Tropical Journal of Pharmaceutical Research May 2021; 20 (5): 973-979
ISSN: 1596-5996 (print); 1596-9827 (electronic)
© Pharmacotherapy Group, Faculty of Pharmacy, University of Benin, Benin City, 300001 Nigeria.

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v20i5.13

Original Research Article

Analysis of the effect of the Chinese herbal pair, Semen Persicae–Carthami Flos, on psoriasis using network pharmacology

Shibo Wang, Jiehao Lei, Xiuzu Song*
Department of Dermatology, Hangzhou Third People's Hospital, Hangzhou, Zhejiang Province 310009, China

For correspondence:* ***Email:* *songxiuzu@sina.com* ***Tel:*** *+86-13958021359*

Sent for review: 3 March 2021 *Revised accepted: 28 April 2021*

Abstract

Purpose: *To investigate the underlying effect of the Chinese herbal pair, Semen Persicae–Carthami Flos (PC), on psoriasis using network pharmacology.*
Method: *The core components and targets of the Chinese herbal pair were screened using TCMSP and BATMAN databases. Psoriasis disease targets were searched in OMIM and GeneCards databases. The common targets of the herbal pair and psoriasis were identified using a Venn diagram. The component–psoriasis-target network map was constructed using Cytoscape software. Protein interaction analysis, Gene Ontology, and Kyoto Encyclopedia of Genes and Genomes enrichment analysis were performed on STRING website, R Project, and DAVID 6.8 database. Molecular docking was performed using AutoDock Vina software to predict the binding of herbal pair PC to psoriasis targets.*
Results: *A total of 45 components and 105 potential targets of PC, as well as 3729 psoriasis-related genes, were screened from the databases. Venn diagram shows that there were 62 common targets of PC and psoriasis. These common targets involved biological processes such as DNA transcription factor receptor binding, cytokine receptor binding, and regulation of molecular function. The targets also involved apoptosis and the advanced glycation end-products (AGE)-receptor for AGEs (RAGE), tumor necrosis factor, and phosphatidylinositol 3-kinase/protein kinase B signaling pathways. In addition, the main active components of PC spontaneously bound to the targets.*
Conclusion: *The Chinese herbal pair PC provides an alternative clinical therapeutic strategy for patients with psoriasis.*

Keywords: *Network pharmacology, Molecular docking, Semen Persicae – Carthami Flos (PC), Chinese herbal pair, Psoriasis*

This is an Open Access article that uses a fund-ing model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Psoriasis is a chronic recurrent inflammatory skin disease with a global incidence of 1 %–2 %, which approaches 0.5 % in China [1]. The etiology of psoriasis is known to be related to genetic, environmental, and immune factors; drugs; and infection. At present, psoriasis is treated mainly with systemic application of retinoids, immunosuppressive agents,

© 2021 The authors. This work is licensed under the Creative Commons Attribution 4.0 International License

cyclosporine, biological agents, topical glucocorticoids, and vitamin D3 analogues as the main therapeutic measures [2]. Although the main existing therapeutic measures are effective, they do not relieve psoriasis for a long time and adverse reactions to the medication are serious. Therefore, the development of new drugs for the treatment of psoriasis has been an important topic of research in dermatology.

In traditional Chinese medicine (TCM), blood stasis syndrome is common in quiescent psoriasis and is one of the main symptoms of psoriasis. Semen Persicae–Carthami Flos (PC) is an herbal pair that promotes blood circulation and eliminates blood stasis in TCM [3]. Semen Persicae and Carthami Flos activate blood circulation, remove blood stasis, and relieve pain [3]. Modern pharmacological studies of PC have found that PC effectively promotes blood circulation, reduces blood viscosity, and exerts antithrombotic as well as anti-inflammatory effects [4]. Cyberpharmacology is a new discipline to study the pharmacological mechanisms of TCM, which can provide a comprehensive analysis of the mechanism of TCM through the integration of herbal pharmacology, high-throughput bioinformatics, and data analysis software systems.

In this study, the major components, key targets, and signaling pathways of PC were investigated through network pharmacology in order to provide a more comprehensive understanding of potential mechanisms and a reference basis for the basic and clinical research of PC on the treatment of psoriasis.

EXPERIMENTAL

Screening of active ingredients and potential targets of PC

All chemical components of PC were retrieved from the TCM Systematic Pharmacology analysis platform (TCMSP) and Bioinformatics Analysis Tool for Molecular Mechanism of Traditional Chinese Medicine (BATMAN-TCM). TCMSP contains more than 499 herbal medicines and their corresponding components (about 30,000) and provides relatively comprehensive drug activity data for each compound. BATMAN-TCM systematically displays the chemical composition of each herbal medicine, predicts its important targets, and performs bioinformatics analysis, thus helping researchers to comprehensively understand the pharmacological effects of herbal medicines. Using oral bioavailability (OB) ≥ 30 % and drug-likeness (DL) ≥ 0.18 as screening conditions, a PC-target dataset was then established by combining the composition-predicted targets of TCMSP and BATMAN-TCM.

Screening of disease targets

Psoriasis-related target information was obtained by searching Online Mendelian Inheritance in Man (OMIM, https://omim.org) and the Gene Cards database (https://genealacart.genecards.org) for relevant targets with a correlation ≥ 5 using the keyword "psoriasis" and deleting duplicate targets.

Construction of PC active-ingredient–target network

The common targets of the herbal pair and psoriasis were obtained by constructing a drug–disease-target Venn diagram, in order to obtain the mapping information of PC-component–psoriasis targets. The regulatory network of PC active-ingredients–targets was constructed using Cytoscape 3.7.2 software. In the construction process, the "node" information included TCM, active pharmaceutical ingredients, and a target. The relationship between nodes is represented by interaction lines.

Construction of protein-protein interaction network

Protein-protein interaction (PPI) analysis was performed by importing the common targets of psoriasis and PC in the STRING database (https://string-db.org/). "Homo sapiens" was selected as the screening condition and the minimum interaction score was chosen as 0.400 to construct the PPI network graph. The PPI results were imported into Cytoscape 3.7.2 software for visualization. The top 30 core target genes were filtered on the basis of the count value, and the potential core targets finally predicted.

Analysis of Gene Ontology function and Kyoto Encyclopedia of Genes and Genomes pathway enrichment

Gene Ontology **(**GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed on the common target proteins using R software and the DAVID database (https://david.ncifcrf.gov/). GO functional analysis is mainly used to depict the functions of gene targets, such as cellular, molecular, and biological functions. KEGG enrichment analysis can identify the signaling pathways enriched by the common targets of PC and psoriasis. GO functional analysis and enrichment analysis were statistically significant

at $p < 0.05$. The top 20 KEGG-ranked pathways were screened and combined with document searches to identify pathways that may be relevant to psoriasis treatment.

Potential active-ingredient–target-protein molecular docking study

The 3D structures of the core active ingredients of PC and the key targets were obtained from the PubChem database and the PDB database, respectively. These 3D structures were dehydrated, hydrogenated, and converted into PDBQT format, and then the batch molecular docking analysis was performed using AutoDock Vina 1.1.2 software. Usually, if the binding energy is < 0, the ligand and the receptor bind spontaneously. If the binding energy is ≤ -5.0 kJ/mol, the molecules will be well docked to the targets.

RESULTS

Active ingredients and potential targets of PC

After searching the active ingredients of PC in TCMSP and BATMAN-TCM and screening these active ingredients according to OB ≥ 30 % and DL ≥ 0.18, 45 potential core active ingredients and their 105 corresponding targets were finally obtained. The basic profile of major active ingredients in PC is detailed in Table 1.

Screening of psoriasis targets

A total of 3729 targets was obtained after searching psoriasis-related targets in OMIM and GENECARD databases and removing duplicate data. As shown in Figure 1, 62 common targets of PC and psoriasis were obtained by constructing a Venn diagram.

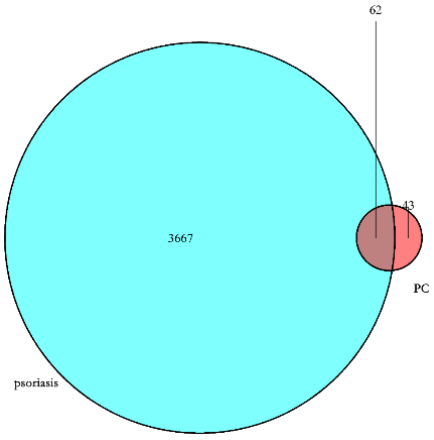

Figure 1: Venn diagram of PC and psoriasis targets

Table 1: Basic profile of major active ingredients of PC

Mol ID	Molecule Name	OB (%)	DL
MOL001328	2,3-Didehydro ga70	63.29	0.5
MOL002712	6-Hydroxykaempferol	62.13	0.27
MOL002717	qt_Carthamone	51.03	0.2
MOL000098	Quercetin	46.43	0.28
MOL002757	7,8-Dimethyl-1h-pyrimido[5,6-g]quinoxaline-2,4-dione	45.75	0.19
MOL002721	Quercetagetin	45.01	0.31
MOL000449	Stigmasterol	43.83	0.76
MOL002695	Lignan	43.32	0.65
MOL000422	Kaempferol	41.88	0.24
MOL001368	3-o-P-coumaroylquinic acid	37.63	0.29
MOL000493	Campesterol	37.58	0.71
MOL002773	Beta-carotene	37.18	0.58
MOL000296	Hederagenin	36.91	0.75
MOL000358	Beta-sitosterol	36.91	0.75
MOL000006	Luteolin	36.16	0.25
MOL002714	Baicalein	33.52	0.21

DL, drug-likeness; OB, oral bioavailability

Construction of PC active-ingredient–psoriasis target network

The information on the common targets and the mapping relationships between the active ingredients of PC and psoriasis were used to build a network diagram of PC active-ingredient–psoriasis targets (Figure 2). The constructed network was analyzed using the Network Analyzer function in Cytoscape 3.7.2 software, and the node importance was expressed using the degree function. The top five active ingredients in this network are quercetin, luteolin, kaempferol, β-sitosterol, and baicalein.

Construction of PPI network

The 62 common targets were imported into STRING, and the high confidence level of 0.900 was selected. The PPI.tsv file was downloaded to obtain a PPI network graph (Figure 3), which shows that there were 62 nodes and 624 interaction lines in the PPI network graph. The top 30 core target genes were selected based on the count value, and Figure 4 shows that the top 5 core target genes were serum albumin (ALB), interleukin 6 (IL-6), vascular endothelial growth factor A (VEGF-A), epidermal growth factor receptor (EGFR), and caspase-3. Moreover, the core target-related gene signaling pathways involved angiogenesis, inflammation, and apoptosis.

GO function enrichment analysis

In order to better understand the potential pharmacological activity of PC for the treatment of psoriasis, GO and KEGG enrichment analyses of common targets were performed using R software and the DAVID 6.8 database. Results of GO enrichment (Figure 5) showed that the targets of PC for psoriasis treatment affected 89 biological processes, including DNA transcription factor receptor binding, cytokine receptor binding, and regulation of molecular function.

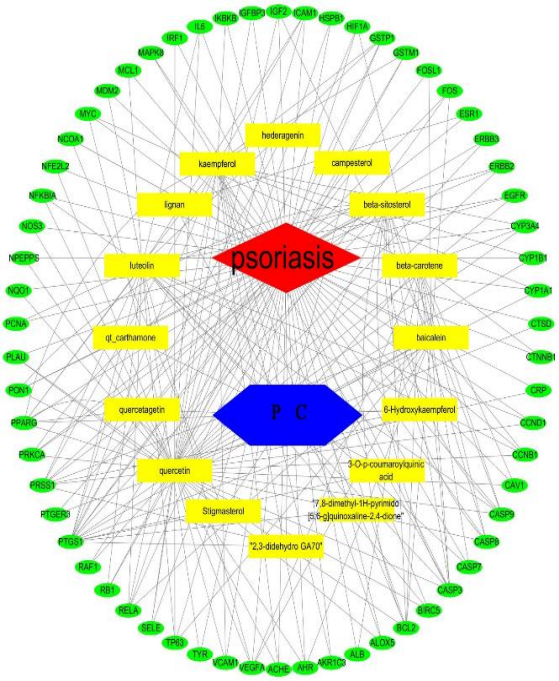

Figure 2: Regulatory network of PC-ingredient–psoriasis targets

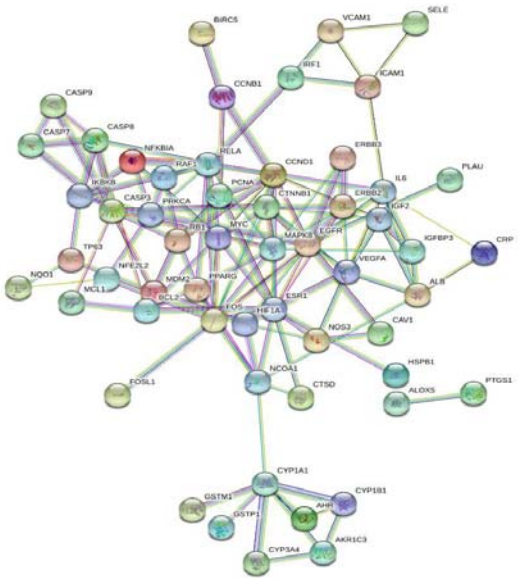

Figure 3: The interaction network of candidate targets of PC in psoriasis.

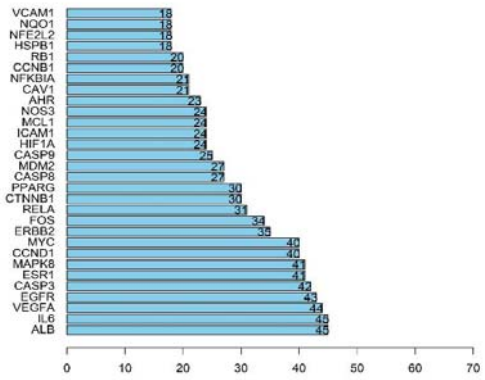

Figure 4: Interaction network of the top 30 PC candidate targets in psoriasis

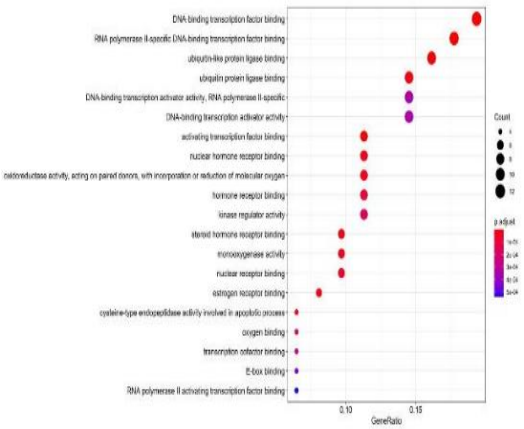

Figure 5: Bubble diagram of GO functional enrichment analysis of PC and psoriasis common target proteins

KEGG functional enrichment analysis

KEGG enrichment analysis yielded 121 signaling pathways. The top 20 pathways with high significance were selected for the bar graph based on the *p*-value magnitude in combination with literature search. The results (Figure 6) show that significant signaling pathways associated with psoriasis include fluid shear stress and atherosclerosis, the advanced glycation end-products (AGE)-receptor for AGEs (RAGE) pathway, apoptosis, tumor necrosis factor (TNF) pathway, and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway.

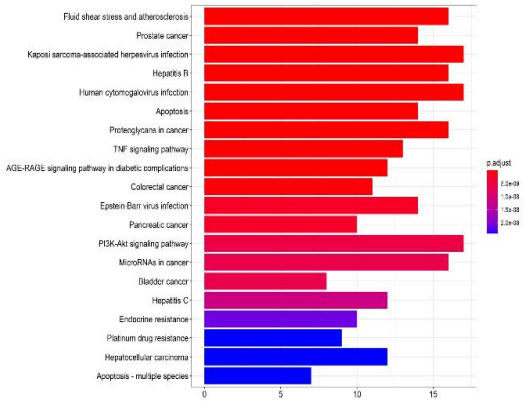

Figure 6: Histogram of the top 20 signaling pathways identified in KEGG pathway enrichment analysis

Potential active-ingredient–target-protein molecular docking analysis

The 3D structures of the five active ingredients (quercetin, luteolin, kaempferol, β-sitosterol, and baicalein) and the crystal structures of the five targets (ALB, IL-6, VEGF-A, EGFR, and caspase-3) were obtained from the PubChem database and the PDB database, respectively, and then subjected to bulk molecular docking analysis using AutoDock Vina 1.1.2 software. The results are shown in Table 2 and Figure 7. The binding energy of the five active ingredients docked to the main target was ≤ -5.0 kJ/mol, demonstrating that the molecules docked well to the targets. Notably, the most tightly bound was EGFR with luteolin. Therefore, quercetin, luteolin, kaempferol, β-sitosterol, and baicalein are the main active ingredients of PC for the treatment of psoriasis.

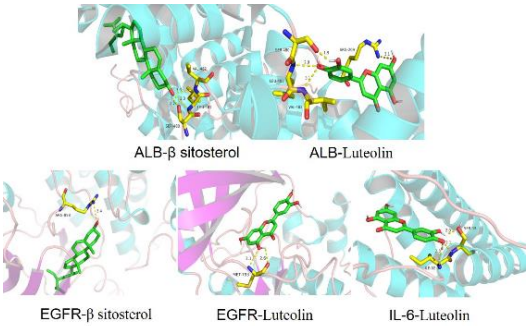

Figure 7: Molecular docking pattern. ALB, serum albumin; EGFR, epithelial growth factor receptor; IL-6, interleukin 6

DISCUSSION

The common symptoms of psoriasis include blood heat, blood dryness, and blood stasis [5]. The main dialectical idea of modern TCM treatment of psoriasis is “treatment based on different blood situation.” The main TCM treatment principles of psoriasis include cooling blood, nourishing blood, and promoting blood circulation. In TCM, PC is commonly used in psoriasis therapy, and PC is mostly used as a core medicine in TCM prescriptions. Semen Persicae is bitter and sweet in taste, neutral in nature, and activates blood circulation, eliminates blood stasis, loosens the bowel, and relieves cough and asthma. Carthami Flos is pungent in taste, warm in nature, and can activate blood circulation, disperse blood stasis, and relieve pain. Pharmacological studies have shown that Semen Persicae and Carthami Flos both have anti-inflammatory, anti-apoptosis, and immunity-enhancing effects. However, the mechanism of PC in psoriasis remains unclear.

Table 2: Molecular docking results of active ingredients in PC

Active ingredient	EGFR (kJ/mol)	ALB (kJ/mol)	IL-6 (kJ/mol)	CASP3 (kJ/mol)	VEGFA (kJ/mol)
β-Sitosterol	-9.2	-10.1	-7.7	-7	-6.8
Luteolin	-10.2	-8.1	-8.6	-6.1	-6
Quercetin	-7.4	-8	-7.6	-6.2	-5.6
Baicalein	-7.8	-7.9	-7.9	-6.3	-5.9
Kaempferol	-7.5	-7.8	-7.4	-6	-5.4

ALB, serum albumin; CASP3, caspase-3; EGFR, epithelial growth factor receptor; IL-6, interleukin 6; VEGFA, vascular endothelial growth factor A

Therefore, a network pharmacology approach was implemented to further explore the pharmacological mechanism of PC.

Through pharmacological activity screening, 45 active ingredients of PC were identified, including quercetin, luteolin, kaempferol, β-sitosterol, and baicalein. Quercetin is a flavonoid with anti-inflammatory and antioxidant activity [6]. Studies have shown that inflammatory factors, such as TNF-α, IL-6, and IL-17, are associated with the development of psoriasis, and the levels of TNF-α, IL-6, and IL-17 are significantly increased in the serum of psoriasis patients. Additionally, quercetin significantly promotes miR-146a expression, and miR-146a inhibits the levels of TNF-α, IL-6, and IL-17. Therefore, quercetin can be used to treat psoriasis by indirectly suppressing increases of TNF-α, IL-6, and IL-17 in serum of patients. Luteolin reduces the ratio of helper T cells (Th) 1/Th2 and Th17/regulatory T cells (Treg) in peripheral blood and suppresses the levels of Th1 and Th17, exerting an anti-inflammatory effect [7].

Kaempferol clearly reduces the levels of IL-6, IL-17A, nuclear factor kappa B (NF-κB), and TNF-α in serum, thus improving the inflammatory response in psoriatic lesions [8]. β-sitosterol exerts anti-inflammatory effects by inhibiting the expression of TNF-α [9]. Baicalein arrests the growth of keratinocytes by inhibiting their proliferation but does not accelerate keratinocyte apoptosis [10]. The results of this study showed that the binding energies of quercetin, luteolin, kaempferol, β-sitosterol, and baicalein were less than -5.0 kJ/mol, suggesting that these core active ingredients bind strongly to their targets.

The results of network pharmacological analysis showed that the potential targets of PC for the treatment of psoriasis include ALB, IL-6, VEGF-A, EGFR, and caspase-3. IL-6 is an inflammatory cytokine secreted by macrophages and is involved in the inflammatory response in the body. The level of IL-6 is significantly elevated in the skin lesions of psoriasis patients [11]. Li *et al* found that VEGF can be one of the targets for clinical treatment of psoriasis [12]. An early pathological change in psoriatic lesions is the infiltration of T lymphocytes. When activated, T lymphocytes invade the epidermis and release large amounts of epidermal growth factor and inflammatory mediators, which in turn promote the secretion of cellular chemokines, stimulating epidermal cell proliferation and inducing inflammatory responses by causing leukocytes in the blood to act on vascular endothelial cells. The caspase (CASP) family plays an important role in the biological process of apoptosis. Caspase-3 belongs to the effector CASPs, and its expression determines apoptosis [13]. In recent years, it has been found that in the CASP family, the expression of caspase-1, caspase-4, and caspase-5 is increased in psoriatic lesions, and caspase-5 shows especially high psoriasis specificity [14]. However, the relationship between caspase-3 expression and psoriasis has not yet been experimentally confirmed and is worthy of further research and exploration. GO functional enrichment analysis of the intersecting genes in this study showed that PC genes in psoriasis regulate DNA transcription factor receptor binding, RNA polymerase II promoter transcription, and the process of apoptosis. These results revealed that PC affects protein binding, enzyme binding, and transcription factor activity in psoriasis. The KEGG enrichment analysis showed that PC played a key role in the therapeutic targets of psoriasis mainly through TNF, AGE-RAGE, PI3K-AKT, and the apoptotic signaling pathway. The TNF pathway is the core signaling pathway of the inflammatory response and has an important role in psoriasis [15].

Network pharmacological analysis showed that PC mainly affects the NF-κB pathway in TNF-related pathways. The extracellular stimulation of TNF-α activated IκB kinase-2 (IKK-2)/NF-κB, and then produced IL-2, IL-6, and IL-8, thereby contributing to the pathological process of psoriasis [16]. The AGE-RAGE signaling pathway exacerbates the inflammatory response by affecting the NF-κB pathway [17]. The PI3K/AKT pathway is involved in cell proliferation, differentiation, apoptosis, and glucose transport. PI3K is an important kinase of inositol and phosphatidylinositol (PI), which can reduce the level and transcriptional activity of FOXO proteins in the nucleus through a series of signaling pathways, inhibiting FOXO-regulated cell cycle and apoptosis [18]. Caspase-3, caspase-8, Bax, and Bcl-2 are the important apoptotic regulators. Although caspase-3 and caspase-8 are highly expressed in psoriatic lesions, the precise regulatory effect in psoriasis needs further investigation.

A limitation of this study is that the accuracy of the pharmacologically active ingredients and targets found in this study was not verified experimentally.

CONCLUSION

The findings of the present study show that network pharmacology facilitates an understanding of the therapeutic effects of PC on psoriasis and also demonstrate the properties of

the Chinese herbal pair which may involve regulation of psoriasis target genes.

DECLARATIONS

Acknowledgement

This work was supported by the National Natural Science Foundation of China (Grant no. 81872517).

Competing interests

No conflict of interest is associated with this work.

Contribution of authors

We 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 the authors. Shibo Wang, Jiehao Lei, and Xiuzu Song designed the study, supervised the data collection, analyzed the data, interpreted the data, prepared the manuscript for publication, and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

Open Access

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

REFERENCES

1. *Karczewski J, Dobrowolska A, Rychlewska-Hańczewska A, Adamski Z. New insights into the role of T cells in pathogenesis of psoriasis and psoriatic arthritis. Autoimmunity 2016; 49(7): 435-450.*
2. *Kim WB, Jerome D, Yeung J. Diagnosis and management of psoriasis. Can Fam Physician 2017; 63(4): 278-285.*
3. *Fu J, Li X, Lu H, Liang Y. Analysis of volatile components in herbal pair Semen Persicae-Flos Carthami by GC-MS and chemometric resolution. J Sep Sci 2012; 35(21): 2940-2948.*
4. *Liu L, Duan JA, Tang Y, Guo J, Yang N, Ma H, Shi X. Taoren-Honghua herb pair and its main components promoting blood circulation through influencing on hemorheology, plasma coagulation and platelet aggregation. J Ethnopharmacol 2012; 139(2): 381-387.*
5. *Li Y, Dai X, Li J, Deng J, Wan C, Xu X, Liang F, Wang F, Zhong J. Notoginseng root enhances healing in imiquimod-induced psoriasis mice model via anti-inflammatory and antiproliferative properties. Trop J Pharm Res 2018; 17(12): 2365-2370.*
6. *Xiao J. Dietary flavonoid aglycones and their glycosides: Which show better biological significance? Crit Rev Food Sci Nutr 2017; 57(9): 1874-1905.*
7. *Lv J, Zhou D, Wang Y, Sun W, Zhang C, Xu J, Yang H, Zhou T, Li P. Effects of luteolin on treatment of psoriasis by repressing HSP90. Int Immunopharmacol 2020; 79: 106070.*
8. *Liu C, Liu H, Lu C, Deng J, Yan Y, Chen H, Wang Y, Liang CL, Wei J, Han L et al. Kaempferol attenuates imiquimod-induced psoriatic skin inflammation in a mouse model. Clin Exp Immunol 2019; 198(3): 403-415.*
9. *Yang Q, Yu D, Zhang Y. β-Sitosterol Attenuates the Intracranial Aneurysm Growth by Suppressing TNF-α-Mediated Mechanism. Pharmacology 2019; 104(5-6): 303-311.*
10. *Huang KF, Ma KH, Liu PS, Chen BW, Chueh SH. Baicalein increases keratin 1 and 10 expression in HaCaT keratinocytes via TRPV4 receptor activation. Exp Dermatol 2016; 25(8): 623-629.*
11. *Lai Y, Li D, Li C, Muehleisen B, Radek KA, Park HJ, Jiang Z, Li Z, Lei H, Quan Y et al. The antimicrobial protein REG3A regulates keratinocyte proliferation and differentiation after skin injury. Immunity 2012; 37(1): 74-84.*
12. *Li W, Man XY, Chen JQ, Zhou J, Cai SQ, Zheng M. Targeting VEGF/VEGFR in the treatment of psoriasis. Discov Med 2014; 18(98): 97-104.*
13. *Porter AG, Jänicke RU. Emerging roles of caspase-3 in apoptosis. Cell Death Differ 1999; 6(2): 99-104.*
14. *Salskov-Iversen ML, Johansen C, Kragballe K, Iversen L. Caspase-5 expression is upregulated in lesional psoriatic skin. J Invest Dermatol 2011; 131(3): 670-676.*
15. *Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. Int J Mol Sci 2019; 20(6).*
16. *Viemann D, Goebeler M, Schmid S, Klimmek K, Sorg C, Ludwig S, Roth J. Transcriptional profiling of IKK2/NF-kappa B- and p38 MAP kinase-dependent gene expression in TNF-alpha-stimulated primary human endothelial cells. Blood 2004; 103(9): 3365-3373.*
17. *Byun K, Yoo Y, Son M, Lee J, Jeong GB, Park YM, Salekdeh GH, Lee B. Advanced glycation end-products produced systemically and by macrophages: A common contributor to inflammation and degenerative diseases. Pharmacol Ther 2017; 177: 44-55.*
18. *Tzivion G, Dobson M, Ramakrishnan G. FoxO transcription factors; Regulation by AKT and 14-3-3 proteins. Biochim Biophys Acta 2011; 1813(11): 1938-1945.*