

Wogonin as a potential therapeutic agent for psoriasis: Core target identification and validation

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Abstract. Wogonin exhibits therapeutic effects in various skin diseases. However, the pharmacological effects and mechanisms of wogonin against psoriasis remain unclear. In the present study, the potential targets of wogonin were predicted and disease-related targets were obtained using Gene Expression Omnibus datasets. Intersection targets were identified using Venny 2.1.0 software, followed by input into the Search Tool for the Retrieval of Interacting Genes/Proteins database to generate a drug-target-disease visual network using Cytoscape 3.10.1. Core targets were obtained by protein-protein interaction analysis and the intersection targets were enriched through Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analyses. The binding of wogonin to its core targets was evaluated using molecular docking. Furthermore, a psoriasis mouse model was constructed to assess the therapeutic effect of wogonin on skin lesions, and core targets of wogonin were verified by immunohistochemistry, including cyclin-D1 (CCND1), matrix metalloproteinase-9 (MMP9), cyclin-B1, cyclin-A2 (CCNA2), cyclin-dependent kinase 1 and androgen receptor. Molecular docking analysis revealed interactions between wogonin and these targets. *In vivo* results demonstrated that wogonin alleviated psoriasis-like lesions in the mouse model. Immunohistochemical and RNA sequencing analyses results suggested that MMP9, CCNA2 and CCND1 may be the key targets of wogonin in psoriasis. In conclusion, the findings of the present study suggested that wogonin may be a promising therapeutic candidate for psoriasis, potentially exerting its effects through the modulation of multiple molecular targets, including MMP9, CCNA2 and CCND1.

Introduction

Psoriasis is an immune-mediated, polygenic dermatological condition characterized by the formation of scaly, erythematous plaques or lesions. In some cases, patients may also experience psoriatic arthritis as a comorbid condition (1). Additionally, intrinsic factors such as hypertension, diabetes mellitus, obesity and mental stress, along with external environmental factors including sun exposure, trauma and infections, can exacerbate psoriasis. This condition markedly impacts the quality of life of patients, a number of whom experience feelings of shame due to the visible effects of the disease. Consequently, >5% of patients may suffer from depression and suicidal ideations (2,3). Currently, the primary therapeutic strategies for psoriasis include immunosuppressive therapy (such as methotrexate and cyclosporine) (4) and biological agent therapy (such as secukinumab and ustekinumab), which only offer transient symptomatic relief (5). However, these treatments are often associated with relapse upon discontinuation, and prolonged use can lead to adverse effects such as infection and hepatotoxicity. Therefore, developing innovative, effective and safe anti-psoriasis treatments is a pressing need.

Wogonin, a naturally occurring flavonoid derived from the root of *Scutellaria baicalensis* Georgi, has gained attention due to its broad pharmacological properties, including anti-inflammatory, antioxidant and antiproliferative effects. Chemically, wogonin (5,7-dihydroxy-8-methoxyflavone) has a molecular formula of C₁₆H₁₂O₅ and a molecular weight of 284.26 g/mol. Although wogonin exhibits low aqueous solubility, it exhibits good solubility in both DMSO and ethanol, consistent with its lipophilic nature (predicted logP value of ~2.7) (6). Pharmacokinetically, wogonin exhibits moderate oral bioavailability and has been shown to effectively penetrate skin tissue, supporting its topical application in dermatological disorders (7). Used in Traditional Chinese Medicine to treat inflammatory and infectious diseases, wogonin has demonstrated therapeutic potential in various dermatological conditions, such as atopic dermatitis, ultraviolet-induced skin damage and psoriasis, by modulating inflammatory signaling pathways and suppressing keratinocyte hyperproliferation (8-10).

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Psoriasis is characterized by aberrant keratinocyte proliferation, sustained activation of pro-inflammatory cytokines (including TNF- α , IL-17 and IL-23) and dysregulation of innate immune responses (11,12). *In vitro* research using human keratinocyte (HaCaT) models has revealed that wogonin effectively attenuates psoriasis-like inflammation by inhibiting the PI3K/AKT pathway, thereby reducing the expression of inflammatory mediators, such as TNF- α , IL-1 β and IL-6 (10). Furthermore, wogonin suppresses NLR family pyrin domain containing 3 inflammasome activation, caspase-1 cleavage and gasdermin-D-mediated pyroptosis in keratinocytes, outlining its dual role in mitigating both hyperproliferation and inflammatory cascades in psoriatic pathogenesis (13). These findings suggest that wogonin is a promising candidate for psoriasis therapy. However, despite notable evidence from cellular models, the therapeutic efficacy and mechanistic actions of wogonin *in vivo* remain unexplored. Animal studies are therefore key in the validation of the anti-psoriasis effects of wogonin, assessing its systemic safety and elucidating tissue-specific interactions that cannot be fully replicated *in vitro*. Addressing this gap is key for translating preclinical findings into clinical applications.

Network pharmacology is an effective methodology for investigating and elucidating pharmacological mechanisms, encompassing chemical informatics, bioinformatics, network biology and pharmacology (14). In the present study, a network pharmacology approach was employed to predict effective molecular targets and potential mechanisms of wogonin underlying the treatment of psoriasis. Additionally, the effects of wogonin on imiquimod (IMQ)-induced psoriatic lesions of mice were examined and the targets of wogonin were validated. The present study not only bridges the knowledge gap between cellular and animal models but also provides a foundation for developing wogonin-based therapies for psoriasis.

Materials and methods

Network pharmacological and molecular docking analysis

Wogonin target screening. SwissTargetPrediction (15) (<http://www.swisstargetprediction.ch/>), PharmMapper (16) (version 2017; <http://www.ilab-ecust.cn/pharmmapper/>), Similarity Ensemble Approach (17) (<https://sea.bkslab.org/>) and SuperPred databases (18) (<https://prediction.charite.de/index.php>) were used to predict potential targets of wogonin. The UniProt database (<https://www.uniprot.org/>) was used to verify the target information. Duplicate entries were removed to obtain the final list of wogonin targets.

Identifying psoriasis differentially expressed genes (DEGs) and obtaining the wogonin-psoriasis intersection targets. GSE121212 (19) and GSE13355 (20) datasets were obtained from the Gene Expression Omnibus (GEO) database (<https://www.ncbi.nlm.nih.gov/geo/>). Each dataset contained >40 samples, with each group consisting of >20 control and 20 psoriasis samples. GSE121212 included gene expression profiles from 28 patients with psoriasis and 38 healthy controls, while GSE13355 included gene expression profiles from 58 patients with psoriasis and 64 healthy skin samples. GEO2R (<https://www.ncbi.nlm.nih.gov/geo/geo2r/>) was used to analyze the DEGs of each dataset online and volcano plots of each dataset were generated using the online platform

SRplot (<https://www.bioinformatics.com.cn>) (21) for data analysis and visualization. Significantly DEGs were identified using the thresholds of an adjusted P-value <0.05 and $\log_2$ fold change >1.

Intersection target acquisition and action network construction. Wogonin targets and psoriasis DEGs were imported into Venny 2.1.0 software (<https://bioinfogp.cnb.csic.es/tools/venny/index.html>) for common target identification. Venn diagrams of the intersecting targets of wogonin in psoriasis were generated. These selected targets were then imported into Cytoscape 3.10.1 (22) for visualization and a drug-target-disease action network diagram was constructed.

Construction of protein-protein interaction (PPI) networks. A total of 30 potential targets were imported into the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database, with the species set to human and the confidence level set to 0.4, and the options set to 'Hide disconnected nodes in the network'. This allowed for the retrieval of protein interaction network data after the removal of isolated proteins. The data were then imported into Cytoscape 3.10.1 to construct the PPI network. The degree value (the number of direct interactions for a given protein node) of each target was analyzed using the 'CentiScaPe2.2' plug-in and the targets were ranked in descending order of degree value to obtain relevant information regarding the core targets. The 'cytoHubba' plug-in was employed to further analyze the PPI network and determine the core targets, with the top 10 targets selected based on their Matthews Correlation Coefficient (MCC) values.

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis. The Database for Annotation, Visualization and Integrated Discovery (DAVID; <https://davidbioinformatics.nih.gov/>) (23) was employed with the following parameters: i) 'OFFICIAL_GENE_SYMBOL' for the identifier; ii) 'Homo sapiens' for the species; and iii) 'gene list' for the submission list. The GO and KEGG enrichment analysis data of the core targets were collected in an output table. The top 10 most significant results for each category, including biological process (BP), cellular component (CC) and molecular function (MF), were selected for inclusion in the GO analysis. A total of 20 potential signaling pathways, were obtained in descending order of count value ($P < 0.05$) and used for the analysis of KEGG pathways. The resulting data were imported into the SRplot platform to generate a visual representation of the GO function in conjunction with the KEGG pathway enrichment analysis data forming the corresponding enrichment bubble plot.

Molecular docking. Molecular docking was performed using AutoDockTools 1.5.6 (24). The X-ray crystal structures of the key targets were obtained from the Protein Data Bank (PDB) (www.rcsb.org). The 2D structures of the active compounds were retrieved from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>). The structures were processed using AutoDockTools 1.5.6, including the removal of water molecules, the addition of charges and non-polar hydrogen atoms. Both the target and compound structures were saved in PDBQT format. Molecular docking was performed using AutoDock Vina software (25) and good affinity conformations (affinity <-7 kcal/mol) were analyzed and visualized using AutoDockTools 1.5.6 and PyMOL (26).

Experimental verification

Animal modeling and group intervention. A total of 15 male BALB/c mice, aged 6-8 weeks and weighing 20-22 g, were obtained from SPF (Beijing) Biotechnology Co., Ltd. [animal license no. SCXK (Beijing) 2019-0010]. The mice were maintained under the following conditions: Temperature was controlled at $22\pm 2^{\circ}\text{C}$, relative humidity was $50\pm 10\%$, and a 12-h light/12-h dark cycle was maintained. All mice had free access to standard rodent chow and autoclaved drinking water. Male mice were selected for the present study to avoid potential fluctuations in immune response and disease severity associated with the female estrous cycle, thereby minimizing experimental variables, an approach consistent with numerous previous studies utilizing the IMQ-induced psoriasis model (27-29).

The mice were randomly assigned to three groups, a control group, an IMQ group and an IMQ + wogonin group. The dorsal fur of all mice was removed to create an exposed area measuring $\sim 2\times 3$ cm. Subsequently, 42 mg IMQ cream (Sichuan Mingxin Pharmaceutical Co., Ltd.) was applied daily as a modeling inducer for a total of 7 consecutive days (30), while saline was applied to the control group. From days 1-7, the IMQ and IMQ + wogonin groups received 42 mg of IMQ cream daily on their shaved backs, while the mice in the IMQ + wogonin group additionally received an intragastric gavage administration of 30 mg/kg/day wogonin (cat. no. HY-N0400; MedChemExpress) (dissolved in sodium carboxymethyl cellulose solvent). On day 8, all mice were euthanized. Prior to euthanasia, mice were anesthetized through an intraperitoneal injection of 1.5% pentobarbital sodium (50 mg/kg). The depth of anesthesia was ensured by the absence of pedal and corneal reflexes. Euthanasia was then performed by cervical dislocation under deep anesthesia. Mortality was verified by ensuring the cessation of breathing and heartbeat.

Animal health and behavior were monitored at least twice daily throughout the present study. The specific humane endpoints predefined for the present study, which would necessitate immediate euthanasia, included: i) Severe lethargy or unresponsiveness to gentle stimuli; ii) the inability to access food or water; iii) weight loss $>20\%$ of baseline body weight; or iv) signs of severe systemic illness, such as uncontrolled bleeding, seizures or paralysis.

The present animal study protocol was approved by the Animal Experiment Ethics Committee of Yunnan University of Traditional Chinese Medicine (Kunming, China; approval no. R-062021LH048).

Psoriasis Area and Severity Index (PASI) score of mouse skin lesion tissues. Mouse dorsal lesions in each treatment group were scored based on the area and severity of psoriasis using the PASI score (31). The PASI score was assessed on a five-point scale for erythema, infiltrates and scaling ranging from 0 to 4 (0=none, 1=mild, 2=moderate, 3=severe and 4=very severe), and was calculated by combining the scores for erythema, infiltration and scaling. The cumulative score served as a measure of inflammation severity (scale 0-12).

H&E staining and observation of mouse skin lesions. Following euthanasia on day 8, dorsal skin lesion specimens were immediately collected from each mouse. Mouse skin lesion tissues were fixed in 4% paraformaldehyde at 4°C for 48 h, with the fixative being changed once during this period.

The tissues were trimmed to a consistent size ($\sim 5\times 5$ mm) and rinsed. Subsequently, the tissue samples underwent a series of dehydration steps using gradients of ethanol (100, 95, 85 and 75%), followed by treatment with xylene and embedding in paraffin wax. The samples were then sectioned to a thickness of $4\text{ }\mu\text{m}$. Each section was dried, dewaxed in xylene, and then hydrated through a descending ethanol series (100, 95, 85 and 75%). Subsequently, the sectioned samples were subjected to H&E staining, which included hematoxylin staining (5 min), hydrochloric acid ethanol differentiation (1 min) and eosin staining (1 min) at 25°C . Finally, the samples were dehydrated, rendered transparent and sealed. At the conclusion of the experiment, histological alterations in the skin lesion tissues were examined and documented under a light microscope (BX43; Olympus Corporation). Finally, using ImageJ 1.8.0 software (National Institutes of Health), three random fields per section were selected to measure the epidermal thickness of the lesion.

Immunohistochemistry. Immunohistochemistry was performed to assess the expression of matrix metalloproteinase-9 (MMP9), cyclin-D1 (CCND1), cyclin-B1 (CCNB1), cyclin-A2 (CCNA2), cyclin-dependent kinase 1 (CDK1) and androgen receptor (AR) proteins in mouse skin lesion tissues. Mouse skin lesion tissues were sectioned, baked, deparaffinized, hydrated (as aforementioned for the HE staining process) and subjected to antigen retrieval using 10 mM citrate buffer at 95°C for 10 min. Next, endogenous peroxidase activity was blocked by incubation with 3% H_2O_2 for 15 min at 25°C . Following the incubation of sections with 5% BSA (cat. no. A8012; Beijing Solarbio Science & Technology Co., Ltd.) for 30 min at 25°C . Subsequently, the sections were incubated overnight at 4°C with the following primary antibodies diluted in 5% BSA: Anti-MMP9 (1:500; cat. no. AF5228; Affinity Biosciences, Ltd.), anti-CCND1 (1:500; cat. no. AF0931; Affinity Biosciences, Ltd.), anti-CCNA2 (1:500; cat. no. AF0142; Affinity Biosciences, Ltd.), anti-CDK1 (1:500; cat. no. DF6024; Affinity Biosciences, Ltd.), anti-CCNB1 (1:500; cat. no. BF0062; Affinity Biosciences, Ltd.) and anti-AR (1:500; cat. no. AF6137; Affinity Biosciences, Ltd.), followed by overnight incubation with horseradish peroxidase-labeled goat anti-rabbit secondary antibody (1:200; cat. no. S0001; Affinity Biosciences, Ltd.) or horseradish peroxidase-labeled goat anti-mouse secondary antibody (1:200, cat. no. S0002; Affinity Biosciences, Ltd.) at 4°C . The sections were stained with 3,3'-diaminobenzidine, counterstained with hematoxylin for 30-60 sec at 25°C and sealed after dehydration and clearing. Visualization was performed under the BX43 light microscope (Olympus Corporation). Finally, using ImageJ 1.8.0 software (National Institutes of Health), three random fields per section were selected to measure the staining intensity.

RNA sequencing (RNA-seq). Total RNA was extracted from the three groups of skin samples using the RNeasy Plus Mini kit (cat. no. 74134; Qiagen China Co., Ltd.) according to the manufacturer's protocols. RNA concentration was determined using a Qubit fluorometer (Invitrogen; Thermo Fisher Scientific, Inc.) and RNA integrity was assessed using Agilent 4200 TapeStation (Agilent Technologies, Inc.). The assay was performed strictly following the manufacturer's instructions using an RNA ScreenTape assay kit, and data were analyzed with the accompanying TapeStation Analysis

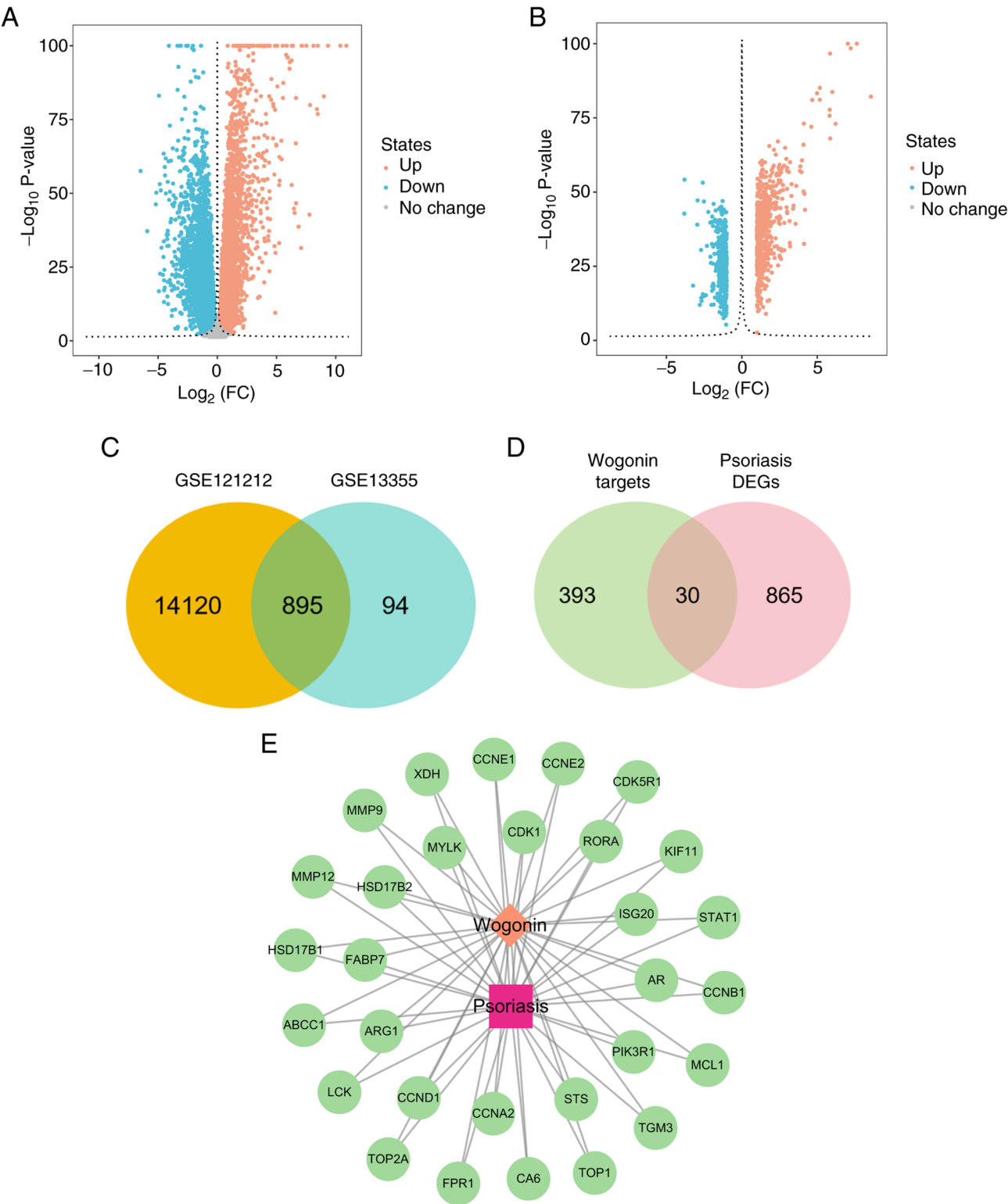


Figure 1. Screening of wogonin-psoriasis intersection targets and construction of the drug-target-disease network. Volcano plots of DEGs in (A) GSE121212 and (B) GSE13355 datasets (adjusted $P < 0.05$). Orange dots represent upregulated genes, while blue dots represent downregulated genes. (C) Venn diagram illustrating the intersecting DEGs from GSE121212 and GSE13355 datasets. (D) Venn diagram of the 30 intersecting genes between DEGs and wogonin target genes. (E) Drug-target-disease network of wogonin targeting psoriasis. DEGs, differentially expressed genes.

Software (version A.02.02). Samples with an RNA integrity score of ≥ 8 were included in the present study. An indexed library was constructed from 500 ng of total RNA according to the manufacturer's instructions using the TruSeq Stranded mRNA sample preparation kit (cat. no. 20020594; Illumina,

Inc.). The library concentration and fragment length distribution were assessed using Qubit fluorometer and the Agilent 2100 Bioanalyzer (Agilent Technologies, Inc.). The concentration was required to be $> 5 \text{ ng}/\mu\text{l}$ and the fragment length was required to be between 300-400 bp. Paired-end sequencing

Table I. Targets of wogonin for the treatment of psoriasis.

Target name	Gene name	UniProt ID
G ₂ /mitotic-specific cyclin-B1	CCNB1	P14635
Signal transducer and activator of transcription 1- α/β	STAT1	P42224
Cyclin-A2	CCNA2	P20248
Cyclin-dependent kinase 1	CDK1	P06493
17- β -hydroxysteroid dehydrogenase type 1	HSD17B1	P14061
DNA topoisomerase 2- α	TOP2A	P11388
Protein-glutamine γ -glutamyltransferase E	TGM3	Q08188
Multidrug resistance-associated protein 1	ABCC1	P33527
Interferon-stimulated gene 20 kDa protein	ISG20	Q96AZ6
Matrix metalloproteinase-9	MMP9	P14780
Induced myeloid leukemia cell differentiation protein Mcl-1	MCL1	Q07820
G ₁ /S-specific cyclin-E1	CCNE1	P24846
G ₁ /S-specific cyclin-D1	CCND1	P24385
Arginase-1	ARG1	Q61176
Cyclin-dependent kinase 5 activator 1	CDK5R1	Q15078
Nuclear receptor ROR- α	RORA	P35398
Macrophage metalloelastase	MMP12	P39900
Tyrosine-protein kinase Lck	LCK	P06239
Xanthine dehydrogenase/oxidase	XDH	P47989
Phosphatidylinositol 3-kinase regulatory subunit α	PIK3R1	P27986
Androgen receptor	AR	P10275
Kinesin-like protein KIF11	KIF11	P52732
G ₁ /S-specific cyclin-E2	CCNE2	O96020
fMet-Leu-Phe receptor	FPR1	P21462
Myosin light chain kinase, smooth muscle	MYLK	Q15746
Steryl-sulfatase	STS	P08842
Carbonic anhydrase 6	CA6	P23280
Fatty acid-binding protein, brain	FABP7	O15540
DNA topoisomerase 1	TOP1	P11387
17- β -Hydroxysteroid dehydrogenase type 2	HSD17B2	P37059

(2x150 bp) was performed on an Illumina NovaSeq 6000 platform using the NovaSeq 6000 S4 Reagent Kit (300 cycles; cat. no. 20028312; Illumina, Inc.). Bioinformatic analysis: Raw sequencing reads (FASTQ files) were quality-controlled and trimmed using fastp (version 0.23.2). Clean reads were then aligned to the mouse reference genome (GRCm39) using STAR (version 2.7.10a). Gene-level counts were obtained using featureCounts (from the Subread package; version 2.0.3). Differential expression analysis was performed using the DESeq2 R package (version 1.38.3).

Statistical analysis. Experimental data were analyzed using SPSS 26.0 (IBM Corp.) and data are presented as the median $\pm$ SD. One-way ANOVA followed by Tukey's post hoc test was used to analyze the statistical significance among multiple groups and unpaired Student's t-test was used for comparisons between two groups (for the analysis of DEGs from the two GEO datasets). Non-parametric PASI score data are presented as the median $\pm$ interquartile range and were analyzed with Kruskal-Wallis followed by Dunn's post hoc test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Acquisition of intersecting targets between wogonin and psoriasis DEGs and construction of the action network. A total of 100 targets of wogonin were obtained from the SwissTargetPrediction database, 196 from the PharmMapper database, 95 from the Similarity Ensemble Approach database and 80 from the SuperPred database. After eliminating duplicates, 423 drug targets were identified (Table SI).

By comparing the differences between patients with psoriasis and healthy controls, 15,015 and 989 DEGs were identified in GSE121212 and GSE13355 datasets, respectively (Fig. 1A and B). The intersection of the two datasets yielded 895 DEGs related to psoriasis (Fig. 1C). Subsequently, the overlap between the DEGs of psoriasis and the targets of wogonin revealed 30 targets, which were defined as wogonin-psoriasis cross-targets (Fig. 1D; Table I), suggesting that these targets may serve a key role in mediating the therapeutic effects of wogonin in psoriasis.

Drug-target-disease network construction and analysis. A drug-target-disease action network was constructed to

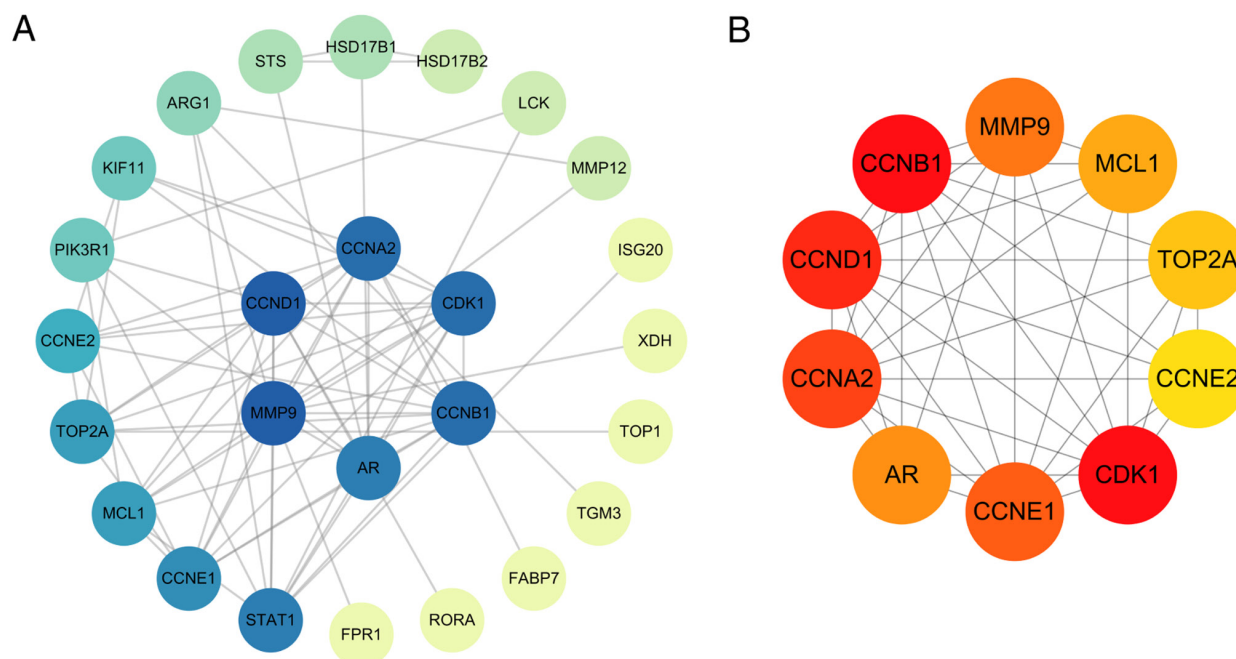


Figure 2. Construction of the PPI network and identification of core target genes. (A) The PPI network of 30 intersection genes. The color depth indicates the degree value, with darker colors representing higher degree values. (B) The top 10 genes based on MCC values. The color depth indicates the MCC value, with darker colors representing higher MCC values. CCND1, cyclin-D1; CCNA2, cyclin-A2; AR, androgen receptor; CCNE1, cyclin-E1; CDK1, cyclin-dependent kinase 1; CCNE2, cyclin-E2; TOP2A, DNA topoisomerase II α ; MCL1, induced myeloid leukemia cell differentiation protein Mcl-1; MMP9, matrix metalloproteinase-9; CCNB1, cyclin-B1.

visualize the complex relationship between wogonin, its targets and psoriasis (Fig. 1E). This network illustrates the interaction between wogonin and the 30 cross-targets, highlighting the relationship between these targets and psoriasis. The nodes in the network represent drugs (wogonin), cross-targets and diseases (psoriasis), while the edges represent their interactions. By mapping these interactions, the network provides a comprehensive overview of the potential mechanisms underlying the effects of wogonin on psoriasis.

PPI network analysis of wogonin-psoriasis intersection targets and screening of core genes. STRING was used to construct a PPI network of wogonin-psoriasis cross-targets and the network was further analyzed using Cytoscape 3.10.1. The PPI network consisted of 26 nodes and 71 edges, with 4 unconnected nodes hidden. Next, the degree value of each target was obtained through the 'CentiScaPe2.2' plug-in. The top 10 targets with a higher degree value were CCND1, MMP9, CCNB1, CCNA2, CDK1, AR, STAT1, G1/S-specific cyclin-E1 (CCNE1), induced myeloid leukemia cell differentiation protein Mcl-1 (MCL1) and DNA topoisomerase II α (TOP2A; Fig. 2A). The MCC value for each target was obtained using the 'cytoHubba' plug-in to identify the core targets. The top 10 targets with higher MCC values were CDK1, CCNB1, CCND1, CCNA2, CCNE1, MMP9, AR, MCL1, TOP2A and CCNE2 (Fig. 2B). By taking the intersection of the top 10 targets ranked by degree values and the top 10 targets ranked by MCC values, CCND1, MMP9, CCNB1, CCNA2, CDK1 and AR were selected as core targets for subsequent molecular docking and validation in animal experiments.

GO and KEGG pathway enrichment analysis. A total of 30 intersecting targets were subjected to gene enrichment analysis using DAVID. Among the 579 entries related to BP, the majority of the targets were involved in the 'regulation of cyclin-dependent protein serine/threonine kinase activity', 'regulation of cyclin-dependent protein kinase activity' and the 'negative regulation of epithelial cell differentiation'. CC yielded 29 entries, primarily 'serine/threonine protein kinase complex', 'cyclin-dependent protein kinase holoenzyme complex' and 'protein kinase complex'. MF yielded 93 entries, which predominantly included 'cyclin-dependent protein serine/threonine kinase regulator activity', 'kinase regulator activity' and 'protein kinase regulator activity'. The results with the top 10 count values were selected for visualization through bar graphs, demonstrating the BP, CC and MF components (Fig. 3A; Table SII).

KEGG pathway enrichment analysis was conducted using DAVID, resulting in the identification of 51 signaling pathways. These pathways were primarily associated with the 'cell cycle', 'PI3K-Akt signaling pathway', 'p53 signaling pathway' and 'JAK-STAT signaling pathway' amongst others. Subsequently, the top 20 pathways were selected based on their count value and a KEGG signaling pathway sankey diagram and dot plot was constructed (Fig. 3B; Table SIII).

Molecular docking results. Molecular docking was used to analyze the binding activities of six core targets (CCND1, MMP9, CCNB1, CCNA2, CDK1 and AR) to wogonin. It is generally considered that a docking energy value of <-7 kcal/mol indicates that the target protein binds strongly to small molecules, while a docking energy value of <-5 kcal/mol indicates a moderate binding affinity (32). The molecular

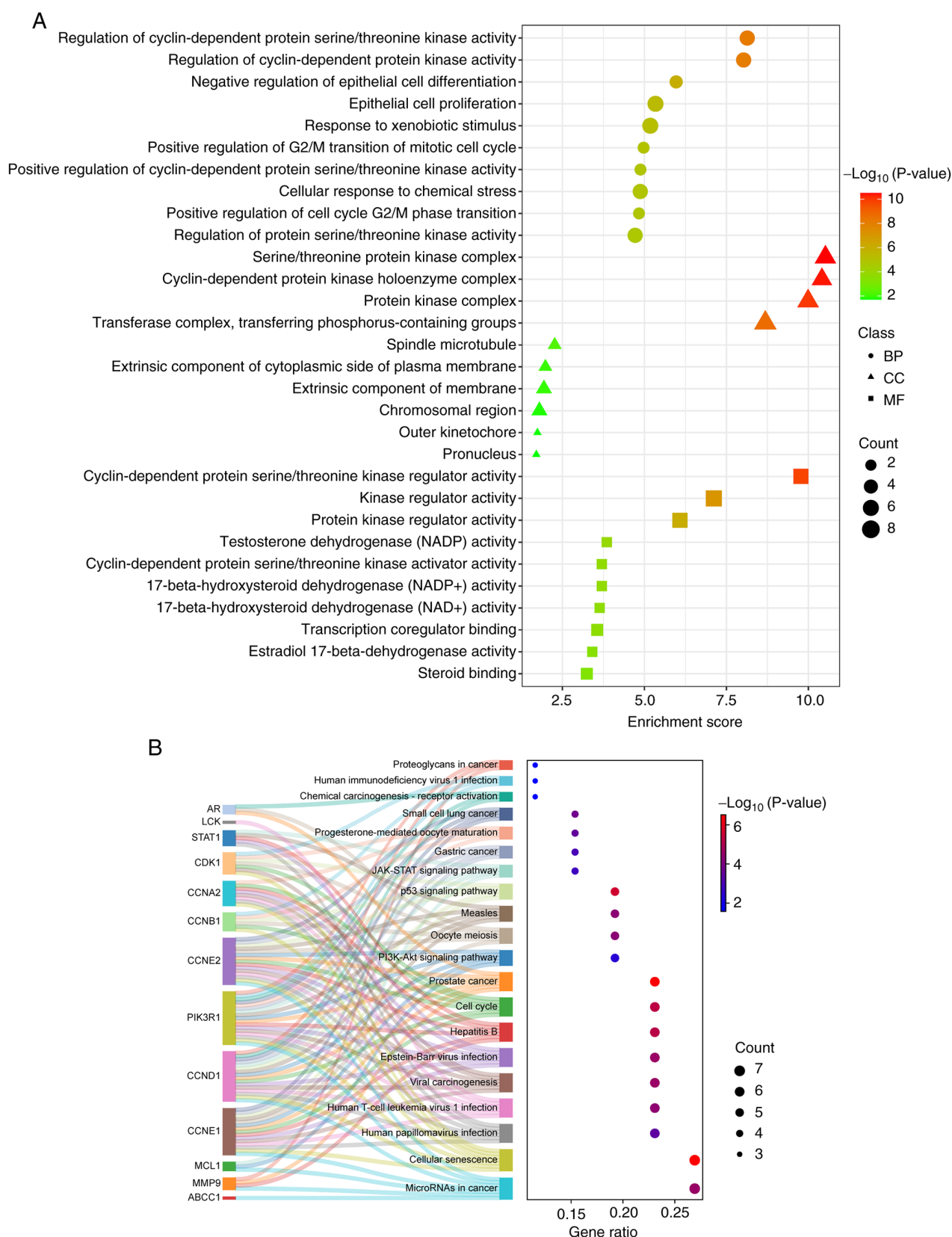


Figure 3. Results of GO and KEGG analysis. (A) GO analysis results for BP, CC and MF. The vertical axis represents the GO function name and the horizontal axis represents the enrichment score. (B) Sankey diagram and dot plot representing KEGG analysis results. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; BP, biological process; CC, cellular component; MF, molecular function.

docking results (Fig. 4; Table II) showed that the conformation of the active compound exhibited a strong binding effect to the protein targets, showing reliable interactions.

Wogonin alleviates psoriasis-like lesions in the IMQ-induced mouse model. To evaluate the ameliorative effect of wogonin on psoriasis-like lesions in IMQ-induced

Table II. Molecular docking results of wogonin and corresponding core targets.

Target name	PDB ID	Affinity, kcal/mol	Binding site (amino acid residues)
MMP9	1L6J	-8.080	ARG-424
CCND1	2W96	-7.644	LYS-33
CCNA2	6GVA	-9.378	LEU-83
CDK1	4Y72	-9.703	LEU-83 and GLU-81
CCNB1	6GU2	-8.178	LEU-83
AR	1E3G	-7.730	VAL-685

PDB, Protein Data Bank; MMP9, matrix metalloproteinase-9; CCND1, cyclin-D1; CCNA2, cyclin-A2; CDK1, cyclin-dependent kinase 1; CCNB1, cyclin-B1; AR, androgen receptor.

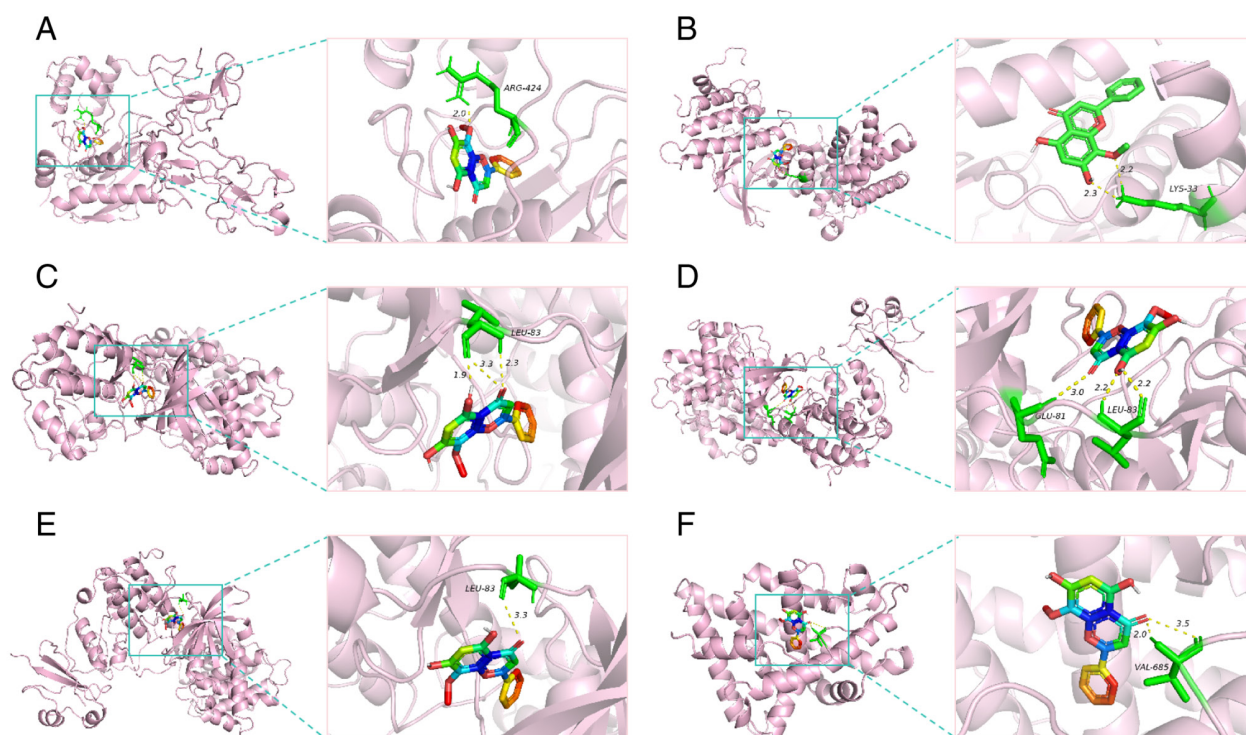


Figure 4. Molecular docking results. (A) Wogonin-matrix metalloproteinase-9, (B) wogonin- cyclin-D1, (C) wogonin-cyclin-A2, (D) wogonin-cyclin-dependent kinase 1, (E) wogonin- cyclin-B1 and (F) wogonin-androgen receptor. The values represent the lengths of hydrogen bonds, and the amino acids refer to the protein amino acid residues that have specific interactions with the ligand molecules.

mice, wogonin was administered to psoriasis mice (Fig. 5A). Following a 7-day intervention period, skin lesions were scored using the PASI system and pathological changes in the skin were observed using H&E staining. The PASI scores (Fig. 5B and C) of mice in the IMQ intervention group were significantly higher than those in the control group ($P<0.05$), while the PASI scores of mice in the IMQ + wogonin group were lower than those in the IMQ group, albeit not significantly different. The H&E staining results (Fig. 5D and E) demonstrated that the epidermis was thickened and epidermal protrusions were elongated in the IMQ group compared with those in the control ($P<0.05$), whereas the thickness of the epidermis was significantly reduced after wogonin treatment ($P<0.05$). These findings suggest that wogonin may be an effective intervention to improve skin damage in psoriasis-induced mice.

Regulation of core target proteins by wogonin. To further clarify the effect of wogonin on the expression of CCND1, MMP9, CCNB1, CCNA2, CDK1 and AR proteins in the skin of psoriasis-induced mice, protein expression was detected by immunohistochemistry. The results (Fig. 6) showed that, compared with that in the control group, CCND1 and CCNB1 expression in the skin tissues of mice in the IMQ group was significantly decreased ($P<0.05$), while MMP9, CCNA2, CDK1 and AR protein expression was significantly increased ($P<0.05$). Compared with that in the IMQ group, CCND1 and CCNB1 expression in the skin tissues of mice in the IMQ + wogonin group was significantly increased ($P<0.05$), while MMP9, CCNA2 and CDK1 protein expression was significantly decreased. These results suggest that CCND1, MMP9, CCNB1, CCNA2 and CDK1 may be key targets of wogonin in the treatment of psoriasis.

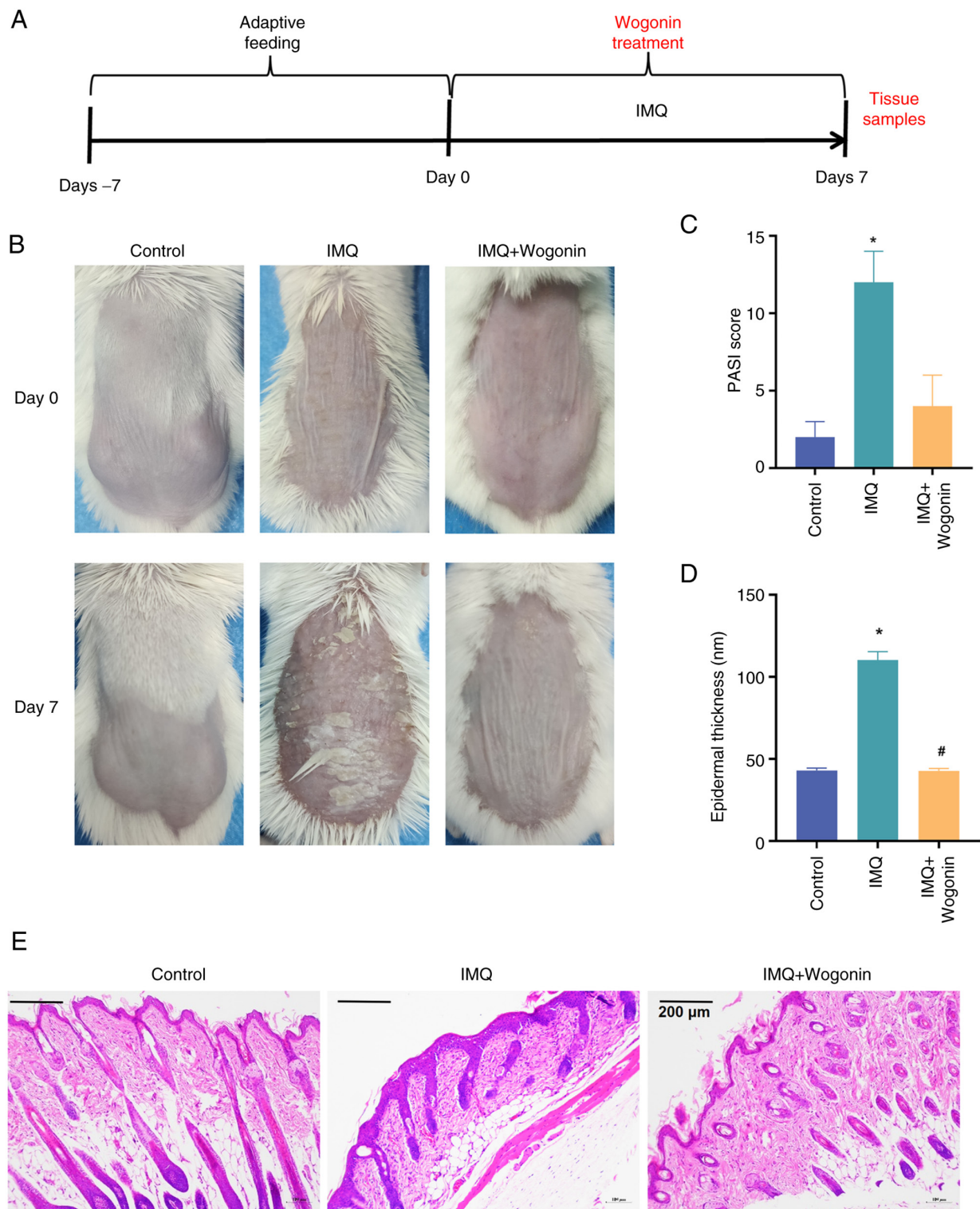


Figure 5. Wogonin intervention improves skin damage in psoriasis mice. (A) Schematic diagram of the animal experiment process. (B) Skin lesions of mice in each group after 0 and 7 days of treatment. (C) PASI scores of each group after 7 days of treatment. (D) Comparison of epidermal thickness in mice across groups. (E) H&E staining results (magnification, x100; scale bar, 200 μm). *P<0.05 vs. control; #P<0.05 vs. IMQ. IMQ, imiquimod; PASI, Psoriasis Area and Severity Index.

Verification of core targets through RNA-seq. To further validate the selected core targets, RNA-seq analysis was performed. The volcano plot illustrating the DEGs between the IMQ and control groups is shown in Fig. 7A, while Fig. 7B displays the corresponding plot for the wogonin group vs. the IMQ group. Fig. 7C summarizes the log₂ (fold change) values

and adjusted P-values of the core targets across pairwise comparisons among the three groups. The results showed that, compared with the control group, CCND1, CCNB1 and CDK1 were significantly downregulated in the IMQ group, while MMP9 and CCNA2 were significantly upregulated. By contrast, compared with the IMQ group, MMP9, CCNA2 and

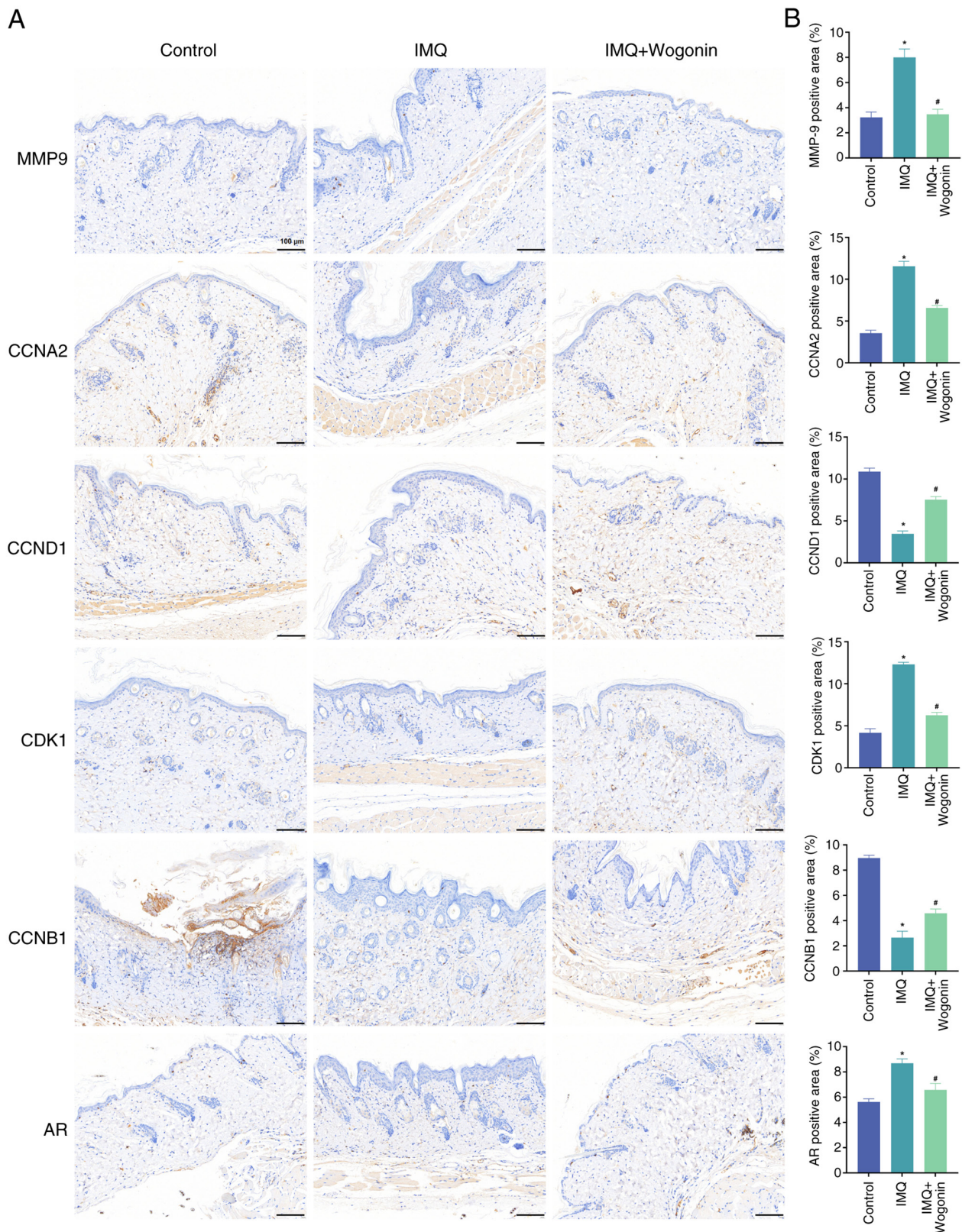


Figure 6. Wogonin reverses the expression of core proteins in psoriasis mice. (A) Representative image of immunohistochemical results for each protein (magnification, x40). (B) Histogram of relative expression levels for each protein. * $P < 0.05$ vs. control; # $P < 0.05$ vs. IMQ. IMQ, imiquimod; MMP9, matrix metalloproteinase-9; CCNA2, cyclin-A2; CCND1, cyclin-D1; CDK1, cyclin-dependent kinase 1; CCNB1, cyclin-B1; AR, androgen receptor.

CDK1 were significantly downregulated in the wogonin group, while CCND1 was significantly upregulated. These changes in MMP9, CCNA2 and CCND1 expression were consistent with the immunohistochemical findings.

Discussion

In the present study, the potential therapeutic effects of wogonin in the treatment of psoriasis were investigated using an

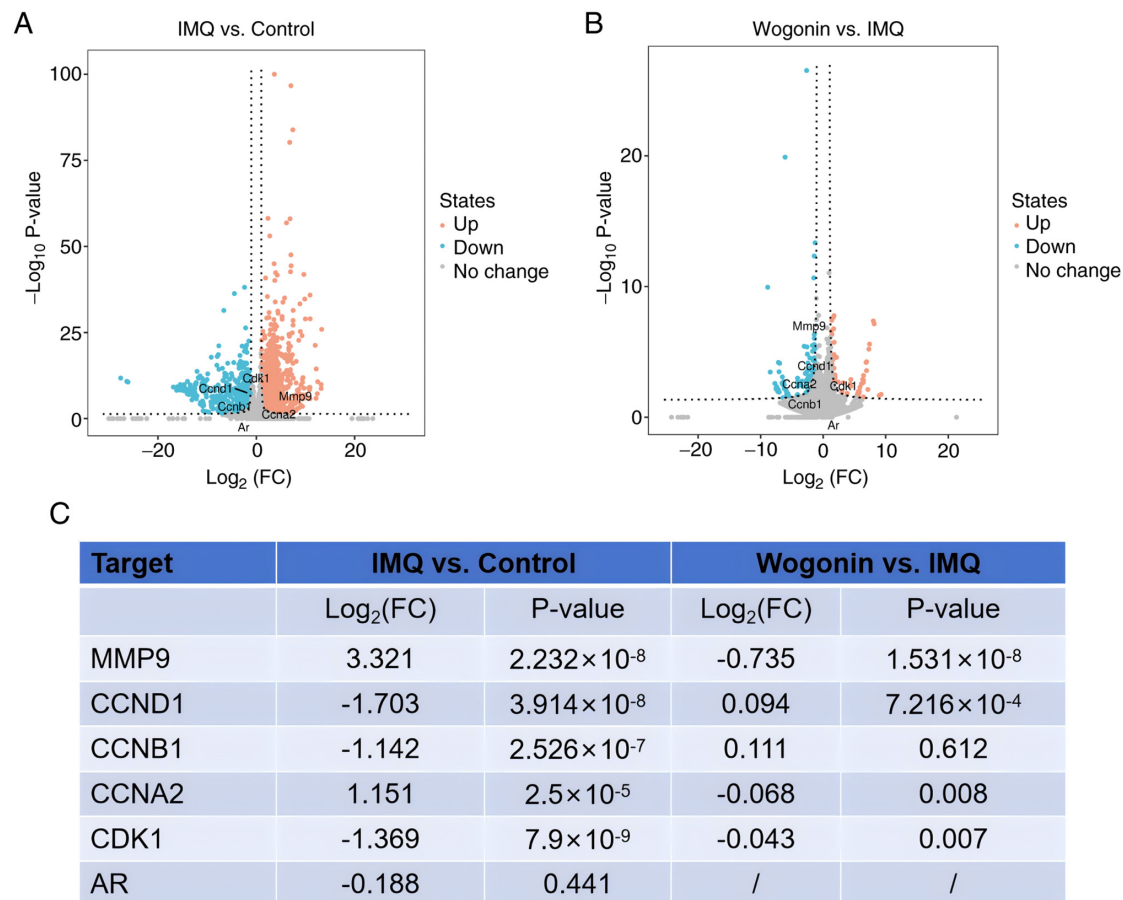


Figure 7. RNA sequencing analysis of core proteins in psoriasis mice. (A) Volcano plot of differentially expressed genes between the IMQ group and the control group. (B) Volcano plot of differentially expressed proteins between the wogonin group and the IMQ group. (C) $\log_2$ (FC) values and adjusted P-values of the core targets. IMQ, imiquimod; FC, fold change; MMP9, matrix metalloproteinase-9; CCND1, cyclin-D1; CCNB1, cyclin-B1; CCNA2, cyclin-A2; CDK1, cyclin-dependent kinase 1; AR, androgen receptor.

integrative methodology that combined network pharmacology, molecular docking and *in vivo* experiments. The present findings suggested that wogonin may alleviate psoriasis symptoms by targeting key proteins involved in the pathogenesis of psoriasis, including CCND1, MMP9 and CCNA2 (33-35). These results provide notable insights into the molecular mechanisms underlying the therapeutic effects of wogonin and emphasize its potential as a treatment option for psoriasis.

A key finding from the present network pharmacology analysis was the prominence of cell cycle regulators (CCND1 and CCNA2) among the core targets of wogonin. While MMP9 is a well-established mediator of inflammation, the identification of cell cycle components suggests a mechanism primarily focused on controlling keratinocyte hyperproliferation. However, accumulating evidence indicates that dysregulated cell cycle progression in keratinocytes is closely associated with the initiation and perpetuation of inflammation in psoriasis, creating a feedback loop (36,37). The accelerated proliferation of keratinocytes disrupts their normal differentiation, leading to the release of damage-associated molecular patterns and a repertoire of pro-inflammatory cytokines (such as IL-1 β , IL-6 and TNF- α), further amplifying the local immune response (38). Therefore, wogonin potentially disrupts this key source of inflammation by targeting and normalizing the cell cycle.

Additionally, the present network pharmacology analysis and molecular docking results identified CCND1, MMP9, CCNB1, CCNA2, CDK1 and AR as potential targets of wogonin. Immunohistochemical and RNA-seq analyses *in vivo* revealed that MMP9, CCNA2 and CCND1 may be key targets of wogonin in psoriasis. It is important to note that the observed incomplete consistency between RNA-seq (transcriptome level) and immunohistochemistry (protein level) for some targets (e.g., AR and CCNB1) is a recognized biological phenomenon. This discrepancy primarily arises as mRNA expression levels and final protein abundance are not always linearly correlated, being regulated by complex mechanisms including post-transcriptional regulation, translation efficiency and protein degradation. Consequently, differences in the magnitude of change and statistical significance between the two levels are not uncommon. The present study design followed the standard paradigm in genomic research: Using high-throughput RNA-seq for initial large-scale screening, followed by independent validation (e.g., immunohistochemistry) of core targets at the protein and tissue localization level, which is closer to the pathophysiological reality. The general concordance in the directional trends for the core targets (MMP9, CCNA2 and CCND1) between the two techniques supports the conclusions, while the specific variations highlight the value and necessity of integrated multi-omics

analysis. These proteins are involved in various cellular processes, such as cell cycle regulation, matrix remodeling and immune response modulation, all of which are key for the development and progression of psoriasis (39-41).

CCND1 is a key regulator of the cell cycle, facilitating the transition from the G₁ phase to the S phase (42,43). In psoriasis, CCND1 is often upregulated, leading to keratinocytes hyperproliferation, a hallmark of the disease (44). Notably, CCND1 overexpression has been shown to directly influence the expression of inflammatory genes in keratinocytes, thereby associating uncontrolled proliferation to a pro-inflammatory environment (45). Contrary to these studies, the present study found that CCND1 was significantly downregulated in the skin of mice induced by IMQ. However, treatment with wogonin could effectively restore its expression. This indicates that in the present model, the therapeutic effect of wogonin involves correcting the dysregulation of CCND1, which may help normalize the cell cycle process and inhibit the excessive proliferation of keratinocytes.

MMP9 is involved in the degradation of extracellular matrix components and is upregulated under inflammatory conditions, including psoriasis (46,47). This regulation contributes to the exacerbation of inflammation. Recent research has emphasized the involvement of MMP9 in the pathogenesis of psoriasis, with elevated levels of this enzyme being associated with greater disease severity (48). In the present study, wogonin was observed to downregulate MMP9, potentially contributing to the attenuation of inflammatory responses in psoriasis.

CCNA2 serves a key role in cell cycle regulation, particularly during the transition from the G₁ to the S phase (49). Dysregulation of CCNA2 has been observed in psoriasis, leading to abnormal proliferation of epidermal cells (50). A previous study reported upregulation of CCNA2 in psoriatic lesions, highlighting its importance in the pathogenesis of psoriasis (51). The present findings suggested that wogonin may downregulate CCNA2 to control keratinocyte proliferation and mitigate skin damage in psoriasis.

The *in vivo* animal experiments conducted in the present study corroborated the findings of network pharmacology and molecular docking analyses. Wogonin treatment resulted in a notable improvement in the skin lesions in a mouse model of psoriasis, as demonstrated by reductions in epidermal thickness.

Furthermore, immunohistochemical and RNA-seq analyses indicated that wogonin modulated the expression of key targets, including MMP9, CCNA2 and CCND1, in the skin tissue, thereby elucidating its potential mechanism of action in psoriasis treatment. Collectively, the present findings suggested that wogonin exerts therapeutic effects against psoriasis by modulating key targets involved in cell cycle regulation, matrix remodeling and immune response modulation.

We hypothesize that the anti-proliferative effect achieved through cell cycle modulation is associated with an anti-inflammatory outcome. Rather than being independent, normalizing the aberrant proliferation of keratinocytes directly may contribute to mitigating inflammation in psoriatic lesions. By targeting MMP9, CCNA2 and CCND1, wogonin may mitigate excessive cell proliferation and inflammation, which are hallmark features of psoriasis, thus providing a novel therapeutic strategy for managing this challenging dermatological condition.

Furthermore, KEGG pathway enrichment analysis revealed that the identified core targets are significantly involved in key inflammatory and immune-related signaling pathways implicated in psoriasis, such as the PI3K-Akt, JAK-STAT and p53 pathways (52-54). This suggests that the therapeutic effect of wogonin may extend beyond the direct modulation of individual targets such as MMP9, and also involve the broader normalization of dysregulated keratinocyte phenotype and immune response through these pivotal pathways.

However, the present study did not further validate these pathways, which constitutes a limitation. Although the present study provided promising preclinical evidence regarding the therapeutic effects of wogonin, further research is required to fully elucidate the specific molecular mechanisms underlying its action. In addition, clinical trials are essential to validate the efficacy and safety of wogonin in patients with psoriasis. The present study has also other limitations that should be considered when interpreting the results. Firstly, the anti-psoriatic efficacy of wogonin was evaluated at a single oral dose of 30 mg/kg/day. This dosage was selected as it lies within the established effective dose range (25-100 mg/kg) reported for wogonin in murine inflammatory disease models (55) and was supported by positive trends observed in preliminary experiments of the present study. While this dose was effective in alleviating psoriatic phenotypes, the lack of a full dose-response analysis means that the optimal therapeutic dose for psoriasis remains to be precisely determined. Secondly, a dedicated vehicle control group (IMQ-induced mice receiving the 0.5% sodium carboxymethyl cellulose solvent through gavage) was not included. This omission, primarily due to logistical constraints, limits the ability to completely rule out potential effects of the solvent or the gavage procedure itself. Future studies should incorporate multiple dosing regimens and a complete set of control groups to build upon these promising initial findings.

In summary, the present findings suggested that wogonin is a promising therapeutic agent for psoriasis, potentially exerting its effects by modulating multiple molecular targets, including MMP9, CCNA2 and CCND1. These results provide a foundation for future investigations into the application of wogonin as a potential treatment for psoriasis and other inflammatory skin disorders.

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Availability of data and materials

The sequencing data generated in the present study may be found in the Sequence Read Archive database of the National Center for Biotechnology Information under accession number PRJNA1344434 or at the following URL: <https://www.ncbi.nlm.nih.gov/sra/?term=PRJNA1344434>. The other data

generated in the present study may be requested from the corresponding author.

Authors' contributions

YL and XZ conceptualized the present study. DY, YG and JG contributed towards the design and formulation of the experimental plan. FZ was responsible for the statistical analysis/bioinformatics. FZ, JW and YX contributed towards to evaluation of the ultimate credibility of research results. Results analysis was conducted by YX and DY. The experimental investigation was conducted by YL, FZ and YL. DY contributed towards the acquisition of funding. JW and YL were responsible for data curation. YL was responsible for writing and preparing the original draft. DY reviewed and edited the manuscript. XZ contributed towards molecular docking visualization. DY supervised the study. YL performed project administration. DY acquired the funding. All authors read and approved the final version of the manuscript. YL and DY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The animal study protocol was approved by the Animal Experiment Ethics Committee of Yunnan University of Traditional Chinese Medicine (approval no. R-062021LH048).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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