Exploring Action Mechanism of Wuling Decoction in Treating Sjögren's Syndrome Based on Network Pharmacology and Molecular Docking

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Abstract [**Objectives**] To explore the action mechanism of Wuling Decoction (the combination of Wumei Pill and Wuling Powder) in treating Sjögren's syndrome (SS) based on network pharmacology and molecular docking techniques. [**Methods**] The active components and their targets of Wuling Decoction were collected from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP). The targets related to SS were obtained from the GeneCards database. The intersection targets between Wuling Decoction and SS were identified using the Venny platform. The "Chinese medicinal-active component-common target" network was constructed using Cytoscape. The potential targets were improted into STRING to establish the protein-protein interaction (PPI) network, and the topological parameters were evaluated using Cytoscape to determine the key targets. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the DAVID database. Molecular docking of core components and key targets was conducted using the CB-Dock2 online tool. [**Results**] Wuling Decoction contained 121 active components of Chinese medicinals and 190 related targets. There were 1 447 SS-related targets obtained from GeneCards databases. 50 potential targets of Wuling decoction for SS were obtained. Network topology analysis revealed that quercetin, stigmasterol, and β-sitosterol were core components. PPI network analysis indicated that TNF, IL-6, and IL-1β were key targets. These targets were primarily involved in biological processes such as positive regulation of gene expression, inflammatory response, negative regulation of apoptosis, lipid and atherosclerosis pathways, AGE-RAGE signaling, fluid shear stress and atherosclerosis pathway, IL-17 signaling, and TNF signaling. Molecular docking demonstrated strong binding affinity between core components and targets, with stigmasterol exhibiting the highest binding activity. [**Conclusions**] Network pharmacology and clinical practice have demonstrated that Wuling Decoction exhibits remarkable efficacy and safety in the SS treatment. Through the synergistic effects of multiple components, multiple targets, and multiple pathways, it regulates immune, inflammatory, and endocrine signaling pathways, thereby improving the state of impaired triple-warmer qi transformation and fluid distribution. This provides both clinical and mechanistic evidence for treating the SS by TCM.

Key words Wuling Decoction, Sjögren's syndrome (SS), Molecular docking, Action mechanism

1 Introduction

As an autoimmune disorder, Sjögren's syndrome (SS) mainly affects the exocrine glands. Its pathogenesis is closely associated with immune dysregulation, lymphocyte infiltration, and the secretion of proinflammatory cytokines[1]. The etiology of SS involves genetic susceptibility, viral infections, hormonal imbalances, and disruption of the glandular microenvironment[2]. Clinically, in addition to prominent symptoms of dryness such as dry mouth and dry eyes, the disease can also involve damage to other organs, including interstitial pneumonia, renal tubular acidosis, atrophic gastritis, and liver impairment[3]. Conventional Western medicine primarily focuses on symptom relief and suppression of the immune response; however, long-term use of immunosuppressants may lead to adverse effects[4]. In contrast, Traditional Chinese Medicine (TCM) offers unique advantages in the treatment of SS and has demonstrated significant clinical efficacy[5].

Professor Zhang Xiaoqiang's team has dedicated their research to exploring SS through both clinical and experimental studies[6-8]. This work aims to identify the active components of Wuling Decoction, a modified formulation based on Wumei Pill and Wuling Powder, and to elucidate its mechanism for treating SS. In this study, we employed network pharmacology and molecular docking to uncover the core targets of Wuling Decoction in SS treatment, thereby providing a pharmacological basis for its clinical application.

2 Data and methods

2.1 Screening of active components and targets in Wuling Decoction We used Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (https://old.tcmsp-e.com/tcmsp.php) to retrieve active components of Wuling Decoction (Mume Fructus, Coptidis Rhizoma, Angelicae Sinensis Radix, Alismatis Rhizoma, Poria, Cinnamomi Ramulus, Artemisiae Argyi Folium, Rehmanniae Radix Praeparata, Glycyrrhizae Radix Et Rhizoma), with oral bioavailability (OB) ≥ 30% and drug

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likeness (DL) ≥0.18 as the screening criteria[9], and obtained the effective active components in the formula and the information of the corresponding target points, and deleted the effective active components without the target point information. Then, we input the selected targets into the UniProt database (https://www.uniprot.org/), and converted and standardized the targets to determine the information of the targets of the active components of Wuling Decoction.

2.2 Collection of disease related targets Through the GeneCards database (https://genealacart.genecards.org/), the SS-related disease targets were searched with the keyword "Sjögren's syndrome", and the SS-related target information was collected and sorted out, and the duplicate targets were removed.

2.3 Intersection targets of Wuling Decoction for treating SS and construction of "Drug – Active component – Common targets" network The targets of the active components from the formula were intersected with the disease-associated targets using the Venny 2.1.0 online platform (https://bioinfogp.cnb.csic.es/tools/venny/index.html) to generate a Venn diagram. The overlapping targets, representing the key targets for Wuling Decoction in treating SS, were identified. Subsequently, a "Drug – Active Component – Common Targets" network was constructed with Cytoscape software.

2.4 Construction of protein-protein interaction network (PPI) We used the STRING database (https://string-db.org/) to construct a PPI network from the overlapping targets, setting the confidence threshold to 0.40. This network was then exported to Cytoscape software for visualization and topological analysis, which helped determine the key targets.

2.5 Gene Ontology (GO) enrichment analysis and and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis We performed both GO and KEGG enrichment analyses on the core targets using the STRING database. The GO analysis covered three aspects: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). Significant enrichment results were screened, and the results were visualized.

2.6 Molecular docking verification We selected the top 4 core components ranked by degree value in the "Drug – Active Component – Common Targets" network and the top 3 target proteins ranked in the PPI network for docking analysis, downloaded the 3D structure files of the proteins from the PDB database (https://www.rcsb.org) as ligands, and downloaded the 2D structure files of the core components from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) as receptors. Then, used the CB-Dock2 online website for molecular docking, where a docking binding energy ≤ −5.0 kcal/mol indicates that the receptor and ligand can spontaneously bind.

3 Results and analysis

3.1 Screening of drug active components and targets Through retrieval and screening via the TCMSP database, a total of 121 active components of Wuling Decoction were obtained. The detailed information on the shared active components is provided in Table 1, with 190 corresponding targets identified.

Table 1 Common active components

MOL ID	Abbrev.	Drugs
MOL000098	A01	Mume Fructus, Coptidis Rhizoma, Artemisiae Argyi Folium, Glycyrrhizae Radix Et Rhizoma
MOL000358	A02	Mume Fructus, Angelicae Sinensis Radix, Cinnamomi Ramulus, Artemisiae Argyi Folium
MOL000449	A03	Mume Fructus, Angelicae Sinensis Radix, Artemisiae Argyi Folium, Rehmanniae Radix Praeparata
MOL001040	C01	Mume Fructus, Artemisiae Argyi Folium
MOL000422	C02	Mume Fructus, Glycyrrhizae Radix Et Rhizoma
MOL000359	B	Cinnamomi Ramulus, Alismatis Rhizoma, Rehmanniae Radix Praeparata

3.2 Collection of disease-related targets and intersection targets A total of 1 447 targets related to SS and 190 targets of the active components in Wuling Decoction were identified. Their intersection was presented in a Venn diagram (Fig. 1), revealing 50 common targets.

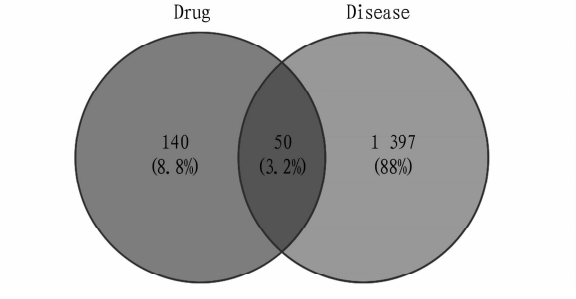

Fig. 1 Venn diagram of drugs and targets

3.3 Network construction and analysis The constructed "Drug – Active Component – Common Targets" network contained 321 nodes and 2 057 edges (Fig. 2). Through network topology analysis, key active components with higher degree values were identified, such as quercetin, stigmasterol, and beta-sitosterol. Detailed chemical information is provided in Table 2.

Table 2 Top 5 active components in "Drug – Active Component – Common Targets" network

Molecular ID	Name	Degree
MOL000098	Quercetin	480
MOL000449	Stigmasterol	140
MOL000358	Beta-sitosterol	123
MOL000422	kaempferol	96
MOL001040	(2R)-5, 7-dihydroxy-2-(4-hydroxyphenyl) chroman-4-one	87

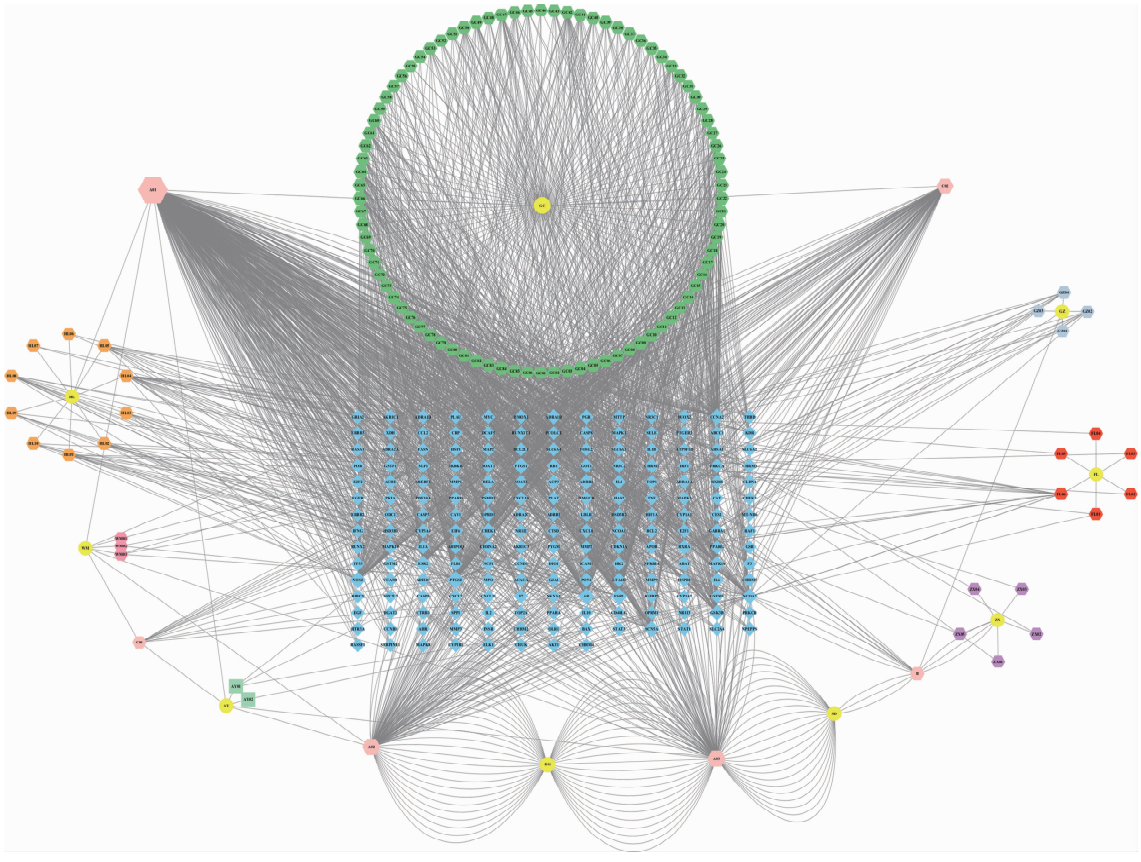

Fig. 2 "Drug – Active Component – Common Targets" network

3.4 PPI network analysis The potential targets were imported into the STRING database to construct a PPI network, which contained 48 nodes and 595 edges. The PPI network data file was organized into a table and imported into Cytoscape software. Screening was performed based on closeness centrality, betweenness centrality, and degree values, and the results were visualized. After screening, 8 nodes and 28 edges were obtained. The top three ranked targets were selected as core targets, including Tumor Necrosis Factor (TNF), Interleukin-1 beta (IL-1β), and Interleukin-6 (IL-6). The screening flowchart is shown in Figure 3. The top five targets ranked by node degree value after topological analysis are listed in Table 3.

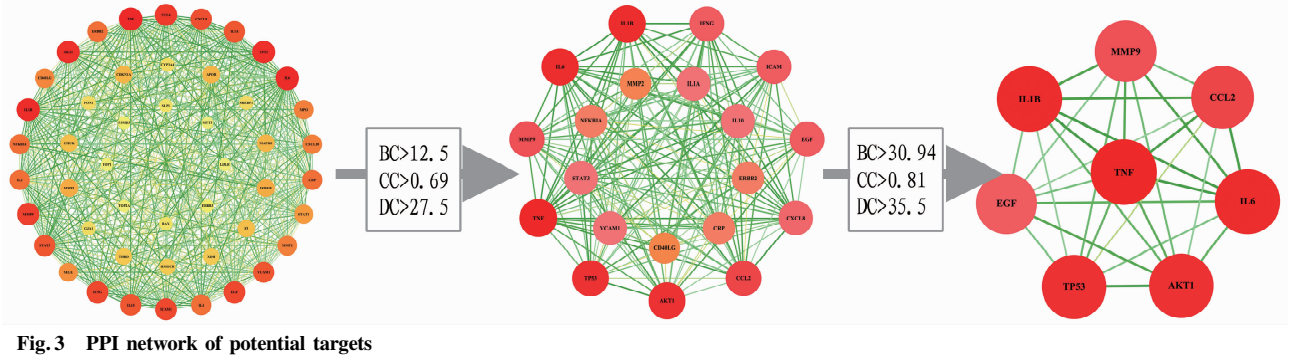

Fig. 3 PPI network of potential targets

Table 3 Top 5 targets in PPI network

Targets	Name	Degree
TNF	Tumor necrosis factor	42
IL-1β	Interleukin-1 beta	41
IL-6	Interleukin-6	41
AKT1	RAC-alpha serine/threonine-protein kinase	40
TP53	Cellular tumor antigen p53	40

3.5 GO functional enrichment analysis and KEGG pathway enrichment analysis The GO functional enrichment analysis results indicated that the core targets were primarily involved in biological processes such as positive regulation of gene expression, inflammatory response, and negative regulation of apoptosis. They were mainly located in cellular components such as the extracellular space and extracellular region, and possessed molecular functions including cytokine activity and protein binding. The KEGG

pathway enrichment analysis results revealed that the core targets were predominantly enriched in pathways such as lipid and atherosclerosis, the AGE-RAGE signaling pathway in diabetic complications, and the Fluid shear stress and atherosclerosis pathway (Fig. 4).

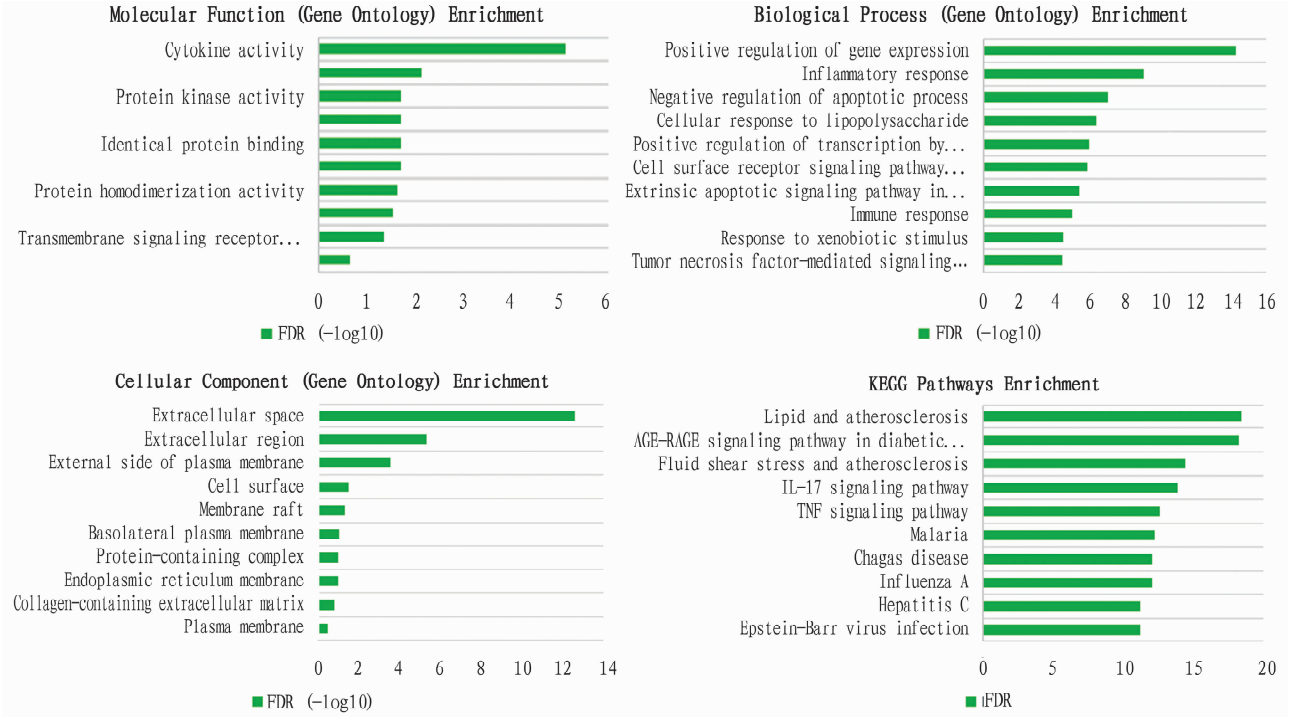

Fig. 4 Enrichment analysis chart

3.6 Molecular docking verification The molecular docking results (Table 4) showed that all four core compounds (quercetin, stigmasterol, β-sitosterol, and kaempferol) exhibited strong binding capabilities with three key target proteins (TNF, IL-1β, IL-6), with binding energies all < -5 kcal/mol. This suggests that these compounds may exert their therapeutic effects on SS by acting on these key targets, among which stigmasterol demonstrated the strongest binding activity with the three targets (Fig. 5).

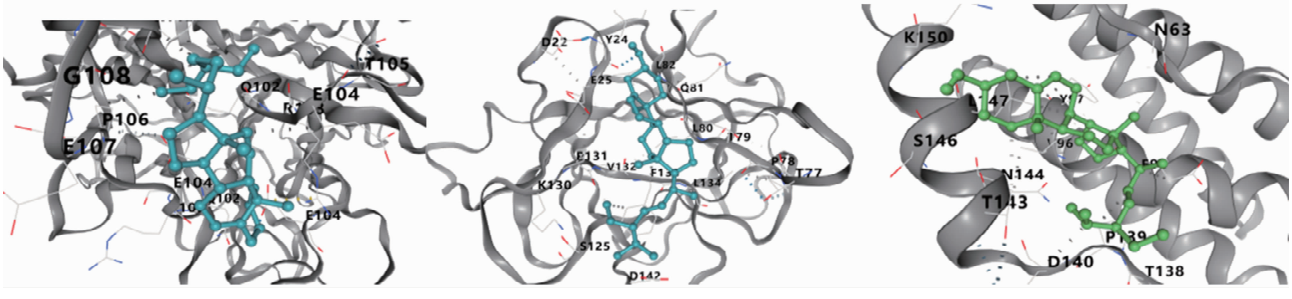

Fig. 5 Molecular docking diagram of stigmasterol with TNF, IL1β, IL-6

Table 4 Molecular docking results

Targets	Binding energy//kcal/mol			
	A Quercetin	B stigmasterol	C Beta-sitosterol	D Kaempferol
TNF	-8.6	-7.5	-6.2	-8.5
IL-1β	-6.9	-7.9	-8.2	-6.7
IL-6	-6.5	-7.0	-6.8	-6.3

4 Discussion

SS is the second most prevalent autoimmune disease[10], with its underlying pathology being "autoimmune epitheliitis"[11]. Persistent B-cell activation in the advanced stages of disease progression can lead to systemic manifestations[12]. Based on its clinical symptoms and signs, SS is categorized in traditional Chinese medicine as "dryness arthralgia," "dryness toxin," or "diabetes"[13]. Professor Zhang Xiaoqiang proposes that both fluid retention and the transformation and distribution of body fluids are equally crucial for patients with SS. The persistent dryness observed in SS patients results from pathogenic dryness reverting yin liver system, leading to an inability to retain body fluids[8]. Based on the treatment principles for dryness pathogen cited by Qing Dynasty physician Chen Baoshan in his *Overview of Dry Qi*: "When dryness persists chronically, it permeates the three energizers… causing stagnation in both nutritive and defensive qi, disrupting fluid distribution. The treatment should combine pungent-cooling with bitter-warming herbs… Since dryness inherently contains elements of fire, damp-

ness, and cold, its treatment must address these concomitant factors. While employing pungent, cold, and warm properties, one must strictly avoid excessive bitter flavor." Integrating the dual approaches of transforming qi to distribute fluids and preserving body liquids, the "Fluid – Distribution and Liquid – Preservation Method" was developed (primary formula: Wuling Decoction, comprising Wumei Pill combined with Fuling Decoction). The statement "When dryness prevails, the liver wood is susceptible to pathogen" from *Plain Questions* Chapter on Major Patterns of Qi Interaction and the synopsis of reverting yin disease in *Treatise on Cold Damage Diseases*, "In reverting yin disease, there is wasting-thirst …", collectively indicate a close relationship between dryness blockage and the reverting yin liver. Wumei Pill serves as the primary formula for treating Reverting Yin syndrome. Zheng Qin'an, in his work *Medical Principles and Clinical Applications*, explains its mechanism as follows: Fructus Mume, with its intensely sour nature, aligns with the characteristic of the Wood phase. It is combined with warming and acrid herbs such as Cinnamomi Ramulus, Aconiti Lateralis Radix Praeparata, Asari Radix et Rhizoma, Zingiberis Rhizoma, and Zanthoxyli Pericarpium to guide yang qi downward. Meanwhile, Coptidis Rhizoma and Phellodendri Chinensis Cortex are included to clear pathogenic Dryness. Ginseng Radix et Rhizoma and Angelicae Sinensis Radix nourish the spleen yin and restore the function of the Middle Jiao (Earth), thereby ensuring the free flow of reverting yin. The formula acts to drain excess Wind – Wood and stabilize the deficient Middle Earth. By calming the Wind – Wood, the Middle Earth is pacified; by armonizing the spleen and stomach, it supports Earth to restrain wood. This achieves simultaneous treatment of both the root cause and manifestations. Reverting yin Wind – Wood originates from kidney water and matures through spleen earth. It internally houses the ministerial fire. When wood-fire blazes excessively, it leads to upper heat and wasting-thirst. As the saying goes: "Earth is regulated by Wood, and Wood is nurtured by Earth". The two mutually restrain and promote each other[8]. Dysfunction of qi transformation in the San Jiao (Triple Energizer) constitutes a key pathogenesis of dryness blockage. Wuling Powder, a primary formula for Taiyang disease recorded in the *Treatise on Cold Damage Diseases*, addresses symptoms such as "difficult urination, mild fever, and wasting-thirst". Its therapeutic mechanism lies in rectifying impaired San Jiao qi transformation, which causes failure in fluid distribution, retention of water-dampness, and accumulated heat that damages fluids to generate dryness[7]. The combined formula acts synergistically to transform qi for fluid distribution and nourish yin to preserve liquids: Cinnamomi Ramulus and Artemisiae Argyi Folium warm yang and transform qi to promote fluid circulation; Alismatis Rhizoma and Poria promote urination and drain dampness to regulate metabolism; Rehmanniae Radix Praeparata and Angelicae Sinensis Radix nourish yin and moisten dryness; while Mume Fructus and Glycyrrhizae Radix Et Rhizoma utilize sour-sweet properties to nourish yin and prevent dissipation. This formulation also aligns with the "salty-sweet combination for dryness elimination" theory from *Supplementary Treatments*, where the salty nature of Alismatis Rhizoma breaks stagnation, and the sweet properties of Poria and Glycyrrhizae Radix Et Rhizoma strengthen the spleen, collectively restoring fluid distribution and storage through balanced draining and tonifying.

Wuling Decoction exerts its therapeutic effects through three core components that demonstrate significant anti-inflammatory, antioxidant, and immunomodulatory activities. Quercetin modulates the NF-κB signaling pathway, leading to reduced transcription and release of pro-inflammatory cytokines such as TNF and IL-6, while downregulating the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), thereby mitigating inflammatory responses[14]. It also bidirectionally regulates immune cell function by enhancing macrophage activity and modulating T-cell differentiation to maintain immune homeostasis. Its antioxidant capacity is attributed to the phenolic hydroxyl groups that directly scavenge reactive oxygen species (ROS), coupled with the activation of endogenous antioxidant enzymes such as glutathione peroxidase (GSH-Px), which collectively protect cells from lipid peroxidation and slow the progression of chronic diseases[15]. Stigmasterol suppresses B-cell overactivation, reducing the production of autoantibodies (for example, anti-SSA/SSB)[16], modulates helper T-cell activity to mitigate glandular damage, and inhibits the TGF-β signaling pathway to delay glandular fibrosis[17]. Beta-sitosterol alleviates inflammation by suppressing Toll-like receptor 4 (TLR4) signaling and Th17 cell differentiation, enhances salivary secretion via activation of aquaporins and M3 receptors, and promotes mucin production to reinforce the mucosal barrier[18]. Additionally, it competitively inhibits cholesterol absorption, indirectly improving the metabolic profile in SS patients[19]. Together, these three constituents function synergistically within a multi-target therapeutic network, contributing to the efficacy of Wuling Decoction in the treatment of SS.

PPI network analysis identified TNF, IL-1β, and IL-6 as the three core inflammatory cytokines driving the pathogenesis of SS. These cytokines collectively exacerbate exocrine gland inflammation and dysfunction by amplifying inflammatory responses, inducing apoptosis, and modulating immune activity. Specifically, TNF and IL-1β promote the release of inflammatory mediators through activation of the NF-κB signaling pathway, leading to glandular cell apoptosis, lymphocyte infiltration, and ultimately glandular fibrosis[20-22]. IL-1β further activates the caspase signaling pathway to induce glandular cell apoptosis and promotes Th17 differentiation, intensifying autoimmune damage[22]. In contrast, IL-6 operates through a distinct mechanism by activating the JAK/STAT signaling pathway to enhance inflammation. It also modulates B-cell and T-cell activation, facilitating autoantibody production and aggravating SS pathology[23]. Together, these three cytokines contribute to SS progression via complementary signaling pathways and mechanisms. Therapeutic interventions targeting TNF, IL-6, or IL-1β, such as inhibiting their expression or activity, have been shown to attenuate inflammatory responses, reduce glandular apoptosis and dysfunction, and consequently alleviate SS symptoms.

GO and KEGG pathway enrichment analyses revealed that the core mechanism of Wuling Decoction in treating Sjögren's syndrome (SS) is closely associated with three interrelated pathways: the lipid and atherosclerosis pathway, the AGE-RAGE signaling

pathway, and the fluid shear stress and atherosclerosis pathway. Together, these pathways promote inflammation, dysregulated immune responses, and vascular injury, which collectively drive SS pathogenesis. Abnormal lipid metabolism is frequently observed in SS patients[24]. Lipid accumulation activates macrophages to release large quantities of pro-inflammatory factors, directly exacerbating inflammatory infiltration and oxidative stress in glandular tissues. Moreover, it contributes to the formation of atherosclerotic plaques, causing vascular endothelial injury and further amplifying local inflammatory responses. Concurrently, microcirculatory perfusion deficits reduce glandular blood supply, aggravating glandular dysfunction and atrophy[25]. When the atherosclerosis pathway is activated, it upregulates NADPH oxidase expression, stimulating a burst of reactive oxygen species (ROS) that directly impair glandular cell function[26-27]. It also activates the NF-κB signaling pathway, leading to elevated expression of pro-inflammatory factors and ultimately promoting cellular and tissue apoptosis[28]. The AGE-RAGE signaling pathway contributes to SS progression by inducing autoantigen release, which directly triggers autoimmune activation and promotes glandular fibrosis, resulting in irreversible structural damage[29]. In addition, fluid shear stress (FSS) in the microvasculature of SS patients is significantly lower than the physiological threshold. This hemodynamic abnormality enhances the release of inflammatory mediators via NF-κB activation, attracting more immune cells to infiltrate the glands. It also induces vasoconstriction, leading to glandular ischemia and hypoxia that severely suppress secretory function, while increasing vascular permeability to facilitate inflammatory cell exudation[30]. Molecular docking results further demonstrated that the core components of Wuling Decoction exhibit strong binding affinity with key target proteins in these pathways. In particular, stigmasterol showed excellent binding capacity with targets across the critical pathways described, providing direct molecular evidence that Wuling Decoction exerts its therapeutic effect through multi-pathway intervention.

Based on the above analysis, the active components of Wuling Decoction (quercetin, stigmasterol, β-sitosterol, *etc.*) Can target and regulate the expression of core inflammatory factors such as TNF, IL-1β, IL-6, and further inhibit the activation of key signaling pathways such as NF-κB, thereby blocking the inflammatory response. Wuling Decoction is not only limited to traditional anti-inflammatory and immunomodulation, but also involved in AGE-RAGE signaling pathway, fluid shear stress and lipid and atherosclerosis-related pathways, indicating that it can improve multi-dimensional mechanisms such as metabolic disorders, vascular endothelial dysfunction and abnormal mechanical signal transduction. Synergistically reduces glandular damage.

5 Conclusions

Employing network pharmacology and molecular docking technology, this study demonstrates that Wuling Decoction exhibits synergistic therapeutic effects in treating SS through multi-component, multi-target, and multi-pathway mechanisms. The therapeutic strategy of Wuling Decoction reflects the characteristic "holistic concept" of traditional Chinese medicine, emphasizing the integrated regulation of autoimmune processes, inflammatory responses, and metabolic functions. By orchestrating multi-level adjustments, it promotes a shift of the immune status and fluid metabolism toward dynamic equilibrium, thereby effectively ameliorating the pathological state of SS. This research identifies core targets and signaling pathways involved in the therapeutic action of Wuling Decoction, providing a pharmacological foundation for its clinical application in SS treatment.

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Our findings indicate that acetylenic phenols exert anti-TNBC effects through multi-target and multi-pathway synergism, with a potential toxicity advantage over conventional chemotherapeutic agents. Notably, the diacetylenic phenolic structure demonstrated strong binding affinity in molecular docking, suggesting its high potential for drug development. These results provide a theoretical foundation for further research on acetylenic phenols in TNBC treatment and propose a new direction for developing novel anti-cancer agents.

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