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Original Research Article

Elucidation of the active components and molecular mechanisms of action of Xiaoyin granules (XYG) against psoriasis and its synergism with acitretin using network pharmacology and molecular docking

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Abstract

Purpose: *To characterize the active components and molecular mechanisms of action of Xiaoyin Granule (XYG), and also to determine its synergistic effect with acitretin on psoriasis.*
Methods: *Bioactive targets of XYG, acitretin targets, and psoriasis-related targets were retrieved from public databases. Key bioactive compounds and targets were identified by bioinformatic and network pharmacology analysis. The binding affinities between bioactive compounds and crucial targets were evaluated through molecular docking analysis.*
Results: *A comprehensive screening of XYG revealed the identification of 323 bioactive compounds and 324 corresponding targets. A total of 47 acitretin targets and 1706 psoriasis-related targets were identified. Venn plot identified 155 candidate targets that contributed to the synergistic effects of XYG and acitretin against psoriasis. Bioinformatics analysis demonstrated that the candidate targets were associated with diverse pathways that participate in signaling transduction. A clustering analysis of protein-protein interaction (PPI) revealed the presence of three distinct clusters, with cluster 3 exhibiting a significant association with immunity and potentially serving a crucial function in the therapeutic mechanisms of XYG and acitretin capsule in the treatment of psoriasis. A herb-compound-target-pathway network was constructed and revealed a variety of bioactive compounds, including quercetin, apigenin, and luteolin, and targets, viz, PTGS2, PRKACA, and MAPK14. Molecular docking demonstrated that the key bioactive compounds had favorable binding affinities with hub targets.*
Conclusion: *This study provides insights into the potential mechanisms underlying the therapeutic effects of XYG when combined with acitretin capsules for treatment of psoriasis, thus laying a solid foundation for further investigations into its mechanism and clinical applications.*

Keywords: *Xiaoyin granules, Acitretin, Psoriasis, Molecular docking, Network pharmacology*

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease usually characterized by an excessively aberrant hyperproliferation of keratinocytes. Psoriasis prevalence in adults differs amongst countries, and ranges from 0.51 to 11.43 % [1]. The pathogenesis of psoriasis was considered to be

associated with genetics, infections, autoimmune reaction, and psychological factors. Psoriasis mostly presents pathologically as aberrant capillary and epidermal growth as a result of the invasion of activated immune cells. The aberrant production of inflammatory cytokines from various immune cells act on keratinocytes to activate further inflammatory mediators and create an inflammatory loop. Psoriasis imposes a significant psychological cost because the teratogenicity and ugliness of this disease adversely lowers quality of life [2].

Western medicine such as glucocorticoids and vitamin D derivatives are usually applied in the treatment of psoriasis [3]. Acitretin, an active metabolite of etretinate, has been approved for the treatment of psoriasis since 1997. As long-term use of acitretin often leads to adverse reactions, it is imperative to identify safe and effective treatment approaches for psoriasis.

Traditional Chinese medicine (TCM) is a comprehensive system with multiple components and multiple targets that works in concert to treat a wide range of disorders and with fewer adverse effects. In recent years, the effects of therapeutics used in TCM in psoriasis has been attracting great attention. Xiaoyin granules (XYG), a well-known Chinese patent medicine with a blend of 13 traditional Chinese herbs, i.e Kushen, Chishao, Dihuang, Mudanpi, Xuanshen, Danggui, Daqingye, Niubangzi, Jinyinhua, Honghua, Fangfeng, Chantui, and Baixianpi. Previous reports have indicated that the addition of XYG to acitretin treatment resulted in superior clinical outcomes compared to acitretin monotherapy, as evidenced by improvements in the PASI score and amelioration of inflammation in patients with psoriasis vulgaris [4]. Modern pharmacological research has gradually revealed the favorable effects of herbs in XYG, such as Kushen, Chishao. Bioactive components extracted from Kushen, including oxymatrine, matrine and kurarinone were demonstrated to be effective in attenuating psoriasiform skin lesions [5]. While the efficacy and active constituents of certain medicinal components have been established, the precise mechanism underlying the therapeutic effects of XYG in combination with acitretin for the treatment of psoriasis remains elusive.

Network pharmacology has been considered as a powerful tool in investigating the underlying mechanism of TCM, and has been applied to various diseases [6]. In this study, a network pharmacology-based strategy was used to forecast the potential targets and relevant pathways that involved in the therapeutic effects of XYG in combination with acitretin for psoriasis treatment. Additionally, the binding affinities among core targets and bioactive compounds were determined using molecular docking.

METHODS

Data mining and preparation

The Traditional Chinese Medicine Systems Pharmacology Database (TCMSP, http://tcmspw.com/tcmsp.php) was used to identify chemical components and targets of XYG. Two pharmacokinetic parameters including oral bioavailability (OB) ≥ 20 % and drug-likeness (DL) ≥ 0.10 were adopted to filter bioactive components. The targets belong to homo sapiens were retained and their symbols were standardized using the UniProt database (https://www.uniprot.org). The targets of acitretin were retrieved from the PubChem database, which contains target information from the Comparative Toxicogenomics Database (CTD, http://ctdbase.org/), Drug-Gene Interaction Database (DGIdb, https://www.dgidb.org/), DrugBank (https://www.drugbank.ca/drugs), the Therapeutic Target Database (TTD, https://db.idrblab.net/t/td/), and PubChem BioAssay (https://pubchem.ncbi.nlm.nih.gov/). Potential psoriasis-related targets were retrieved from the GeneCards (https://www.genecards.org/), Online Mendelian Inheritance in Man (OMIM, https://www.omim.org), PharmGKB (https://www.pharmgkb.org/), TTD, and the DisGeNET Database (https://www.disgenet.org/) using the keyword ‘psoriasis’.

Protein-protein interaction (PPI) analysis

The gene symbols of candidate targets were submitted to the Metascape platform (http://metascape.org/), an online web server for gene annotation and analysis. The PPI network of candidate targets was generated, and clustering analysis was also conducted using the molecular complex detection (MCODE) method. Enrichment analysis of each cluster was also conducted.

Enrichment analysis

The official gene symbols of the candidate targets were converted to Entrez ID and utilized to conduct Gene Ontology (GO) annotations and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. Enrichment analysis was carried out using the cluster profiler package, with statistical significance established for $p < 0.05$. Bubble

chart was utilized to visualize the enrichment results of GO annotation and KEGG pathways.

Network construction and analysis

The Cytoscape software was used for the visualization and topological analysis of multiple networks, including the herb-compound network, the PPI network of candidate targets, the compound-target network, and the herb-compound-target-pathway network. Topological analysis was conducted using the Analyze Network method, and clustering analysis was performed using the MCODE plugin in the Cytoscape. The size and color of the nodes were redrawn according to the degree value, in order to visually show the importance of the node.

Molecular docking

Molecular docking is a commonly used method for prediction the optimal binding site of active compounds and targets, as well as evaluating their binding affinities. The core targets and important bioactive compounds were selected for molecular docking analysis. Firstly, the structure file of the target proteins was obtained from the PDB database (https://www.rcsb.org/). After the removal of solvent and organic molecules using the PyMOL software, the pdbqt formatted files of protein structure were generated using AutoDockTools after adding hydrogens and computing charges. The 3D structure files of bioactive compounds were downloaded and transformed to pdbqt formatted files using Open Babel software. The docking process was executed through AutoDock Vina software employing the grid box information derived from the Getbox plugin within PyMOL software. The binding conformations with the lowest binding energy were selected and compared.

RESULTS

Identification of candidate targets of XYGR in the treatment of psoriasis

First, psoriasis-related targets were retrieved from five publicly available databases. The outcomes demonstrated that 1706 prospective targets displayed a close association with psoriasis (Figure 1 A). The Venn diagram of the psoriasis-related targets revealed that 3 targets, including IL12b, TNF, and VDR were shared by all databases. As shown in Figure 1 B, XYG contains 13 traditional Chinese herbs, and the number of bioactive compounds in each herb was 60 (Kushen), 46 (Chishao), 19 (Dihuang), 18 (Mudanpi), 13 (Xuanshen), 10 (Danggui), 15 (Daqingye), 21 (Niubangzi), 55 (Jinyinhua), 45 (Honghua), 53 (Fangfeng), 3 (Chantui), and 37 (Baixianpi). After eliminating duplications, a total of 323 bioactive compounds were identified.

Of these, 195 bioactive compounds had 323 targets which belonged to *Homo sapiens*. Additionally, 47 targets of acitretin were identified, resulting in a combined total of 351 targets for XYG and acitretin. The interactions between the bioactive compounds of XYG and acitretin with these targets are graphically illustrated in Figure 1 C. To identify candidate targets of XYG and acitretin against psoriasis, the Venn diagram of the drug targets and disease targets was constructed, and 155 genes in the interaction region were considered as candidate targets.

Clustering analysis of PPI network

The PPI network of the 155 candidate targets was visualized in Figure 2 A. It contains 155 nodes and 1726 edges, where each node signifies protein and each edge corresponds to a protein-protein interaction. Clustering analysis of the PPI network was conducted using the MCODE plugin, which generated 3 clusters (cluster1, cluster2 and cluster3). The cluster1 contains 31 nodes and 122 edges, with the top 3 nodes having higher degree values being APP, EDN1, and NOS3. Cluster2 and cluster3 consist of 28 and 25 nodes, respectively. As shown in Table 1, enrichment analysis showed that all clusters were dramatically associated with cancer- and interleukin-related GO terms. In addition, cluster 3 was also significantly associated with the negative regulation of cell differentiation.

Functional enrichment

To further investigate the biological process and pathways that may be involved in the action of XYG and acitretin against psoriasis, function enrichment analysis of 155 candidate targets was performed. It was observed that the candidate targets were significantly enriched in 2547 terms of biological processes, 147 terms of molecular functions, 64 terms of cellular components, and 196 KEGG pathways. The top 20 GO terms and KEGG pathways were selected for drawing the bubble charts (Figure 3 and Figure 4). Besides disease-related pathways, diverse pathways associated with signaling tranduction were enriched, such as PI3K-Akt signaling, MAPK signaling, and TNF signaling pathway. In addition, multiple biological processes involved in response to oxidative stress were enriched, suggesting that the therapeutic effects of XYG and acitretin on

psoriasis might be attributed to the positive effects of candidate targets on oxidative stress.

Herb-compound-target-pathway network

To identify potential hub compounds and targets, the top 10 non-disease-related pathways with lower *p*-values were chosen to construct the pathway-gene network. Subsequently, the herb-compound-target-pathway network was generated by merging the herb-compound, compound-target, PPI network of candidate targets, and the pathway-gene network. As shown in Figure 5, the herb-compound-target-pathway network contained 13 herb nodes, 75 target nodes, 138 compound nodes, 10 pathway nodes, as well as 1244 edges. The topological characteristics of the network were analyzed and the nodes excerpt for acitretin were replotted according to the degree value. A larger size indicated a greater degree value. Among the bioactive compounds, quercetin (MOL000098) was a core compound that acted on 52 targets. In addition, PTGS2 had the highest degree value targeting by 128 bioactive compounds.

Binding affinities between compounds and targets

To assess the binding affinities among bioactive compounds and targets, some hub compounds and target nodes were selected according to the degree value. As a result, 14 bioactive compounds and 9 targets were chosen for molecular docking analysis. Figure 6A displays a range of binding energies that spanned from -4 to -10.3 kcal/mol, with an average binding energy of -7.9 kcal/mol. The most stable binding conformation was the PPKACA-indirubin complex (-10.3 kcal/mol) and the most unstable conformation was the AKT1-oleic acid complex (-4 kcal/mol). The average binding energy of targets and compounds are illustrated in Figure 6 B and Figure 6 C**,** respectively. It revealed that PPKACA exhibited the minimum average binding energy with the 14 bioactive compounds, while indirubin showed the lowest average binding energy with the 9 targets.

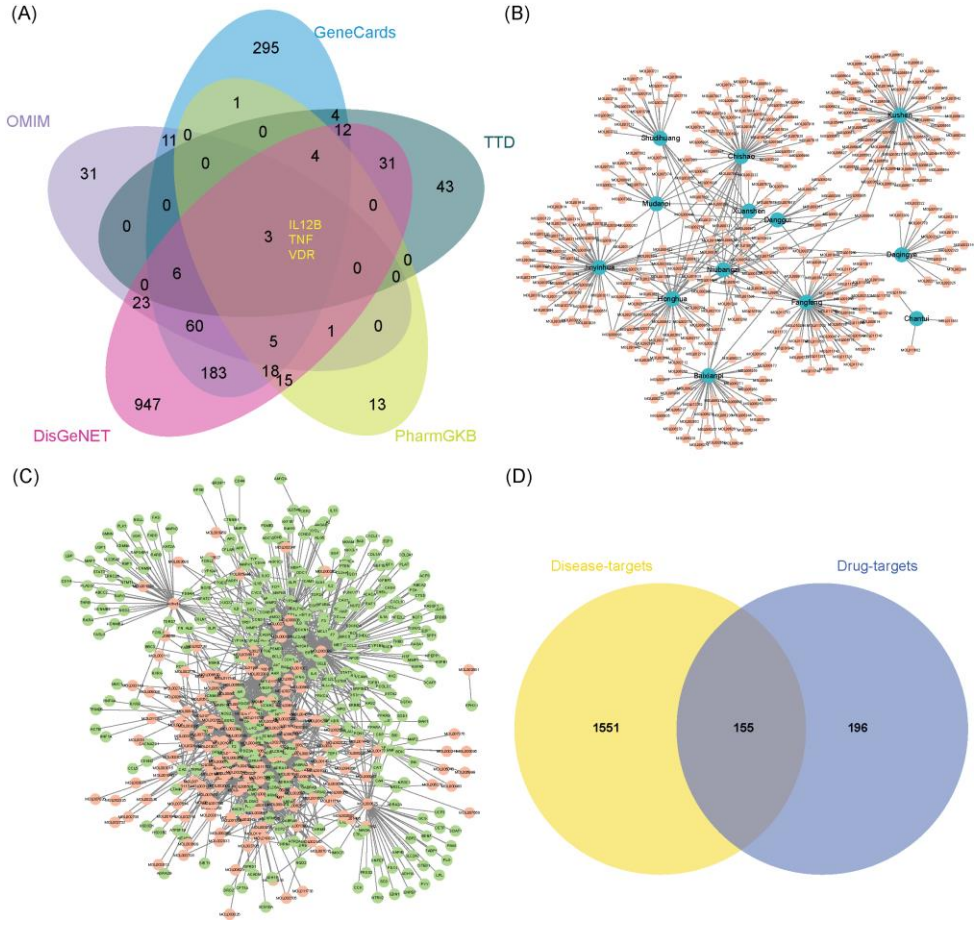

Figure 1: Identification of candidate targets of the action of XYG against psoriasis. (A): psoriasis targets were obtained from 5 public databases (GeneCards, OMIM, TTD, DisGeNET, and PharmGKB); (B): The herb-bioactive compounds network of XYG; (C): The compound-targets network of XYG and acitretin; (D): Venn diagram of the drug targets and psoriasis targets retained 155 candidate targets

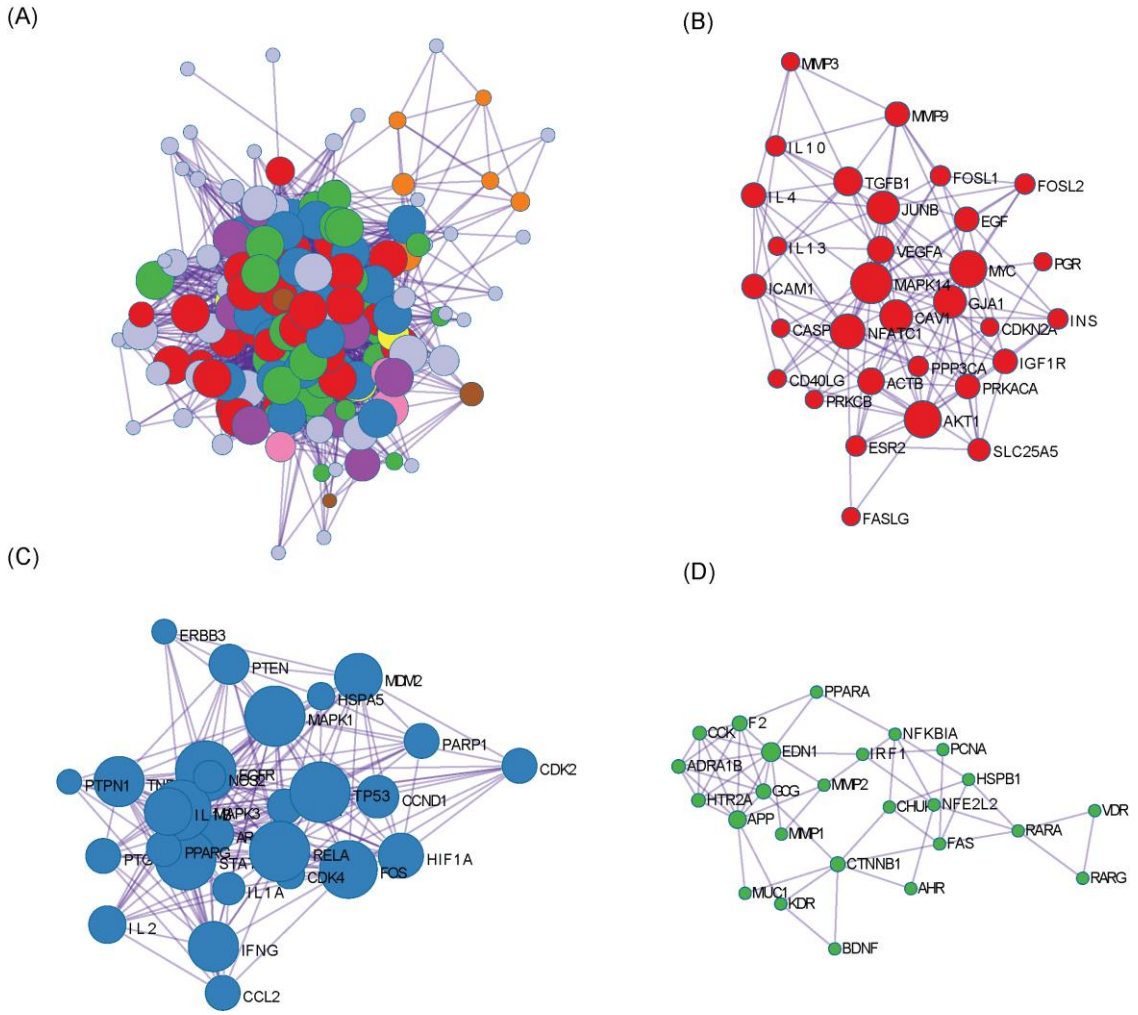

Figure 2: Generation and subsequent clustering analysis of the protein-protein interaction (PPI) network of the candidate targets. (A): The PPI network derived from the Metascape platform comprised of 155 nodes and 1503 edges; (B-D): clustering analysis of the PPI network generated 3 stable clusters (cluster1, cluster2, and cluster3)

Table 1: The top enriched three terms of proteins in cluster1, cluster2, and cluster3

Cluster	GO	Description	Log10(P)
Cluster1	R-HSA-6785807	Interleukin-4 and Interleukin-13 signaling	-21.5
Cluster1	M167	PID AP1 PATHWAY	-21.4
Cluster1	hsa05205	Proteoglycans in cancer	-20.1
Cluster2	WP2431	Spinal cord injury	-31.3
Cluster2	hsa05200	Pathways in cancer	-28.8
Cluster2	R-HSA-449147	Signaling by Interleukins	-23.5
Cluster3	hsa05200	Pathways in cancer	-11.2
Cluster3	WP4754	IL-18 signaling pathway	-10.4
Cluster3	GO:0045596	negative regulation of cell differentiation	-9.9

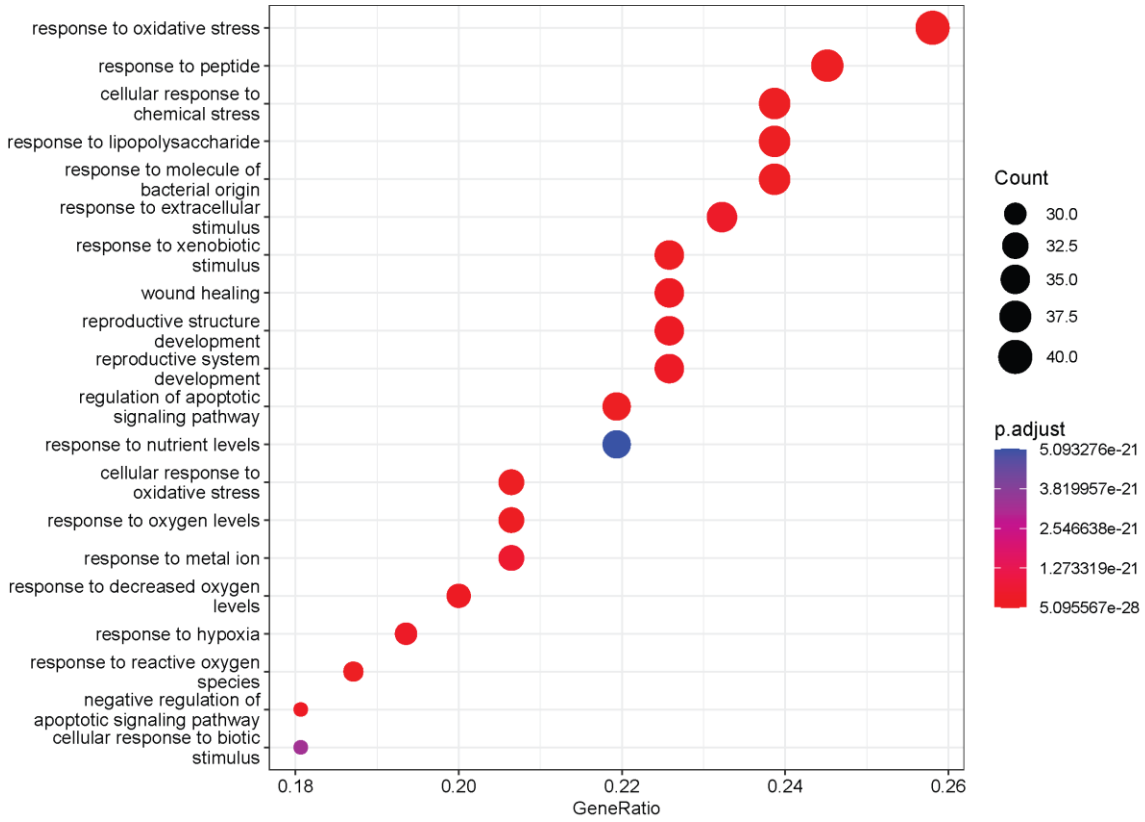

Figure 3: A bubble chart depicting the gene count-based ranking of the top 20 enriched GO terms

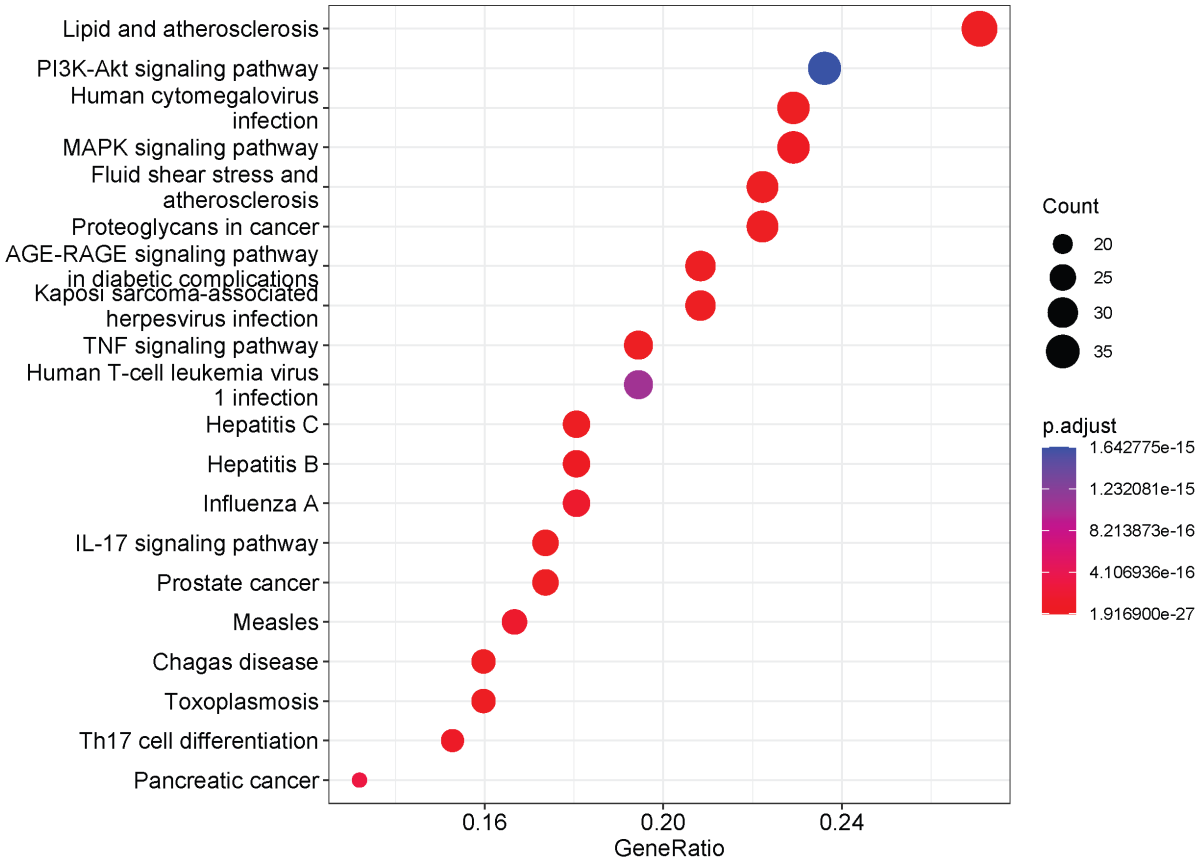

Figure 4: A bubble chart depicting the gene count-based ranking of the top 20 enriched KEGG pathways

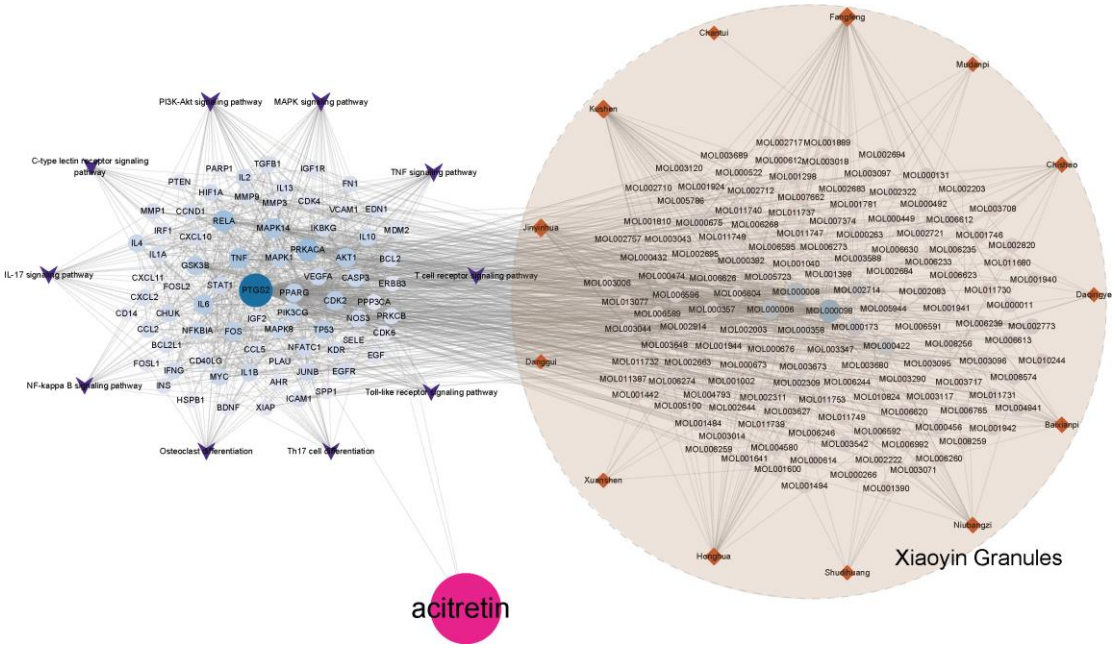

Figure 5: Herb-compound-target-pathway network of XYG combined with acitretin in psoriasis therapy

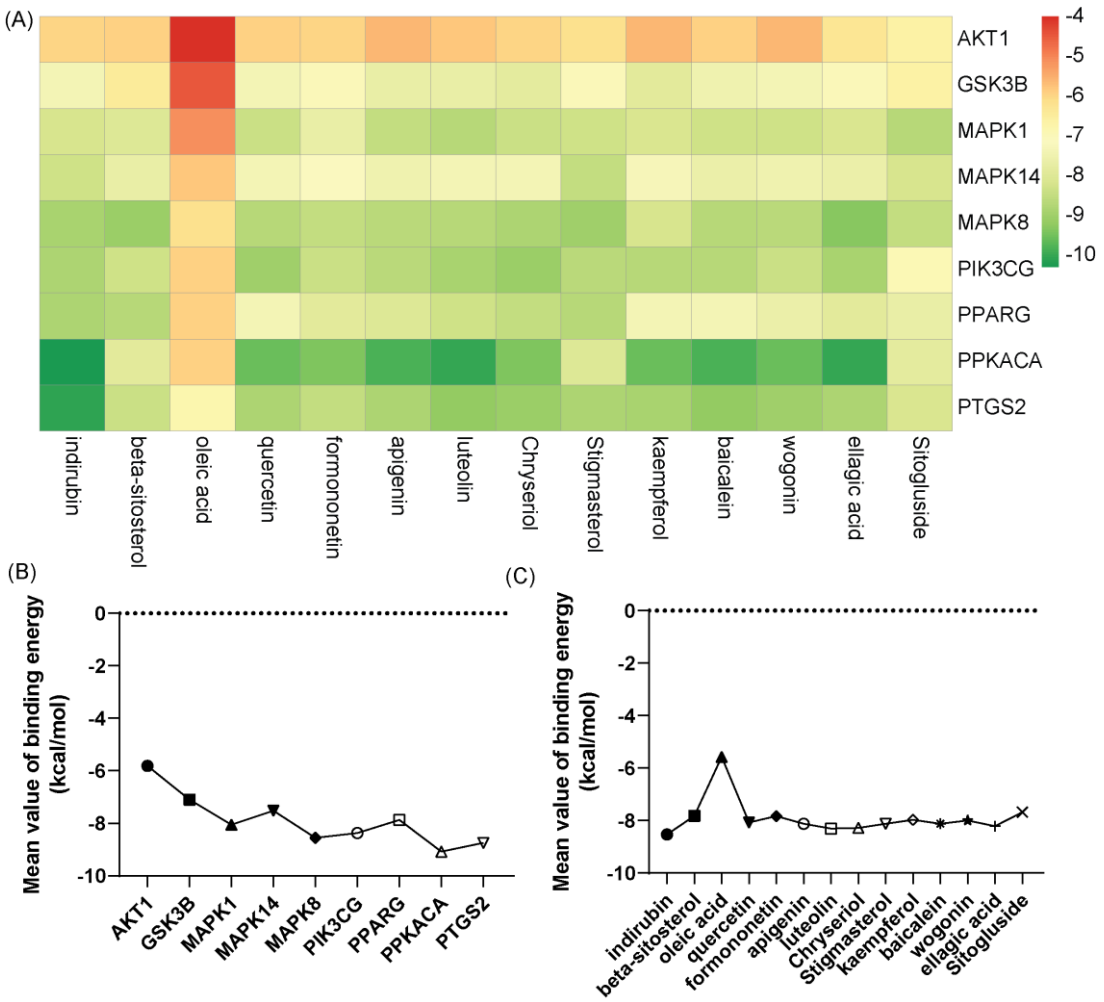

Figure 6: Molecular docking results amongst 14 compounds and 9 targets. (A): Heatmap of the lowest binding energy of each compound-target complex; (B): The mean binding energy value of hub targets to overall bioactive compounds; (C): The mean binding energy value of bioactive compounds to overall hub targets

DISCUSSION

Psoriasis is a chronic autoimmune skin disease, which has a long course and is prone to relapse. Psoriasis is generally believed to be related to genetics, viral infection, bacterial infection, drugs, autoimmune reactions and psychological factors [7]. Psoriasis has a long course and is prone to relapse. Acitretin is an oral vitamin-A derivative used to treat psoriasis, and a meta-analytic study revealed that the combination of XYG and acitretin in capsule form exerted a more favorable therapeutic effects on psoriasis vulgaris [4]. However, little is known about the pharmacological mechanism of the therapeutic action of XYG and acitretin on psoriasis.

Xiaoyin granule is composed of 13 kinds of traditional Chinese herbs, i.e., *Kushen, Chishao, Dihuang, Mudanpi, Xuanshen, Danggui, Daqingye, Niubangzi, Jinyinhua, Honghua, Fangfeng, Chantui, and Baixianpi*. Kushen is the dried root of Sophora flavescens, which is the most commonly used herb in the management of psoriasis [8]. Chen *et al* investigated the potential of oxymatrine, an active component extracted from Kushen as a psoriasis therapy, and suggested that oxymatrine exerted an anti-proliferation effect on human skin keratinocytes by suppressing p63 expression [5]. In addition, two bioactive compounds of Kushen, including matrine and kurarinone, were also beneficial in alleviating psoriasis-form skin lesions [9]. The total paeony glycoside extracted from Chishao has gained widespread use in China for psoriasis treatment [10]. Although growing evidence also supported the beneficial effects of other herbs on psoriasis, the synergetic effects of these herbs and the pharmacological mechanism of XYG combined with acitretin against psoriasis remains unclear.

To investigate the pharmacological basis and molecular mechanism of action of XYG combined with acitretin in a capsule form in treating psoriasis, network pharmacology was adopted in this study. It was observed that multiple bioactive compounds were shared by the 13 herbs, indicating that there may be stronger effects of superposition by these shared compounds. The results showed that XYG combination with acitretin was associated with 351 targets in humans. By integrating with psoriasis-related targets, 155 candidate targets were identified to contribute to the therapeutic effects of XYG and acitretin against psoriasis. Topological analysis revealed that a variety of bioactive compounds had multiple targets, and are pivotal in the treatment of psoriasis. For example, quercetin is a dietary flavonoid, and has been shown to ameliorate skin inflammation in psoriatic mice by inhibiting the NF-κB signaling pathway [11].

Numerous studies have demonstrated that indirubin showed anti-psoriasis activity, and was a novel topical agent for alleviating psoriasis-like dermatitis. Indirubin alleviates the severity of psoriatic mice by upregulating the CD274 levels in keratinocytes [12]. In addition, indirubin repressed inflammatory responses in psoriatic mice , with the involvement of the Wnt/β-catenin signal pathway and TAK1 signaling pathway implicated in the therapeutic effects of indirubin on psoriasis [13]. Molecular docking demonstrated that indirubin had the lowest average binding energy with hub targets, and if taken together, indirubin might be a pivotal compound in treating psoriasis. Moreover, modern pharmacological research also revealed the beneficial roles of other compounds on psoriasis, such as kaempferol, apigenin, and luteolin.

Subsequently, network analysis also found a branch of hub targets that contribute to the effects of XYG against psoriasis. The top 6 hub targets with higher degree values were PTGS2, PPKACA, PPARG, PIK3CG, MAPK8, and MAPK14, respectively. Compared with normal lesions, prostaglandin-endoperoxide synthase 2 (PTGS2) was highly expressed in psoriatic lesions [14]. Several drugs with anti-psoriasis activity generally reduced the expression of PTGS2, suggesting a possible negative correlation between PTGS2 expression and psoriatic symptoms. Peroxisome proliferator-activated receptors (PPARs) are crucial for skin barrier homeostasis because of their involvement in inflammation modulation, lipid synthesis, and the differentiation and proliferation of keratinocyte. The expression of PPARs was regulated by keratinocyte-derived IL-1β and partly TNF-α following epidermal barrier perturbation.

A high-throughput transcriptome study revealed that the PPARG expression was significantly decreased in psoriasis lesions [15]. Therefore, it was believed that the agonists of PPARG may be promising therapeutic options for psoriasis. As one of the PI3K isoforms, PIK3CG contributes to the immune processes that underpin inflammatory responses. The blockade of PIK3CG ameliorates imiquimod-induced psoriasis-like dermatitis [16]. Mitogen-activated protein kinases (MAPKs) play a crucial role in transmitting signals from the cell surface to the nucleus, and are involved in various cellular processes. The suppression of MAPK14 activity

ameliorates the severity of psoriasiform skin inflammation. Molecular docking analysis revealed favorable binding affinities among bioactive compounds and these core targets, indicating the potential of these core targets as therapeutic targets for psoriasis. Therefore, further investigation into the synergetic effects of the bioactive compounds on these core targets might explain the anti-psoriasis activity of XYG and acitretin.

Enrichment analysis provided us with a deeper understanding of the candidate targets in terms of biological process and cellular pathways. It was notably observed that the candidate targets were related to diverse pathways that participate in signal transduction, such as the PI3K-Akt, MAPK, and TNF signaling pathway. The PI3K-Akt signaling pathway is a central pathway mediating multiple cellular functions. Dysregulation of this pathway was observed in psoriatic lesions, which ultimately affects the proliferation of keratinocytes. It was suggested that the suppression of the PI3K-Akt signaling pathway ameliorates psoriasis [17]. Several candidate targets were involved in the MAPK signaling pathway, including MAPK1, MAPK8, and MAPK14. The expression of phosphorylated MAPK1 in lesion tissues was dramatically elevated, and the inhibition of MAPK1 activation repressed keratinocyte proliferation in psoriasis. The candidate targets were also significantly associated with Th17 cell differentiation, which was involved in the pathogenesis of psoriasis. TIL-17, IL-21, IL-23, and other Th17-derived proinflammatory cytokines influence keratinocytes, so as to intensify psoriatic inflammation [18].

Induction of Th17 cell differentiation promotes psoriasis pathogenesis of psoriasis, whereas the inhibition of Th17 cell differentiation might be beneficial for psoriasis. The putative targets were engaged in numerous biological processes linked to oxidative stress, according to GO enrichment analysis of the data. The pathophysiology of psoriasis involves oxidative stress, and excessive oxidative stress can be responsible for the onset of psoriasis complications. Therefore, developing antioxidants and drugs with antioxidant activity might be a promising direction for the management of psoriasis.

CONCLUSION

This study has systematically examined the pharmacological mechanism of action of the therapeutic effects of XYG and acitretin on psoriasis. The combination of XYG and acitretin acts on various core targets, such as PTGS2, PPARG, and PPKACA, in order to exert anti-psoriasis effects. Abundant bioactive compounds of XYG have been identified to synergistically regulate potential targets. The therapeutic effects of XYG/ acitretin combination on psoriasis are associated with various signaling pathways and multiple biological processes related to oxidative stress. However, these findings require further validation through *in vitro* and *in vivo* experiments.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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