine targets skin nerve endings to relieve itching[20]; pseudolaric acid B specifically inhibits the proliferation of dermatophytes[21]. The targets of various components overlap with one another and their pathways are complementary. A single component has limited efficacy, whereas the full formula compatibility forms a complete antibacterial-anti-inflammatory-antipruritic molecular regulatory network, explaining the TCM theory of compound formula compatibility for enhanced efficacy.

4.2 Biological functions of core PPI targets and their association with tinea pathology The PPI network identified TNF, IL6, IL1B, and PTGS2 as core pro-inflammatory targets. After dermatophytes colonize the stratum corneum of the foot, they stimulate keratinocytes to release large amounts of TNF, IL6, and IL1β, inducing local redness, swelling, vesicles, and burning pruritus[22]. PTGS2 (COX-2) catalyzes the synthesis of the inflammatory mediator prostaglandin, thereby amplifying pruritus and edema[23]. The active components of the compound formula can simultaneously regulate the expression of the above targets, block the inflammatory cascade, and rapidly alleviate skin lesions in the acute phase of tinea. AKT1, TP53, and BCL2 regulate apoptosis and proliferation of keratinocytes: tinea pedis fungi disrupt the homeostasis of stratum corneum cells, causing hyperkeratosis,

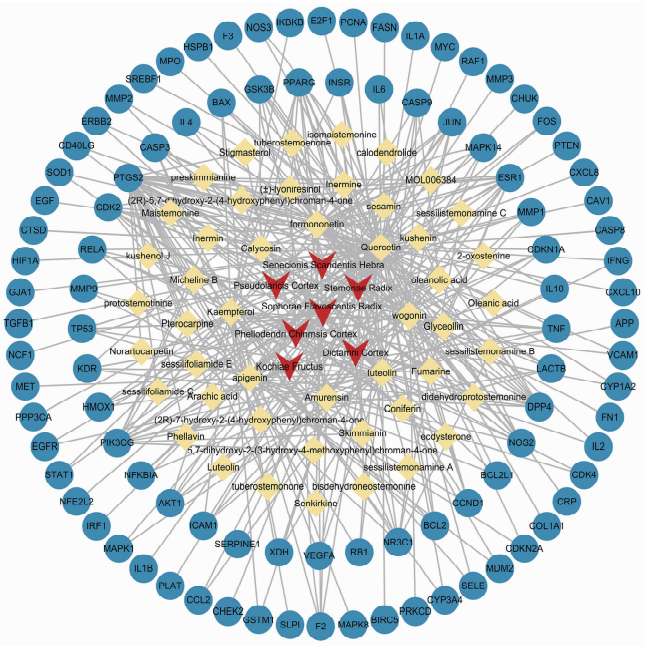


Fig. 2 Network diagram of the traditional Chinese medicine-active component-action target interactions

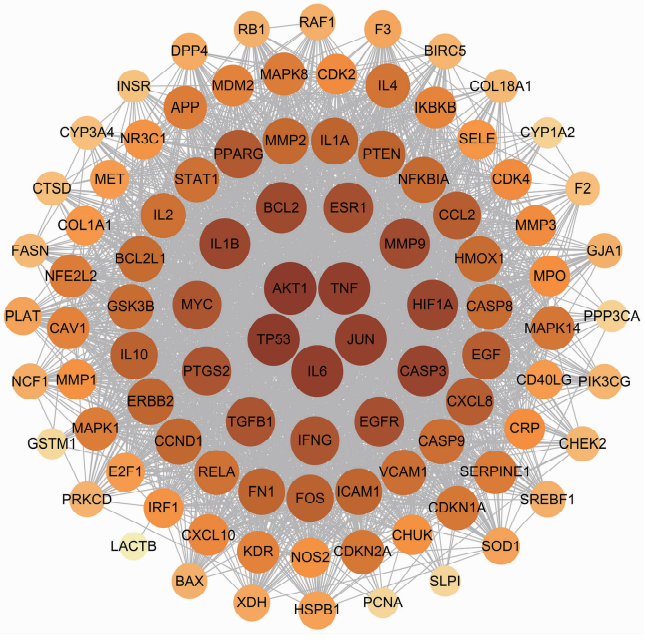


Fig. 3 PPI network diagram

desquamation, and erosion[24-26]. Normal activation of the AKT1 pathway promotes keratinocyte repair, while TP53 and BCL2 balance apoptosis, restoring an intact skin barrier. Proteins associated with the C-type lectin receptor pathway are responsible for keratinocyte recognition of fungal cell wall chitin, initiating local innate immunity, clearing colonized dermatophytes, and reducing the probability of recurrence.

4.3 GO enrichment results elucidating the overall biological regulatory logic of the compound formula The GO enrichment results comprehensively explain the mode of action of the

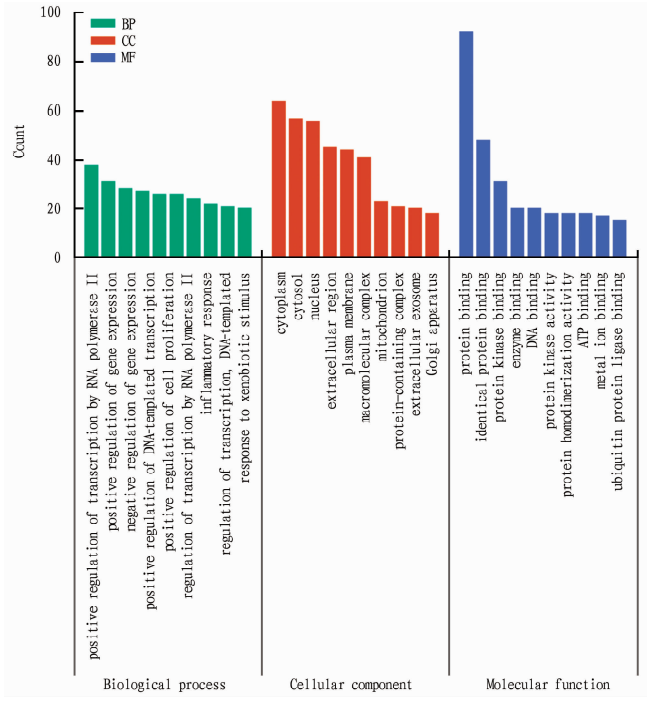


Fig. 4 GO functional enrichment analysis

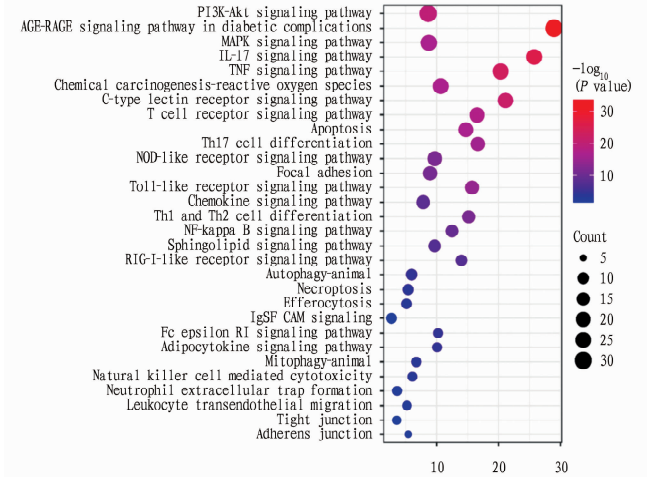


Fig. 5 KEGG enrichment bubble plot

spray from three dimensions. At the cellular localization level (CC): targets are widely distributed in the plasma membrane, cytoplasm, and mitochondria, demonstrating that lipophilic active components can smoothly penetrate the foot stratum corneum and enter target cells, and providing a molecular basis for the dosage form advantage of the external spray acting via transdermal penetration. At the biological effect level (BP): targets centrally regulate inflammatory responses, apoptosis, and skin cell proliferation, corresponding to the three core pathologies of tinea pedis: fungal infection-induced inflammation, keratinocyte necrosis and shedding, and skin barrier damage. At the molecular action mode (MF): targets are mostly kinases and transcription-binding proteins, which can simultaneously regulate multiple upstream and downstream signaling pathways, achieving the network effect of

"one target, multiple pathways; multiple targets, coordinated regulation".

4.4 KEGG core pathways collectively delineating the integrated anti-tinea molecular mechanism In conjunction with the bubble plot enrichment findings, the core pathways were categorized into three major functional modules, thereby systematically elucidating the molecular mechanism by which the spray acts against tinea pedis and superficial fungal infections.

4.4.1 Fungal recognition and innate immunity pathways. Pattern recognition receptors located on the cell membrane of the skin stratum corneum are capable of recognizing dermatophyte polysaccharides and chitin, consequently activating downstream immune pathways, promoting the secretion of antimicrobial cytokines, and eliminating fungi on the skin surface. The active components of the compound formula modulate these pathways, thereby strengthening the local innate immunity of the foot skin, inhibiting fungal colonization and proliferation at the source, and reducing the likelihood of recurrence.

4.4.2 Inflammatory and pruritus regulatory pathways. Persistent dermatophyte infection continuously activates the TNF, MAPK, and IL-17 inflammatory axis, leading to the release of abundant pro-inflammatory cytokines and triggering vesicles, exudation, and intense pruritus. By suppressing excessive pathway activation, the compound formula downregulates TNF, IL6, and PTGS2 expression, interrupts inflammatory signal transduction, and rapidly mitigates clinical symptoms including erythema, swelling, pruritus, and erosion.

4.4.3 Skin barrier repair pathways. The PI3K-Akt pathway governs the normal proliferation and migration of keratinocytes, thereby repairing the stratum corneum compromised by fungal invasion[27]. The AGE-RAGE pathway alleviates oxidative stress injury in the foot skin and reduces hyperkeratosis and rough desquamation[28]. Together, these two pathways restore an intact skin barrier, prevent fungal re-invasion, and achieve both symptomatic relief and root-cause treatment.

These three pathway modules are mutually interconnected: the immune module diminishes fungal burden, the inflammatory module alleviates acute-phase symptoms, and the barrier module repairs lesions and prevents recurrence. Collectively, they systematically delineate the molecular regulatory network underlying the triple TCM therapeutic effects of Qingxuan Zhiyang Foot Spray-insecticidal and antimicrobial, anti-inflammatory and antipruritic, and skin-repairing.

4.5 Summary of dosage form advantages and clinical significance Qingxuan Zhiyang Foot Spray is delivered via aerosolized administration, allowing the medicinal liquid to penetrate the interdigital spaces and moisture-prone folds of the sole. This results in high local drug concentrations with negligible systemic absorption and a favorable safety profile. Visualized network pharmacology data demonstrated that, following compatibility of the seven Chinese medicinal herbs, diverse small-molecule active substances (including flavonoids, alkaloids, and terpenoids) synergistically modulate targets across three major pathway categories: immune recognition, inflammatory response, and skin repair. This integrated action simultaneously achieves inhibition of pathogenic dermatophytes, rapid relief of pruritus and inflammation, and restoration of the foot keratin barrier. These findings provide robust bioinformatics evidence supporting its clinical application for tinea pedis, athlete's foot, and various superficial skin fungal infections, while also providing theoretical support for formulation process optimization and the selection of quality control markers for active components.

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(From page 10)

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