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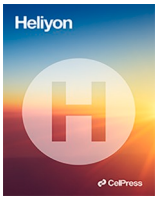

Research article

Exploring shared mechanisms between ulcerative colitis and psoriasis and predicting therapeutic natural compounds through bioinformatics and molecular docking

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ABSTRACT

Introduction: Previous studies have suggested a potential correlation between psoriasis (PS) and ulcerative colitis (UC). However, studies exploring the shared mechanisms of both diseases remain limited. Current treatments primarily involve using immunosuppressive drugs, which can lead to potential side effects and drug resistance. Traditional Chinese medicine has demonstrated favorable efficacy in treating UC and PS with fewer side effects. This study aims to elucidate the shared biological mechanisms underlying UC and PS and to predict natural compounds effective for treating both disorders.

Method: We collected and validated differentially expressed genes associated with UC and PS from the Gene Expression Omnibus database. A protein-protein interaction network was constructed using the STRING database, aiding in identifying core targets. The Gene Ontology and Kyoto Encyclopedia of Genes and Genomes databases were utilized to analyze the functions and genomic enrichment of the identified core targets. The CIBERSORT method was employed to assess the correlation of core targets with immune cells. Compounds with potential therapeutic values were selected from the Coremine and TCMSP databases, and their therapeutic efficacy was predicted via molecular docking.

Results: In UC and PS, 20 common core targets were identified, with matrix metalloproteinase 9 (MMP9), matrix metalloproteinase 1 (MMP1), cluster of differentiation 274 (CD274), C-X-C motif chemokine ligand 10 (CXCL10), and topoisomerase II alpha (TOP2A) emerging as the most relevant targets shared between both conditions. Elevated levels of macrophages and dendritic cells were observed in UC and PS, with CXCL10 exhibiting the closest association with macrophages. UC and PS shared common signaling pathways, including IL-17, TNF, and chemokine signaling pathways, among others. Molecular docking revealed that quercetin, baicalen, irisolidone, rutaecarpine, epigallocatechin-3-gallate, and others held potential as natural compounds for treating both disorders.

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Conclusion: MMP9, MMP1, and CXCL10, central mediators in the inflammatory pathways of UC and PS, establish a shared mechanism by triggering cytokine and chemokine activation, leading to tissue damage and positioning them as promising therapeutic targets for both conditions. Compounds such as quercetin, luteolin, irisolidone, rutaecarpine, and so on may be key drugs for treating both conditions. These findings suggest the potential advancement of therapeutic strategies and the enhancement of patient care by exploring shared mechanisms and predicting promising natural compounds for treating UC and PS.

1. Introduction

Ulcerative colitis (UC) is a type of idiopathic chronic inflammatory bowel disease (IBD) characterized by bloody diarrhea interspersed with periods of exacerbations and remissions [1]. Psoriasis (PS) is a chronic inflammatory skin disease distinguished by salmon-colored plaques with white scales in individuals with lighter skin tones or grayish patches in those with darker skin tones. These plaques are often accompanied by pustules or additional systemic symptoms [2]. A strong correlation exists between the two conditions, leading to an elevated risk of UC in patients with PS [3]. A comprehensive clinical meta-analysis based on a quantitative analysis of 93 studies revealed that among patients with UC, the prevalence of PS is 2.8 %. Conversely, in patients with PS, the prevalence of UC is 0.5 % [4].

The association between PS and UC is multifaceted, encompassing genetic susceptibility loci [5], immune system dysfunction [6,7], intestinal microecological dysregulation [8–10], and various environmental factors [11]. Several pathophysiologic correlations exist between PS and IBD. This includes elevated cytokines, such as TNF-α and IL-23, found simultaneously in the serums and tissues of patients with PS and IBD. Medications inhibiting these cytokines typically improve symptoms in both conditions, demonstrating their shared pathological mechanisms [12]. Moreover, the association between PS and UC might stem from a shared genetic background. The susceptibility locus for both disorders is located at the 6p21 locus, containing the most extensive histocompatibility complex. The IBD3 locus is associated with UC within this region, while the PSORS1 locus is linked to PS [13]. This further confirms the genetic link between the two conditions. Furthermore, several non-major histocompatibility complex-related genes, including the IL-23 receptor and IL-12B gene, have been implicated in both diseases [14–16]. Several PS therapies, such as infliximab and adalimumab, are also utilized in treating IBD [17].

In the pathogenesis of PS and UC, immune system dysregulation assumes a pivotal role. Specifically, the interaction between the innate and adaptive immune systems leads to exacerbated inflammatory responses. Dendritic cells (DCs) and macrophages play a crucial role in recognizing the microbiota and activating T cells. Psoriasis is characterized by a decrease in Langerhans cells and an increase in plasmacytoid DCs within early lesions, which produce the inflammatory mediator IFN-α [18]. In UC, intestinal inflammation and the defect in mucosal barrier allow more luminal antigens to come into contact with DCs, leading to their maturation and activation, thereby enhancing the immune response [19]. The Th17 cell axis activation is a shared feature critical to both conditions. These cells secrete IL-17 and IL-21, cytokines integral to chronic inflammatory processes [20]. In UC, the mucosal inflammatory infiltrate is rich in Th17 cells, with an excessive production of related cytokines in the affected tissues [21]. Similarly, in PS, lesional skin exhibits an increased Th17 cell population, contributing to inflammation and promoting epidermal thickening and keratinocyte dysregulation [22]. Microbial dysbiosis within the skin and gut is intricately linked to the onset and progression of PS and UC. This imbalance not only affects barrier integrity but also enhances the permeation of allergens and pathogens, triggering immune activation [23]. In UC, shifts in the gut microbiota are associated with genetic factors and genes involved in intracellular protein breakdown [24]. Likewise, alterations in the skin microbiota are considered a key element in the pathogenesis of PS [25]. Inflammatory mediators, including cytokines and chemokines, regulate the recruitment and activation of immune cells, playing an essential role in the inflammatory processes of PS and UC. The interplay between IL-23 and IL-17 is particularly significant, driving Th17 cell differentiation and the activation of epithelial and mucosal cells, a central pathway in the pathogenesis of PS and UC [26]. Elevated levels of these mediators in both conditions underscore their role in disease progression.

Although immunosuppressive medications are commonly employed in treating UC and PS, traditional Chinese medicine (TCM) may present a promising alternative with potentially fewer side effects. Many studies currently exist regarding using natural products in treating UC and PS. TCM prescriptions, such as Huai Hua San [27], Huangqin decoction [28], and Shaoyao decoction [29], have been extensively employed in treating UC due to their notable therapeutic effects. Herbal medicines, such as aloe vera gel, Indigo Naturalis, Andrographis paniculata extract, and so on, have shown effectiveness in improving clinical symptoms and increasing the remission rate in patients with UC [30–32]. Indigo Naturalis is also employed to treat PS clinically [33]. Sophora flavescens has shown favorable effectiveness in clinical practice and research studies for treating patients with UC and PS [34–38]. TCM prescriptions commonly used in clinical practice and proven effective in treating PS and UC include: Xijiao Dihuang Decoction contains quercetin, baicalen, kaempferol and ellagic acid; Taohong Siwu Decoction contains quercetin, baicalen, luteolin, beta-carotene, and kaempferol; Duhuo Jisheng Decoction contains quercetin, kaempferol, and wogonin; Gegen Qinlian Decoction, Sishen Pill, Wumei Pill, and Baitouweng Decoction contain quercetin.

This study aims to elucidate shared expressed targets and pathways in UC and PS using bioinformatics and molecular docking techniques. It also aims to identify natural drugs that could potentially exhibit therapeutic effects on UC and PS. The findings of this study are expected to provide valuable insights into the clinical treatment of patients with UC and PS by presenting potential intervention strategies.

2. Materials and methods

2.1. UC and PS datasets and disease target variation analysis

To identify differentially expressed genes (DEGs) in UC and PS, relevant datasets were searched in the GEO database (https://www.ncbi.nlm.nih.gov/gds/). The datasets were filtered based on specific criteria, including a sample size >5, comprising normal and diseased samples. The selected datasets were normalized and processed. The average expression values for each gene across experiments with repeated measurements were calculated. To mitigate the influence of highly expressed genes and improve data distribution, the expression matrix was subjected to logarithmic transformation. Inter-array normalization was carried out to standardize the data across samples and eliminate non-biological variations such as batch effects. In the differential expression analysis, design matrices were constructed to fit linear models, and statistical parameters were estimated using the eBayes method to enhance the accuracy of identifying DEGs. They were further analyzed using the limma package version 3.54.2. The criteria for identifying DEGs were set as a corrected p-value <0.05 and an absolute $\log2|FC| > 1$.

2.2. Protein-protein interaction network analysis

The DEGs identified in UC were compared to those from PS to show shared genes associated with both diseases. Subsequently, these common genes were utilized to construct a protein-protein interaction (PPI) network, leveraging the STRING 10.0 database (https://string-db.org/). The PPI network was visualized and assessed for its topological features using Cytoscape V3.8.0 (http://www.cytoscape.org/). To evaluate the functional significance of each node within a network, the CytoNCA plugin in Cytoscape is utilized to calculate parameters such as betweenness centrality (BC) and closeness centrality (CC), along with degree centrality (DC). These three quintessential centrality measures are employed to assess the importance of network nodes, with higher values indicating a node's proximity to the network's central position. Following these analyses, 20 genes were identified as core targets, categorized based on their upregulated or downregulated expression in UC and PS.

2.3. Validation of hub genes

To validate the findings, a search was conducted in the GEO database (https://www.ncbi.nlm.nih.gov/gds/) for validation datasets regarding UC and PS. The same filtering criteria as the initial analysis were employed to identify DEGs. To assess the correlation of the identified hub genes with autoimmune diseases, the ADEx database (https://adex.genyo.es/) was used. This database incorporates expression and methylation data from various studies on autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SjS), and systemic sclerosis. The expression levels of hub genes were compared between case and control samples, and box plots were generated to illustrate and visualize the obtained results.

2.4. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis

GO enrichment analysis was categorized into three groups: biological process (BP), molecular function (MF), and cellular component (CC), allowing the interpretation of biological functions at different levels. KEGG is a database that integrates gene, chemical, and function information. It is commonly used for annotating genes and comprehending related functions and pathways. GO and KEGG analysis was conducted on these targets to explore the roles of shared core targets in signaling pathways associated with both disorders. The threshold was set at an adjusted P-value <0.05. The top 20 genes for BP, cellular component, and MF were selected based on their ascending order of adjusted P-value. A bar plot was created using the platform (http://www.bioinformatics.com.cn) to represent the top nine GO pathways associated with both disorders. Bubble charts derived from KEGG were generated to visually represent the enriched pathways and potential therapeutic targets for both diseases, sorted based on the adjusted P-value.

2.5. Gene set enrichment analysis (GSEA)

Using the KEGG pathway gene set (c2.cp.kegg.Hs.symbols.gmt) obtained from GSEA software (java GSEA 4.3.2), UC and PS were compared against normal controls via GSEA analysis, performing 1000 tests. p.adjust <0.05 was considered significant.

2.6. Immune cell infiltration analysis

To explore immune infiltration in UC and PS, CiberSort deconvolution was employed to calculate the proportion of immune cells across various samples through 100 iterations of simulation. Data with a significance of $P < 0.05$ were further analyzed to determine the immune cell proportion in different samples. Subsequently, the results were visualized using R software and the ggpubr package.

2.7. Screening of relevant herbal ingredients for targeted treatment of UC and PS

PPI topological analysis was conducted to identify targets with a degree value > 20, establishing them as core targets for predicting TCM and their active ingredients. This process involved a combined approach of prediction and validation. Initially, the core targets were imported into the Coremine Medical database (http://www.coremine.com/medical/), and outcomes with $P < 0.05$ were deemed

statistically significant. TCM related to the core targets were retrieved, and those associated with at least three core targets were filtered. Subsequently, these herbs were imported into the TCMSP database (https://old.tcmsp-e.com/tcmsp.php) to validate the herb-target relationships and predict active ingredients. We employed thresholds of oral bioavailability ≥30 % and drug-like ≥0.18 to filter relevant proteinaceous active ingredients from TCM. The Uniprot database (https://www.uniprot.org/) was utilized to convert the retrieved active proteinaceous ingredients into corresponding gene symbols. Consequently, those without matching results were eliminated. Subsequently, we linked the active ingredients with targets using Perl software and extracted the active ingredients associated with the core targets. The results were imported into Cytoscape 3.9.1 software to construct a network illustrating the relationship between TCM, active ingredients, and their respective target.

2.8. Molecular docking

Molecular docking is a computational simulation technique employed to mimic molecule interactions by utilizing spatial recognition and energy identification. The protein structures of five target proteins, namely MMP9 (PDB ID: 1GKC), MMP1 (PDB ID: 1CGL), CXCL10 (PDB ID: 1O7Z), TOP2A (PDB ID: 1ZXM), and CD274 (PDB ID: 5J89), were searched and downloaded from the PDB database (https://www1.rcsb.org/). The molecular structure files of quercetin, luteolin, epigallocatechin-3-gallate (EGCG), baicalein, ellagic acid, tanshinone IIA, irisolidone, nobiletin, rutaecarpine, beta-carotene, kaempferol, wogonin, and triptolide were downloaded from the PubChem database. The software PyMOL 2.3.0 was employed to eliminate water molecules and original ligands from the

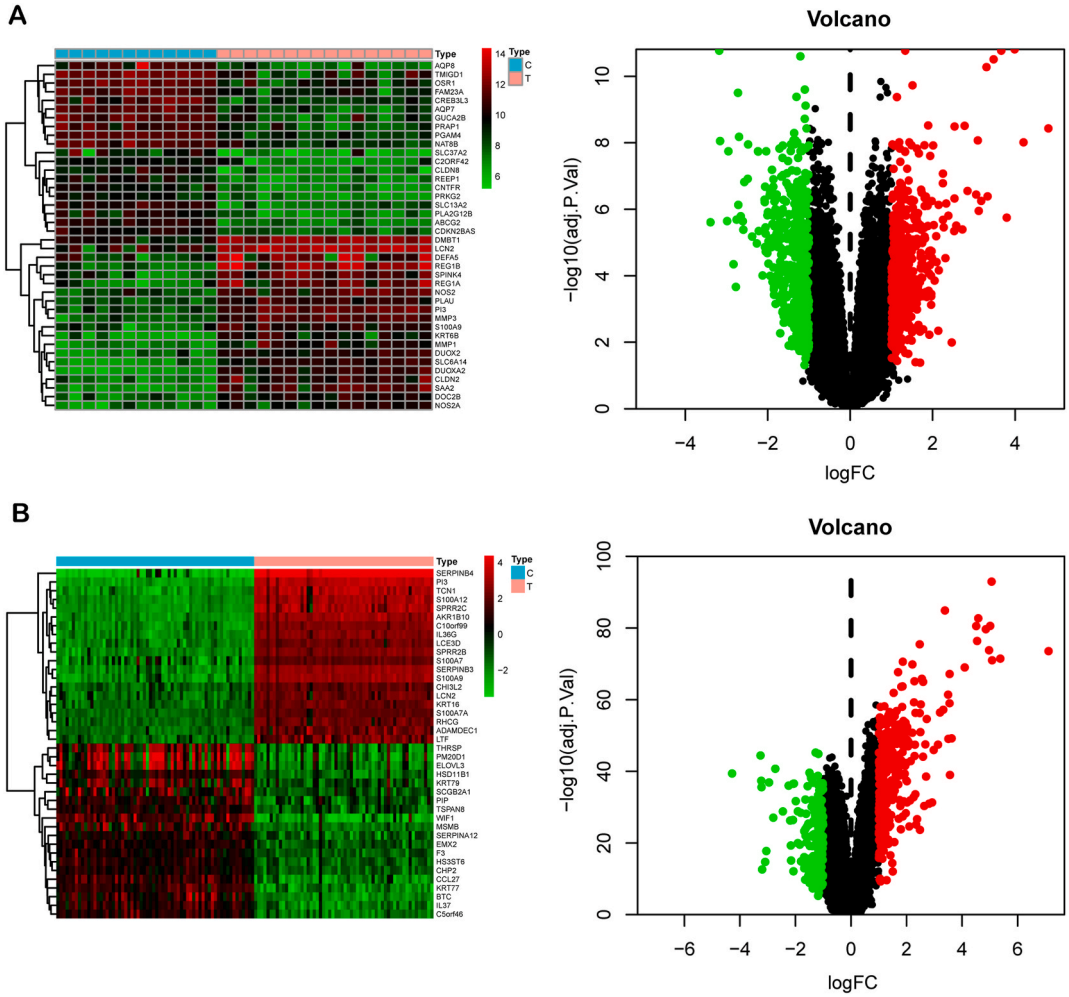


Fig. 1. GSE53306 (A) and GSE13355 (B) dataset differential expression gene heat map and volcano plot. (A) Expression characteristics of differential expression genes (DEGs) in ulcerative colitis (UC) patients. Heat map and volcano plot present the identified DEGs between UC patients and normal controls. Green represents low expression values, and red represents high expression values. C represents the control group, T represents the test group. (B) Expression characteristics of DEGs in psoriasis (PS) patients. Heat map and volcano plot present the identified DEGs between PS patients and normal controls. Green represents low expression values, and red represents high expression values. C represents the control group, T represents the test group.

downloaded target proteins. Subsequently, the Chem3D 19.0 software was employed to perform molecular mechanics optimization on all molecules, allowing for obtaining the energy-minimized optimal conformations. The processed target proteins were prepared for molecular docking using AutoDock Tools 1.5.6, which involved hydrogen addition and charge assignment to generate PDBQT files. Subsequently, the AutoDockTools 1.5.6 software was utilized to identify the active binding sites for the proteins with the following center coordinates: TOP2A (X: 35.9, Y: 0.4, Z: 36.8), MMP9 (X: 65.6, Y: 31.1, Z: 117.8), MMP1 (X: 27.8, Y: 41.8, Z: 0.6), CXCL10 (X: 7.6, Y: 34.3, Z: 35.9), and CD274 (X: 11.3, Y: 19.1, Z: 181.2), with a grid box size of 35 for all dimensions (X: 35, Y: 35, Z: 35). Molecular docking simulations were performed using AutoDock Vina v.1.2.0, employing the Lamarckian genetic algorithm with a semi-flexible docking approach. Finally, the docking results were visualized using PyMOL software for further analysis.

3. Results

3.1. Collection of target genes

We screened the UC and PS gene sets from the GEO database, specifically GSE53306 and GSE13355, respectively. GSE53306 comprised 16 and 12 active UC samples and normal controls, respectively, while GSE13355 included 58 psoriatic lesion samples and 64 normal controls. The datasets were deduplicated and normalized before employing the limma package in R software for differential analysis. This analysis yielded 952 and 499 DEGs from active UC and PS samples, respectively (Fig. 1).

3.2. Protein-protein interaction network analysis

DEGs from PS were compared with those from UC (Fig. 2A) and imported into the STRING11.0 database. This process led to the construction of a PPI network with 62 targets and 503 interactions. The network topology analysis was conducted using the CytoNCA plug-in, specifically focusing on BC, CC, and DC values (Fig. 2B). Core targets were selected based on possessing a degree value > 20. These core targets were then organized in a circular layout, with colors transitioning from lighter to darker shades, reflecting their respective correlations. The top 10 core targets identified were MMP9, CXCL1, MMP1, LCN2, MMP12, S100A9, CCL20, CD274, CXCL10, and IDO1. The remaining targets were presented in a grid format. The targets were ranked based on their disease relevance, where lighter to darker colors represent lower to higher correlation.

3.3. Validation of hub genes

To validate the reliability of the hub gene expression levels, two additional gene sets, namely GSE38713 and GSE181318, were selected. GSE38713 contained 30 and 13 UC and normal control samples, respectively. Conversely, GSE181318 comprised skin tissue samples from three patients with PS and three normal controls. The expression levels of the hub genes exhibited significant variations between the two disorders, similar to the outcomes observed in the paired samples from the GSE53306 and GSE13355 datasets (Fig. 3).

Autoimmune diseases represent a group of complex disorders whose pathogenesis remains not fully understood; however, they might share numerous risk factors and molecular mechanisms [39]. UC, PS, RA, systemic sclerosis, SLE and SjS are all classified as autoimmune diseases. During our validation of hub genes using the ADEx database (https://adex.genyo.es/), we found that MMP9, CXCL1, S100A9, CD274, CXCL10, and IDO1 exhibited differential expression in RA, SjS, and SLE. Additionally, MMP9, MMP1, and LCN2 demonstrated differential expression in SLE and systemic sclerosis. These findings from the validation underscore the association of these hub genes with autoimmune diseases (Fig. 4).

3.4. GO and KEGG term enrichment analysis

To explore the underlying mechanism of UC and PS, we analyzed the GO and KEGG of 63 hub genes. The GO analysis yielded functional information related to 250 genes. Among these, 209 functions were enriched in BP, primarily associated with neutrophil and

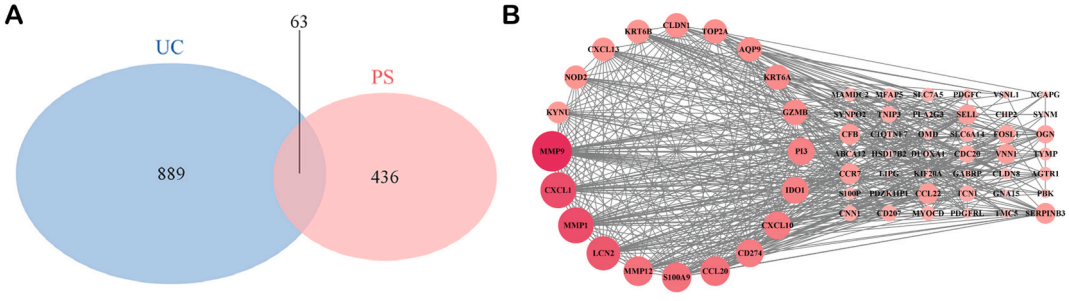


Fig. 2. Venn diagram (A) and protein-protein interaction (PPI) network (B) of differential expression genes (DEGs). (A) Venn diagram showing the two datasets owning an overlap of 63 DEGs. (B) PPI network highlighting the core targets, with lighter to darker colors representing lower to higher correlation.

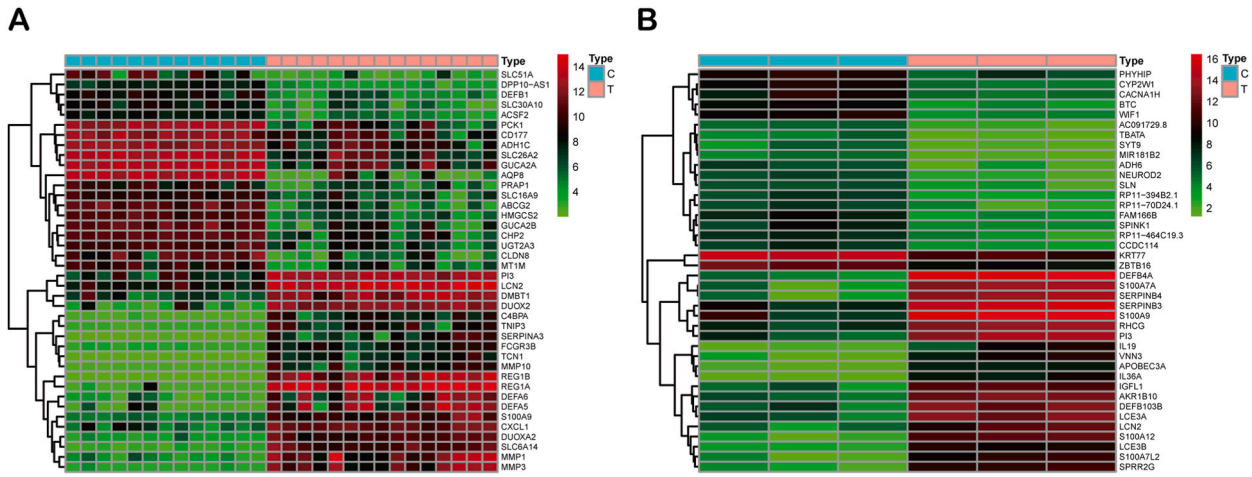


Fig. 3. GSE38713 (A) and GSE181318 (B) dataset differential expression heat map. (A) Expression characteristics of differential expression genes (DEGs) in UC patients. Heat map and volcano plot present the identified DEGs between UC patients and normal controls. Green represents low expression values, and red represents high expression values. C represents the control group, T represents the test group. (B) Expression characteristics of DEGs in PS patients. Heat map and volcano plot present the identified DEGs between PS patients and normal controls. Green represents low expression values, and red represents high expression values. C represents the control group, T represents the test group.

granulocyte chemotaxis and neutrophil migration. Within CC, 18 functions were enriched, primarily on locations such as secretory granule, cytoplasmic vesicle, and vesicle lumina. In MF, 23 functions were enriched, predominantly involved in chemokine activity, chemokine receptor binding, and CXCR chemokine receptor binding. The bar plot illustrates the top nine GO pathways regarding BP, CC, and MF between UC and PS (Fig. 5A). Six signaling pathways were identified during the KEGG analysis. These pathways were ranked in ascending order based on their p-values. They included the IL-17 signaling pathway, viral protein interaction with cytokine and cytokine receptor, TNF signaling pathway, chemokine signaling pathway, and cytokine-cytokine receptor interaction (Fig. 5B).

3.5. GSEA analysis

The GSEA analysis results indicated that compared to normal controls, PS exhibited significant enrichment in the RIG-I-like receptor signaling pathway, cytokine-cytokine receptor interaction, NOD-like receptor signaling pathway, pyrimidine metabolism, and proteasome pathway (Fig. 5C). Compared to normal controls, the active UC group exhibited significant enrichment in pathways such as drug metabolism cytochrome p450, metabolism of xenobiotics by cytochrome P450, cytokine-cytokine receptor interaction, pentose and glucuronate interconversions, and retinol metabolism pathways (Fig. 5D). The cytokine-cytokine receptor interaction pathway was a shared pathway between UC and PS.

3.6. Immune infiltration analysis

The immune infiltration results indicated an increase in plasma cells, macrophages (Mø), and activated DCs in UC than in normal controls (Fig. 6A). Conversely, the results showed an increase in T cells CD4 memory activated, T cells follicular helper, T cells gamma delta, NK cells resting, Mø, macrophages M1, activated DCs, mast cells activated, and neutrophils in PS than in normal controls (Fig. 6B). Upon visualizing the differential immune infiltration results, we observed an increase in plasma cells ($P < 0.05$), Mø ($P < 0.05$), and activated DCs ($P < 0.05$) in UC (Fig. 6C). Furthermore, T cells CD4 memory activated ($P < 0.001$), T cells follicular helper ($P < 0.001$), T cells gamma delta ($P < 0.05$), NK cells resting ($P < 0.001$), Mø ($P < 0.01$), macrophages M1 ($P < 0.001$), activated DCs ($P < 0.001$), mast cells activated ($P < 0.01$), and neutrophils ($P < 0.001$) exhibited an increase in PS (Fig. 6D).

3.7. Screening results of relevant herbal ingredients for targeted treatment of UC and PS

Twenty core targets were selected based on a degree value > 20. Subsequently, we uploaded these core targets into the Coremine Medical database (http://www.coremine.com/medical/) and extracted 554 TCM references related to these core targets. After the screening process, 151 herbs were identified, each associated with at least three-core targets. After screening the TCMSP database, we identified specific natural active ingredients with conclusive matches. These ingredients include quercetin, luteolin, EGCG, baicalein, ellagic acid, tanshinone IIA, irisolidone, nobiletin, rutaecarpine, beta-carotene, kaempferol, wogonin, and triptolide, emerged as the most promising active ingredients for treating UC and PS. Upon exploring the TCMSP database to identify natural sources of active ingredients, we found that several herbs contained these essential components. Safflower was found to contain quercetin, luteolin, baicalein, beta-carotene, and kaempferol. Banzhilian contained quercetin, luteolin, and baicalein. Ephedra and Artemisia were identified to contain quercetin, luteolin, and kaempferol. Quercetin was found in Coptis, Radix Scutellariae, and Centella Asiatica

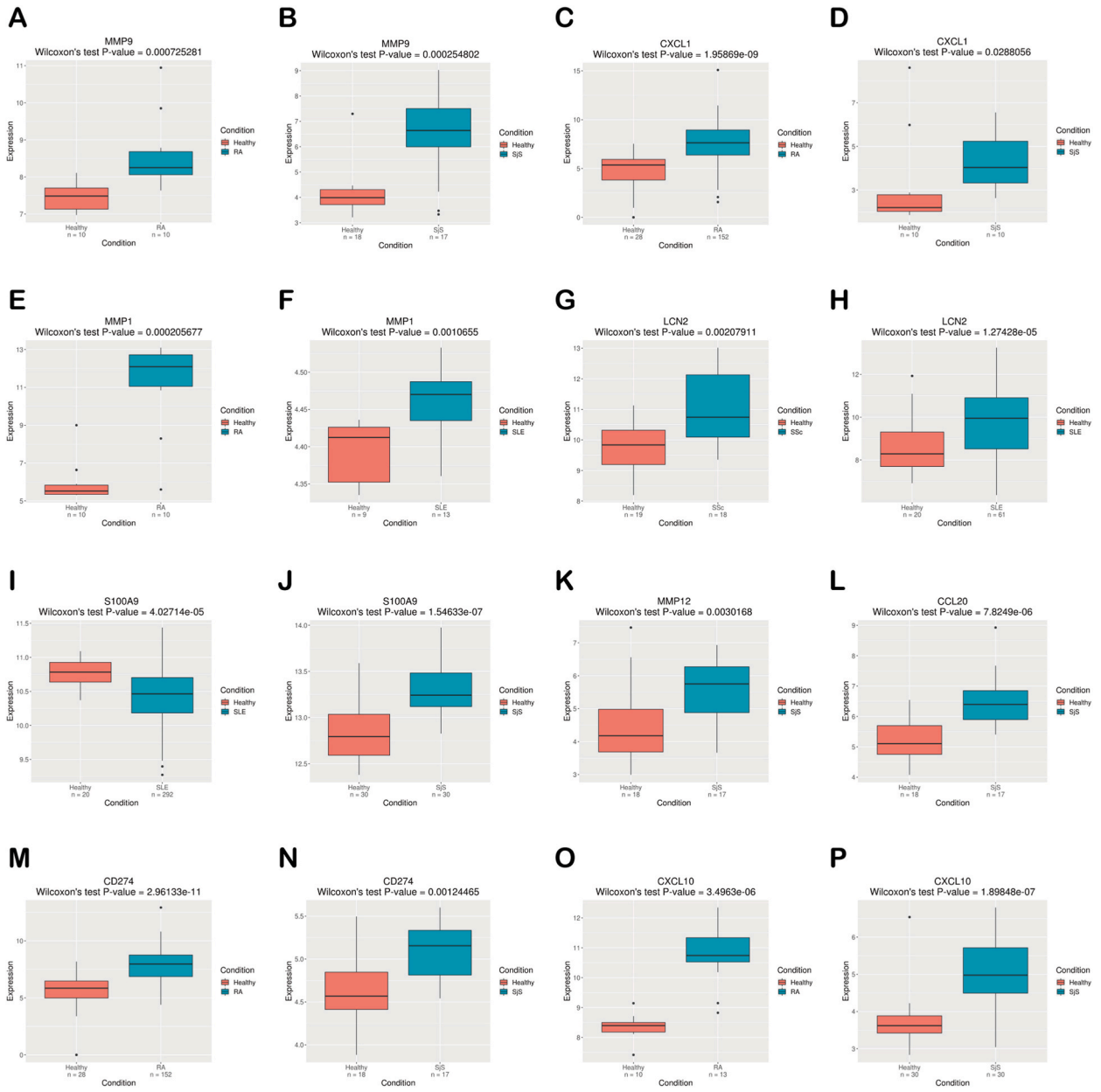


Fig. 4. Validation of core targets in the ADEx dataset. (A, B) Expression levels of MMP9 in rheumatoid arthritis (RA) and Sjögren's syndrome (SjS). (C, D) Expression levels of CXCL1 in RA and SjS. (E, F) Expression levels of MMP1 in RA and systemic lupus erythematosus (SLE). (G, H) Expression levels of LCN2 in systemic sclerosis (SSc) and SLE. (I, J) Expression levels of S100A9 in SLE and SjS. (K) Expression levels of MMP12 in SjS. (L) Expression levels of CCL20 in SjS. (M, N) Expression levels of CD274 in RA and SjS. (O, P) Expression levels of CXCL10 in RA and SjS.

(Table 1). We generated the visual representation of the TCM-active ingredient-target network by importing the active ingredients associated with the core targets into Cytoscape (Fig. 7).

3.8. Molecular docking analysis

We screened the molecular structure files of five proteins, namely MMP9 (PDB ID: 1GKC), MMP1 (PDB ID: 1CGL), CXCL10 (PDB ID: 1O7Z), TOP2A (PDB ID: 1ZXM), and CD274 (PDB ID: 5J89), using the PDB database (https://www1.rcsb.org/). We downloaded the molecular structure files of quercetin, luteolin, EGCG, baicalein, ellagic acid, tanshinone IIA, irisolidone, nobiletin, rutaecarpine, beta-carotene, kaempferol, wogonin, and triptolide from the Pubchem database (https://pubchem.ncbi.nlm.nih.gov/). The obtained protein targets were processed using PyMOL 2.3.0 software to eliminate water molecules and their respective original ligands.

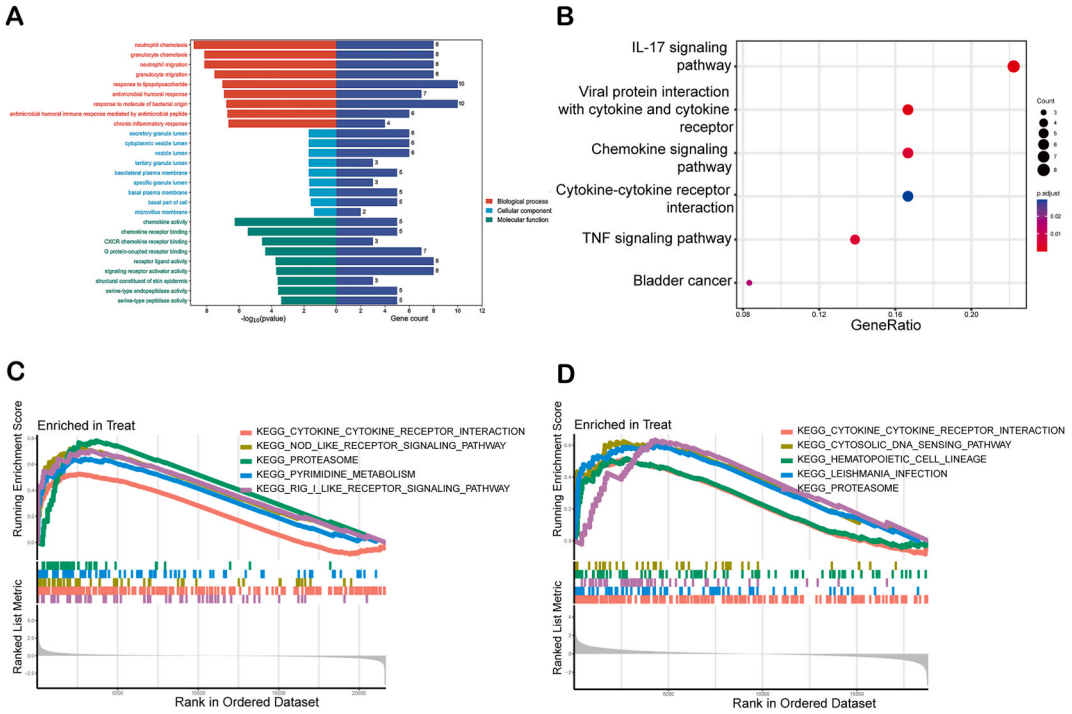


Fig. 5. Related functions and pathways. (A) GO enrichment, (B) KEGG enrichment, and (C, D) GSEA analyses.

Subsequently, molecular docking was performed using AutoDock Vina v.1.2.0. A binding energy < -5.0 kcal/mol (1 kcal = 4.2 kJ) generally indicates a strong binding activity between the compound and target. The molecular docking results showed that the natural active compounds obtained possessed binding energies < -5.0 kcal/mol, suggesting a robust interaction between these compounds and the core targets (Table 1). Discovery Studio 4.5 and Chem3D 19.0 were employed to visualize the docking results. The top eight docking results, with binding energies < -8.8 kcal/mol, were exported to generate a 3D interaction plot (Fig. 8).

4. Discussion

The World Health Organization recognizes UC and PS as intractable diseases, characterized by chronic and relapsing course that significantly influences the daily life and work of patients. Bioinformatics was used in this study to identify common targets in UC and PS, including MMP9, MMP1, and CXCL10. Overproduction of MMP9, MMP1, and CXCL10 disrupts the intestinal and skin microenvironment, thereby contributing to the onset of both disorders. MMP9 and MMP1, zinc-dependent metalloproteinases, play a crucial role in the modulation of immune responses. These enzymes are not only capable of cleaving extracellular matrix proteins but also have the ability to process a variety of non-matrix proteins, including cytokines and chemokines, thereby influencing immune cell behavior and inflammation [40]. *In vitro* culture of colonic epithelial cells from patients with IBD exhibited elevated gene expression levels than those of control epithelial cells [41]. MMP9 and MMP1 trigger the activation of cytokines and chemokines, which promotes chemotaxis and inflammatory cell activation. In most cells, these enzymes are rapidly synthesized and secreted to exert their effects, but during inflammation, they can be stored within the granules of inflammatory cells, ready for release upon appropriate stimulation. This regulated release allows for a controlled and localized response to inflammatory signals [40]. Their dysregulation could result in epithelial barrier impairments and excessive tissue damage. This could potentially create a vicious cycle of MMP activation and inflammation promotion. Elevated levels of MMP9 and MMP1 are similarly observed in the serum of patients with PS [42]. Innate immune cells produce cytokines, including TNF, which activates mDCs to induce Th17 cell differentiation. Consequently, these Th17 cells secrete IL-17 to activate keratinocytes and promote excessive production of pro-inflammatory cytokines and chemokines [43]. This ultimately leads to inflammatory infiltration. Keratinocytes and infiltrating leukocytes produce MMP9 and MMP1, which facilitate the degradation of extracellular matrix proteins and glycoproteins. In patients with UC, the expression of CXCL10 increases than normal controls [44,45]. The overexpression of CXCL10 triggers inflammation and tissue damage by mediating pro-inflammatory cell recruitment [46]. In UC mouse models, studies indicate that anti-CXCL10 antibodies demonstrate the ability to inhibit ulceration [47]. Similarly, in psoriatic plaques, the presence of CXCL10 decreases following successful treatment [48]. In patients with PS treated with etanercept, marked improvements were observed in the inflammatory gene expression and cell infiltration within PS plaques. mRNA expression of CXCL10 was observed to decrease, potentially attributed to the diminished infiltration of T cells, neutrophils, and DCs [49]. The abnormality of these three proteins could serve as a shared basis for PS and UC, presenting them as potential targets for therapeutic interventions.

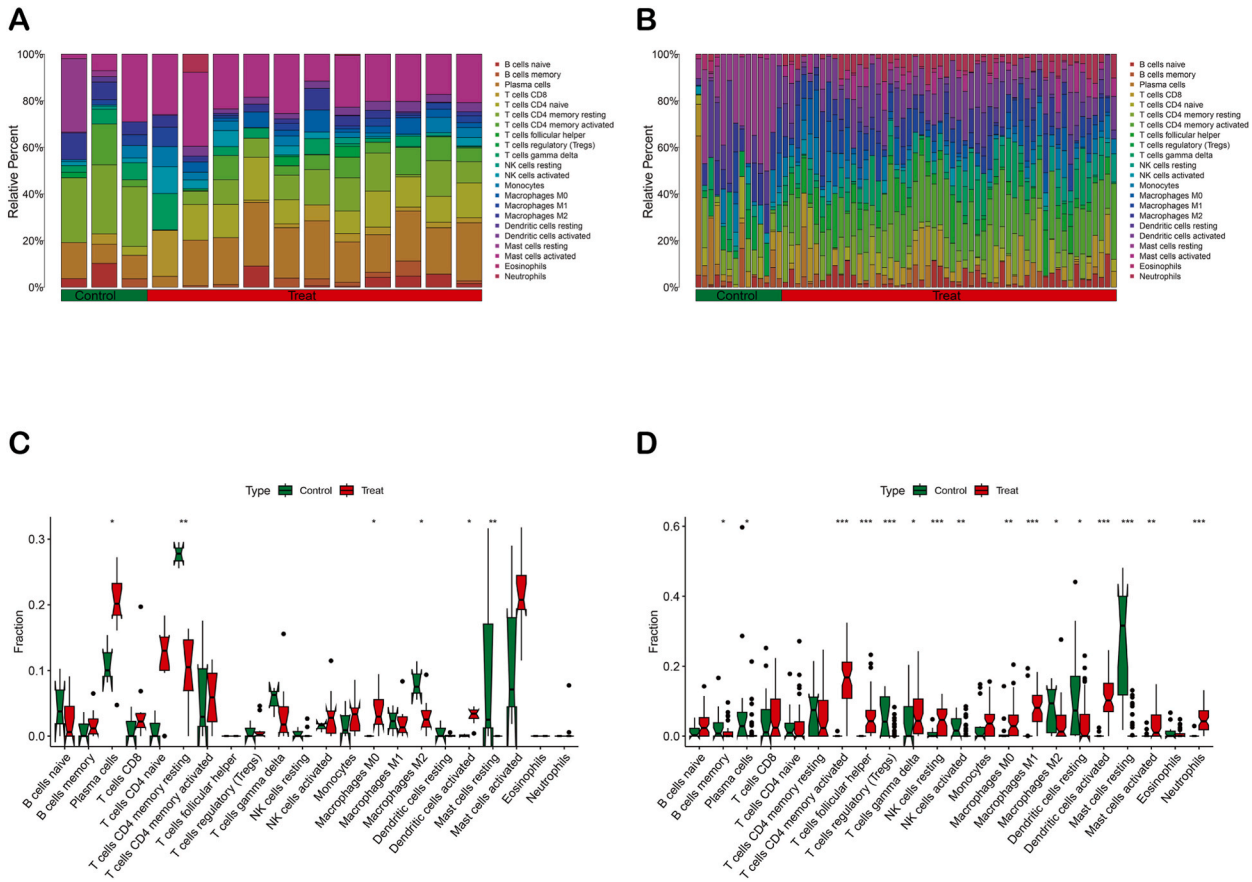


Fig. 6. Visualization of immune cell infiltration results. (A, C) UC and normal controls. (B, D) PS and normal controls.

The IL-17 signaling pathway, TNF signaling pathway, chemokine signaling pathway, and cytokine-cytokine receptor interaction are common pathways associated with UC and PS. IL-17 activates the IL-17 signaling pathway, consequently recruiting and activating Mø and neutrophils, promoting inflammatory factor production. This ultimately mediates intestinal inflammation invasion and tissue damage [36]. Patients with UC exhibit elevated levels of IL-17 in inflamed intestines [50]. Furthermore, IL-17A and IL-17F expression is marked heightened in IBD mucosa than in normal controls [51]. The primary pro-inflammatory effects of IL-17A and IL-17F stem from their induction of TNF-α, CXCL10, MMP9, and similar factors [52–54]. In mice, blocking IL-17 signaling has shown significant potential to alleviate colitis [55]. The TNF signaling pathway, cytokine-cytokine receptor interaction, and chemokine signaling pathway play integral roles in the process of intestinal inflammation [56,57]. TNF-α is primarily mediated through activation of Mø and adhesion molecule stimulation. This process leads to tissue infiltration and edema formation [58]. Elevated expression of TNF-α has been observed in lamina propria monocytes [59] and colon mucosal biopsies [60] of patients with UC. Clinically, monoclonal antibodies targeting TNF, such as infliximab, adalimumab, and golimumab have been used for treating UC [61,62]. PS exhibits increased expression of IL-17 in PS, stimulating the expression of chemokines that lead to the recruitment of neutrophils, T cells, and DCs [63,64]. DCs present with self-antigens linked to PS, activating T17 cells to produce cytokines IL-17 and TNF-α. These cytokines promote pro-inflammatory responses, induce the expression of PS-associated genes, and consequently result in epidermal hyperproliferation. In PS, CXCL10 attracts Th1 cells [65], while IL-17 stimulates the expression of MMP1 and TNF, leading to neutrophil infiltration and inflammation [66]. Moreover, TNF and its receptors are upregulated in plaque-type PS lesions [67,68]. Monoclonal antibodies targeting TNF (such as infliximab and adalimumab) or soluble TNF receptors (including etanercept) have been employed clinically for PS treatment [69]. Additionally, integrative transcriptomics analysis revealed that cytokine-cytokine receptor interactions are implicated in the pathogenesis of PS [70]. These findings are consistent with the outcomes of our study.

In patients with UC and PS, immune cell infiltration exhibited a significantly higher count of Mø and activated DCs. These conditions, UC and PS, are two prevalent chronic inflammatory diseases. While their complete pathogenesis remains unclear, increasing evidence suggests the pivotal role of the immune system in their development. Mø and DCs, as important effector cells in the immune system, have important roles in inflammation and immune response. Mø plays a dual role in intestinal inflammation: they aid in removing harmful microorganisms while maintaining intestinal homeostasis. However, their secretion of pro-inflammatory factors can aggravate intestinal inflammation and potentially trigger UC development. In UC, excessive recruitment and activation of Mø at the inflamed site can induce overreaction, causing the release of excessive cytokines and chemokines such as TNF-α and CXCL10. This

Table 1
Potential natural active component for treating ulcerative colitis and psoriasis.

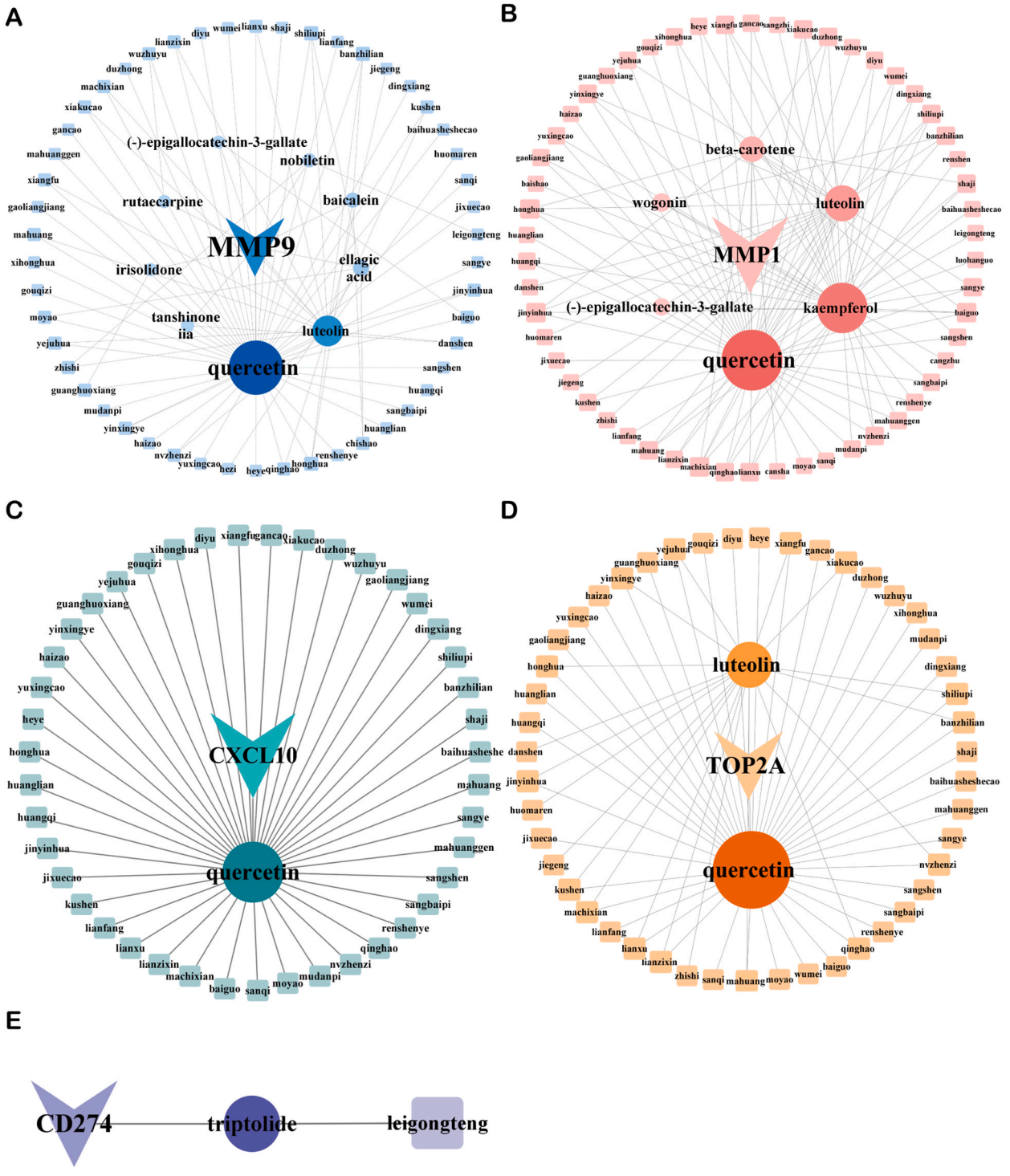
Molecule ID	Molecule Name	MW	Related Herbs	Core Targets	Binding Energy/ (kJ·mol^{-1})
MOL000098	quercetin	302.25	Ardisiae Japonicae Herba, Folium Artemisiae Argyi, Anisi Stellati Fructus, Dysosmae Verspiellis Rhizoma Et Radix, Ginkgo Semen, Ampelopsis Japonica, Dictamni Cortex, Herba Patriniae, Lobeliae Chinensis Herba, Glehniae Radix, and so on. One-hundred and eighty-eight related herbs	MMP9 MMP1 CXCL10 TOP2A	−9.6 −8.7 −6.5 −9.9
MOL000006	luteolin	286.25	Anisi Stellati Fructus, Ajugae Decumbentis Herba, Dictamni Cortex, Herba Patriniae, Lobeliae Chinensis Herba, Menthae Herba, Siphonostegiae Herba, Polygoni Avicularis Herba, and Plantaginis Herba among others. Ninety-four related herbs	MMP9 MMP1 TOP2A	−9.8 −8.6 −9.9
MOL006821	epigallocatechin-3-gallate	458.40	Ginkgo Semen, Eriobotryae Folium, and Phyllanthi Fructus	MMP9 MMP1	−8.3 −8.8
MOL002714	baicalein	270.25	Arum Ternatum Thunb., Scutellariae Barbatae Herba, Plantaginis Herba, and Carthami Flos. Twelve related herbs	MMP9	−9.7
MOL001002	ellagic acid	302.20	Radix Paeoniae Rubra, Euphorbiae Humifusae Herba, Rubi Fructus, Chebulae Fructus, and Myrrha, among others. Seventeen related herbs	MMP9	−7.6
MOL007154	tanshinone iia	294.37	Radix Salviae and Peucedani Radix	MMP9	−8.3
MOL005916	irisolidone	314.31	Iridis Tectori Rhizoma, Puerariae Flos, and Pogostemon Cablin (Blanco) Benth.	MMP9	−10.5
MOL005828	nobiletin	402.43	Citrus Reticulata, Centipedae Herba, Citri Grandis Exocarpium, and so on. Seven related herbs	MMP9	−7.8
MOL002662	rutaecarpine	287.34	Phellodendri Chinrnsis Cortex, Evodiae Fructus	MMP9	−10.2
MOL002773	beta-carotene	536.96	Ginkgo Semen, Jujubae Fructus, and Carthami Flos. Twenty-nine related herbs	MMP1	−7.7
MOL000422	kaempferol	286.25	Ardisiae Japonicae Herba, Ginkgo Semen, Paeoniae Radix Alba, Radix Sanguisorbae, and Portulacae Herba. One-hundred and thirty-three related herbs	MMP1	−8.1
MOL000173	wogonin	284.28	Dictamni Cortex, Scutellariae Barbatae Herba, and Scutellariae Radix and so on. Ten related herbs	MMP1	−7.5
MOL003187	triptolide	360.44	Tripterygii Radix	CD274	−7.2

further disrupts the intestinal tissue, perpetuating the cycle of inflammation. A significant presence of Mø has been observed in PS lesions [71], highlighting their critical role in both disorders. Depletion of Mø could improve PS inflammation [72–74] and normalize TNF-α levels [75]. DCs—a key component of the immune system—capture and present antigens to T cells, thereby initiating and regulating immune responses. The escalation in activated DCs with enhanced stimulatory capacity is associated with disease progression, underscoring their significance in the inflammation observed in UC [76]. In PS, dermal immature DCs secrete pro-inflammatory factors, critically contributing to the progression and persistence of the disease [77,78]. Histopathological examination reveals dermal papillary edema and infiltration of DCs and Mø in PS skin lesions [79].

In this study, the Coremine Medical and TCMSP databases were utilized to identify shared natural active ingredients for treating both diseases. These included quercetin, kaempferol, luteolin, naringenin, rutaecarpine, and EGCG. Quercetin, a flavonoid polyphenol commonly found in fruits and vegetables, demonstrates antioxidant and antiinflammatory properties. It exhibits potential for treating UC by downregulating MMP1, MMP9 [80,81], and CXCL10 expressions [82]. Moreover, it shows significant anti-psoriatic effects in mouse models [83]. Kaempferol and luteolin decrease the expression of inflammatory cytokines and chemokines while reducing the mRNA expression of MMP9 associated with angiogenesis. Therefore, they demonstrate antiangiogenic and anticolitis effects [84]. Luteolin possesses antiinflammatory properties and improves PS-like skin lesions by inhibiting the infiltration of Mø, T cells, and neutrophils into the skin. Additionally, it downregulates the expression of pro-inflammatory cytokines such as TNF-α and IL-17A in mouse skin lesions [85]. Nobiletin demonstrates robust antiinflammatory and antioxidant properties. Research has indicated its efficacy in alleviating symptoms in IBD rats, diminishing inflammation in colitis, and inhibiting the production of pro-inflammatory cytokines by blocking the NF-κB pathway induced by TNF-α [86]. Additionally, it reduced skin lesions and decreased the levels of cytokines such as TNF-α in a mouse model [87]. Our study revealed that quercetin, luteolin, kaempferol, and nobiletin exhibit low binding energies with MMP9, MMP1, and CXCL10. This suggests these flavonoids may possess promising binding activities with these core targets. Quercetin binding energies with MMP9, MMP1, and CXCL10 were −9.6 kcal/mol, −8.7 kcal/mol, and −6.5 kcal/mol, respectively. Luteolin binding energies with MMP9 and MMP1 were −9.8 kcal/mol and −8.6 kcal/mol, respectively. Kaempferol binding energy with MMP1 was −8.1 kcal/mol, while nobiletin binding energy with MMP9 was −7.8 kcal/mol. Rutaecarpine—a bioactive alkaloid derived from Evodiae Fructus—has therapeutic effects on mice colitis [88] and improves imiquimod-induced PS-like dermatitis [89]. Rrutaecarpine binding energy with MMP9 was −10.2 kcal/mol, indicating a robust binding activity between both conditions. EGCG, a natural compound sourced from green tea, exhibits the capacity to suppress the production of pro-inflammatory cytokines such as TNF-α. This inhibition helps mitigate intestinal inflammation and the generation of inflammatory mediators during immune responses [90]. Additionally, it reduces T-cell infiltration in mouse skin, thereby alleviating PS-like inflammation [91]. Our study also demonstrated that the binding energy of EGCG with MMP9 and MMP1 were −8.3 kcal/mol and −8.8 kcal/mol, respectively, suggesting excellent binding activity.

UC and PS, as chronic inflammatory conditions, pose considerable challenges within the therapeutic domain. Current therapeutic approaches, encompassing immunomodulators and biological agents, partially mitigate disease progression. Despite this, they are

associated with significant financial implications, the risk of diminishing efficacy with chronic administration, and adverse effects that warrant attention. Given these factors, the investigation of novel natural compounds has emerged as a viable alternative strategy. These newly identified bioactive constituents, such as quercetin and kaempferol, exhibit promising therapeutic potential and safety profiles, offering the potential to surpass the limitations inherent in contemporary treatment modalities. Flavonoid compounds such as quercetin and kaempferol are renowned for their potent anti-inflammatory and antioxidant capabilities. They exert their effects by



(caption on next page)

Fig. 7. Network depicting the relationships among traditional Chinese medicines, active ingredients, and targets. baiguo - Ginkgo Semen; baihuasheshecao - Hedyotis Diffusae Herba; dingxiang - Caryophylliflos; diyu - Radix Sanguisorbae; duzhong - Eucommiae Cortex; gancao - licorice; gaoliangjiang - Alpiniae Officinarum Rhizome; gouqizi - Lycii Fructus; guanghuoxiang - Pogostemon Cablin (Blanco) Benth.; haizao - Sargassum; heye - Folium Nelumbinis; honghua - Carthami Flos; huanglian - Coptidis Rhizoma; huangqi - Hedysarum Multijugum Maxim.; jinyinhua - Lonicerae Japonicae Flos; jixuecao - Centella Asiatica (L.) Urban[Hydro-Cotyle Asiatica L.]; kushen - Sophorae Flavescentis Radix; lianfang - Receptaculum Nelumbinis; lianxu - Nelumbinis Stamen; lianzixin - Nelumbinis Plumula; machixian - Portulacae Herba; mahuanggen - Ephedrae Radix Et Rhizoma; mahuang - Ephedra Herba; moyao - Myrrha; mudanpi - Cortex Moutan; nvzhenzi - Fructus Ligustri Lucidi; qinghao - Artemisia Annua L.; renshenye - Ginseng Folium; sangbaipi - Mori Cortex; sangshen - Mori Fructus; sangye - Mori Follum; sanqi - Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow; shaji - Hippophae Fructus; shiliupi - Granati Pericarpium; wumei - Mume Fructus; wuzhuyu - Evodiae Fructus; xiakucao - Prunellae Spica; xiangfu - Cyperi Rhizoma; xihonghua - Croci Stigma; yejuhua - Chrysanthemi Indici Flos; yinxingye - Ginkgo Folium; yuxingcao - Houttuyniae Herba; banzhilian - Scutellariae Barbatae Herba; chishao - Radix Paeoniae Rubra; danshen - Radix Salviae; huomaren - Cannabis Sativa L.; jiegeng - Platycodon Grandiforus; zhishi - Aurantii Fructus Immaturus; hezi - Chebulae Fructus; leigongteng - Tripterygii Radix; cansha - Feculae Bombycis; baishao - Radix Paeoniae Alba; luohanguo - Siraitiae Fructus; renshen - Ginseng Radix Et Rhizoma; sangzhi - Mori Ramulus; cangzhu - Atractylodis Rhizoma.

modulating inflammatory pathways, thereby curtailing the synthesis of inflammatory mediators and countering chronic inflammatory processes. The multi-target therapeutic mechanisms of these natural bioactive constituents offer innovative perspectives for the management of UC and PS. They are hypothesized to exert their effects via diverse biological mechanisms, including the suppression of inflammatory cytokine production, modulation of immune cell activity, mitigation of oxidative stress, and intervention in cellular signaling cascades. Furthermore, the inherent safety and reduced side effect profile of these natural compounds present an alternative for prolonged therapeutic regimens. Their extensive historical use in dietary and traditional medicinal contexts provides a foundation for the evidence supporting their safety.

However, the translation of these natural bioactive components into efficacious therapeutic interventions necessitates clinical research to ascertain their safety, efficacy, and optimal dosing regimens in the context of UC and PS. Modern drug delivery systems, including liposomes, nanoparticles, and hydrogels, have the potential to augment the stability, bioavailability, and targeting precision of these natural compounds, thereby potentiating their therapeutic impact [92]. For instance, a nanoemulsion formulation, integrating hydrolyzed quinoa protein and cationic lotus rhizome starch, effectively encapsulates quercetin and EGCG, yielding a core-shell structured Que-HQP-EGCG-CLRS nanoemulsion with superior gastric stability and intestinal targeting properties, offering a novel therapeutic approach for UC [93]. A hydroxypropyl-β-cyclodextrin (HPCD)-stabilized liposomal gel has been shown to enhance the transdermal absorption and stability of quercetin by strengthening interactions with the skin's stratum corneum, effectively mitigating pro-inflammatory cytokines, and presenting a potent delivery system for the topical treatment of psoriasis [94]. A novel kaempferol hydrogel (DK-pGEL), employing deep eutectic solvent technology, has improved the solubility and bioavailability of kaempferol, demonstrating efficacy in alleviating symptoms and downregulating the expression of inflammatory cytokines in a psoriasis-like mouse model [95]. The nanostructured lipid carrier (NLC)-gel system containing luteolin, characterized by high encapsulation efficiency and controlled release properties, has been shown to markedly ameliorate symptoms in a psoriasis mouse model [96]. Additionally, a hyaluronic acid and histidine self-assembled hydrogel system (HHL) has been demonstrated to significantly enhance the bioavailability and anti-inflammatory effects of luteolin, leading to a substantial reduction in intestinal inflammation and restoration of the intestinal barrier. Nonetheless, these technologies require extensive clinical trial validation and must undergo stringent regulatory scrutiny prior to their transition into clinical practice.

Natural compounds show great potential in the treatment of UC and PS, yet their safety profiles and possible side effects warrant careful consideration. Preliminary studies indicate that quercetin has antioxidant properties, but it can be transformed into active oxidative products such as semiquinone and quinone, which may react with thiol groups, resulting in protein dysfunction and cytotoxic effects [97]. Currently, there is limited information on the safety evaluation of quercetin as a single compound, which restricts risk assessment, especially under long-term high-dose supplementation. Therefore, future research should include the incidence of adverse reactions and clinical safety parameters [98]. Oral high doses of EGCG have been confirmed to potentially cause cytotoxicity and damage to multiple organs, including the liver, kidneys, and gastrointestinal tract [99,100]. Animal experiments show that the toxicity induced by EGCG is closely related to dosage, administration route, and treatment time [101–105]. The mutagenic and genotoxic effects of kaempferol have also attracted attention [106]. It neutralizes free radicals by producing phenoxyl radicals, which may play a role in genotoxicity. Studies show that the CYP1A1 enzyme can transform kaempferol into quercetin with genotoxicity, which may trigger carcinogenic effects [107,108]. Currently, there is a lack of clear clinical studies to determine the optimal dosage for the treatment of UC and PS. Although natural compounds have potential in the treatment of these diseases, we still need more data to ensure their safety, determine appropriate dosages, and understand their metabolic mechanisms.

MMP9, MMP1 and CXCL10 are the common targets of UC and PS. They play a role in two diseases in many ways. MMP9 and MMP1 are zinc-dependent metalloproteinases and pro-inflammatory cytokines, which can trigger the activation of cytokines and chemokines, resulting in epithelial barrier damage and tissue damage. Overexpression of CXCL10 can mediate the recruitment of pro-inflammatory cells and cause inflammation and tissue damage. These proteins are related to IL-17 signaling pathway, TNF signaling pathway, chemokine signaling pathway and cytokine-cytokine receptor interaction. IL-17A and IL-17F can induce TNF-α, CXCL10, MMP9 and other factors. TNF signaling pathway plays a role in intestinal inflammation, and IL-17 stimulates the expression of chemokines in PS, which leads to the recruitment of related cells. Some natural medicinal components predicted by us can regulate MMP9, MMP1 and CXCL10. For example, quercetin can down-regulate the expression of MMP1, MMP9 and CXCL10, which shows significant anti-psoriasis effect in mouse model. Kaempferol and luteolin can reduce the expression of inflammatory cytokines and chemokines, as

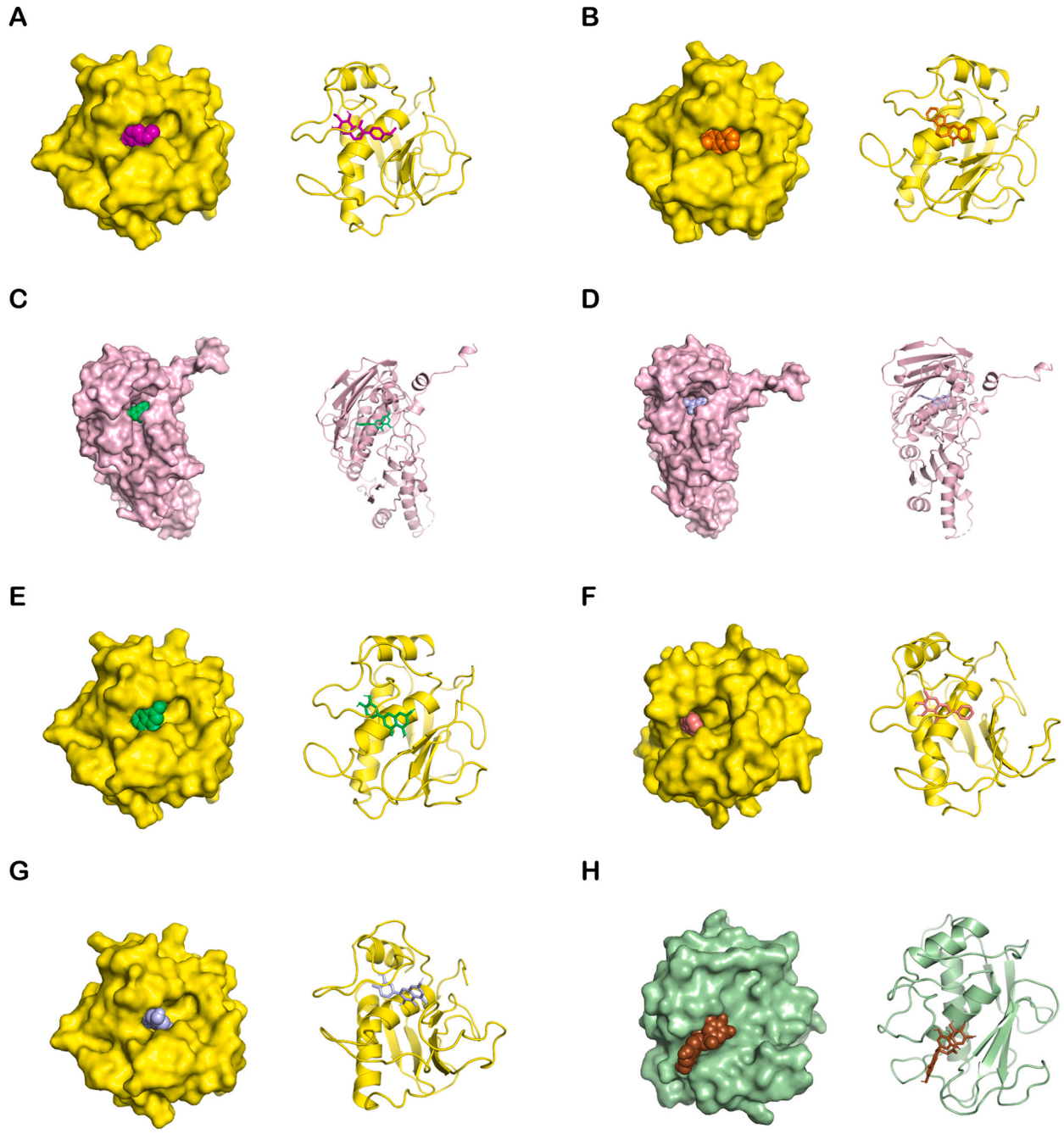


Fig. 8. Molecular docking results of natural active ingredient with core targets (binding energy < −8.8 kcal·mol−1). (A) irisolidone - MMP9. (B) rutaecarpine - MMP9. (C) luteolin - TOP2A. (D) quercetin - TOP2A. (E) luteolin - MMP9. (F) baicalein - MMP9. (G) quercetin - MMP9. (H) epigallocatechin_3_gallate - MMP1.

well as the mRNA expression of MMP9 related to angiogenesis, and have anti-angiogenesis and anti-colitis effects. Luteolin can also improve skin lesions similar to PS by inhibiting the infiltration of M, T cells and neutrophils into the skin, and down-regulate the expression of pro-inflammatory cytokines such as TNF-α and IL-17A in mouse skin lesions. Evodiamine has therapeutic effect on colitis in mice, and can also improve PS-like dermatitis induced by imiquimod, and it has strong binding activity with MMP9. EGCG can inhibit the production of pro-inflammatory cytokines such as TNF-α, reduce the production of inflammatory mediators in intestinal inflammation and immune response, and also reduce the infiltration of T cells in mouse skin to alleviate PS-like inflammation, and has good binding activity with MMP9 and MMP1. These natural drugs affect the related inflammatory pathways, such as IL-17 signaling pathway and TNF signaling pathway, by regulating the common targets in UC and PS, such as MMP9, MMP1 and CXCL10, thus

reducing the production of proinflammatory cytokines and chemokines, alleviating the inflammatory reaction, reducing tissue damage, and further intervening psoriasis and ulcerative colitis. However, whether these natural drugs can become natural drugs to treat these two diseases needs further experimental research and verification, as well as in-depth study of their specific mechanism of action.

The common pathogenesis of UC and PS was systematically analyzed in this study. Moreover, predicted the natural active ingredients for treating both disorders were predicted. However, further experimental investigations and validation are necessary to determine whether these identified components hold the potential to become natural drugs for treating both conditions. Moreover, further studies are warranted to elucidate their specific mechanisms of action. This study offers new insights applicable to treating patients in clinical practice.

We have applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to assess the certainty of evidence within study [109]. This structured approach has been instrumental in enhancing the transparency and robustness of our bioinformatics findings.

First Author (Year of Publication)	Outcome Indicator	Number of Studies	95%CI	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of Evidence
Alinaghi (2020) [4]	Psoriasis in IBD	67	4.2 % (3.4%–5.0 %)	Low	High	Not applicable	Serious concern	Suspected	Moderate to High
	IBD in psoriasis	18	1.2 % (0.6%–2.0 %)	Low	High	Not applicable	Serious concern	Suspected	Low to moderate

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Ethics declarations

Not applicable.

Data availability statement

The UC and PS datasets are publicly available at https://www.ncbi.nlm.nih.gov/gds/. The autoimmune diseases datasets are publicly available at https://adex.genyo.es/.The datasets provided by CMap are publicly available at https://clue.io/. The corresponding natural drugs dataset is publicly available at https://old.tcmsp-e.com/index.php. The R code and part of the data used for analyses are publicly available at https://github.com/Bioconductor/LearnBioconductor.

CRediT authorship contribution statement

Yixuan Yang: Writing – original draft, Visualization, Conceptualization. **Zhuozhi Gong:** Writing – original draft, Visualization. **Jiao Yang:** Project administration. **Ying Cai:** Validation. **Shengwei Hong:** Visualization. **Wenjun Mao:** Validation. **Zijian Guo:** Validation. **Mengting Qiu:** Visualization. **Zhu Fan:** Writing – review & editing, Supervision. **Bingnan Cui:** Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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