IFSCC 2025 full paper (IFSCC2025-679)

"Network Pharmacology and Experimental Validation of a Novel Multi-Herbal Extract in Acne Treatment: Mechanisms of Action"

Yina Sheng[1]*, Jianhui Chen[1], Haoyu Wang[1], Peng Han[1] and Jiaming Xu[1]

[1] Shenzhen Yusu Biotechnology Co., Ltd.

1. Introduction

Acne is a chronic inflammatory disorder of the pilosebaceous unit, commonly affecting the face, chest, and back. It impacts approximately 9.4% of the global population and is associated with clinical sequelae, psychological distress, and social anxiety [1]. According to the Global Burden of Disease (GBD) study, acne remains among the most prevalent inflammatory skin conditions worldwide, with increasing incidence and prevalence [2].

Acne pathogenesis is multifactorial, involving excessive sebum production, follicular hyperkeratinization, *Cutibacterium acnes* (C. acnes) colonization, and an exaggerated inflammatory response. These factors are interrelated and reinforce each other, making monotherapies often insufficient for sustained remission.

Conventional treatments such as retinoids and antibiotics primarily target sebum production, inflammation, or bacterial load, but are limited by adverse effects and the risk of antibiotic resistance [3, 4]. Moreover, these therapies do not address all pathogenic factors simultaneously, often leading to incomplete treatment outcomes [5]. Thus, there is a growing need for multi-targeted, well-tolerated therapies.

Traditional Chinese Medicine (TCM) offers a promising approach through multi-component herbal formulations. Based on classic prescriptions such as *Shizensan* and *Longdan Xiaocuo Fang*, a novel seven-herb formula, Pureduce, was developed using *Sophora angustifolia*, *Phellodendron chinense*, *Gentiana scabra*, *Cnidium monnieri*, *Chrysanthellum indicum*, *Glycyrrhiza inflata*, and *Cinnamomum camphora* [6, 7]. These herbs exhibit anti-inflammatory and antimicrobial properties [8-14], with several components reported to inhibit *C. acnes* growth and reduce sebum production [9, 15-18].

Combining multiple extracts may enhance efficacy and reduce side effects via synergistic interactions [19]. This study investigates the potential mechanisms and biological activities of Pureduce against acne using network pharmacology, molecular docking, and experimental validation of its antimicrobial, anti-inflammatory, and anti-sebum effects.

2. Materials and Methods

Pureduce bioactive component and molecular target screening

The active ingredients associated with *Sophora angustifolia, Gentiana scabra, Cnidium monnieri*, and *Glycyrrhiza inflata* were extracted from the traditional Chinese medicine systems pharmacology database and analysis platform (TCMSP, https://old.tcmsp-e.com/tcmsp.php) (oral bioavailability (OB) ≥ 30, drug-likeness (DL) ≥ 0.18). Subsequently, the active ingredient-related targets were obtained. The active ingredients related to *Phellodendron chinense*, *Cinnamomum camphora* were acquired from the HERB database (http://herb.ac.cn/) based on OB ≥ 30, DL ≥ 0.18 thresholds, while their corresponding targets were retrieved from the TCMSP database. Active ingredients linked to *Chrysanthellum indicum* were sourced from literature reference[20] and their respective targets were predicted utilizing the SwissTargetPrediction database (http://www.swisstargetprediction.ch/). The molecular targets were derived from the combination of the targets of these seven medical herbs.

Collection of targets associated with acne

The GeneCards (http://www.genecards.org) (Relevance score > 1), Online Mendelian Inheritance in Man (OMIM, http://www.OMIM.org), and DisGeNET (http://www.disgenet.org/) databases were queried using "Acne" as keywords to predict targets associated with acne. Then, to clarify the interaction between Pureduce and acne, drugs and disease targets were input into the online Venny tool (https://bioinfogp.cnb.csic.es/tools/venny/index.html) to generate a Venn diagram.

Construction of a "Drug-Active Component- Common Target" Network

A network called "drug-active component-common target" was constructed using the connections between medications, active components and gene symbols The network was visually analyzed using the Cytoscape program (v3.9.0).

Construction of a protein-protein interaction (PPI) network

The candidate targets were inputted into the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (https://cn.string-db.org/) to analyze their interaction at protein levels (confidence > 0.4) and construct a PPI network. Afterthat, the cytoHubba plugin from Cytoscape software (v 3.9.1) [21] was utilized to identify the top 8 genes based on various algorithms, including Maximum Neighborhood Component (MNC), Degree, Edge Percolated Component (EPC), Closeness, and Radiality. The key targets were obtained through the intersection of the top 8 genes in these algorithms. According to the active ingredient-gene relationship, the top 50% significance of key targets were chosen as core targets for visualization of active ingredient-core target network.

GO and KEGG Analysis

The clusterProfiler package (v 4.7.1.3) [22] was utilized to perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses on the common targets of Pureduce associated with acne with an adjusted *P*-value threshold of less than 0.05.

Molecular docking

The active ingredients who interacted with all significant targets were selected for molecular docking. The protein molecular crystal structures of key genes were downloaded from the Protein Data Bank (PDB) database (https://www.rcsb.org/), along with the molecular structures of active ingredients available on PubChem (http://pubchem.ncbi.nlm.nih.gov). AutoDock (v 1.2.0) [23] was adopted to perform molecular docking.

***C. acnes* Proliferation Inhibition Analysis**

The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of Pureduce against *C. acnes* were determined using a two-fold broth dilution method [24]. Briefly, *C. acnes* ATCC 6919 was cultured anaerobically in BHI broth to the stationary phase, adjusted to $OD_{600} \approx 0.9$, and resuspended in a glycerol-based cryopreservation solution (1:4). For MIC testing, 200 μL of bacterial suspension (10^6 CFU/mL) was added to 96-well plates with serially diluted Pureduce. After 48 h of anaerobic incubation, the MIC was recorded as the lowest concentration inhibiting visible growth. For MBC determination, cultures from MIC wells were transferred to fresh BHI plates and incubated for another 48 h; the lowest concentration showing no bacterial growth was defined as the MBC. OD_{600} was measured using a microplate reader (Bio-Tek, USA).

Cell culture

Mouse macrophage-like RAW 264.7 cells were purchased from China cell link bank and were grown in Eagle's minimal essential medium supplemented with 10% fetal calf serum (Gibco, US). Human SZ95 sebocytes were purchased from Qingqi (Shanghai) Biotechnology Development Co., Ltd. and were cultured in Sebomed® Basal Medium (Biochrom, Germany) supplemented with 10% fetal bovine serum (DCELL, China), 100 U/mL penicillin and 100 g/ml streptomycin (Gibco, US). Cells were maintained in a humidified incubator at 37℃ in 5% CO_2 air atmosphere. The culture medium was refreshed every day.

Cytotoxicity analysis

The cytotoxicity of Pureduce was assessed using a CCK-8 assay (Beyotime, China). RAW264.7 and SZ95 cells were seeded in 96-well plates (2×10^4 and 1×10^4 cells/well, respectively) and treated with gradient concentrations of Pureduce for 24 h. After incubation with CCK-8 reagent for 1 h at 37°C, absorbance was measured at 490 nm using a microplate reader (Epoch, BioTek, USA).

Pro-inflammatory cytokine measurement

RAW264.7 cells (5×10^4 cells/mL) were stimulated with 500 ng/mL LPS for 24 h, then treated with various concentrations of Pureduce for another 24 h. Parthenolide (1 μg/mL) was used as a positive control. Levels of IL-1β, IL-6, and TNF-α in the culture supernatants were quantified using ELISA kits (Invitrogen, USA).

Oil red O (ORO) staining

ORO staining was performed to assess lipid accumulation in SZ95 sebocytes. Cells were co-treated with 10 mM oleate/palmitate (2:1, v/v) and different concentrations of Pureduce for 48 h. Isotretinoin (3 μg/mL) served as a positive control. Cells were fixed, stained with ORO solution, de-stained with 60% isopropanol, counterstained with hematoxylin, and imaged under light microscopy (ECOH, USA).

Western blot analysis

Cells were lysed in RIPA buffer with protease inhibitors, and protein concentrations were quantified using a BCA assay (Thermo Scientific, USA). Equal amounts of protein were separated by SDS-PAGE and transferred to PVDF membranes. After blocking, membranes were probed with antibodies against AKT and phospho-AKT. Band intensities were analyzed using ImageJ software (NIH).

Statistical analysis

The data processing and analysis were conducted using the R software (v 4.2.2). A significance level was determined by $p < 0.05$.

3. Results

Screening of Pureduce active ingredients and anti-acne molecular targets

Based on TCMSP databases, HERB databases and published researches, a total of 166 active ingredients of Pureduce were screened. Based on TCMSP databases and Swisstarget prediction, 389 probable Pureduce active targets and gene symbols were identified. After integrating results from GeneCards, OMIM, and DisGeNET databases, 861 targets associated with acne were acquired. The intersection of Pureduce durg targets and acne disease targets included 88 common targets, which were the potential targets of Pureduce in the treatment of acne (Figure 1A).

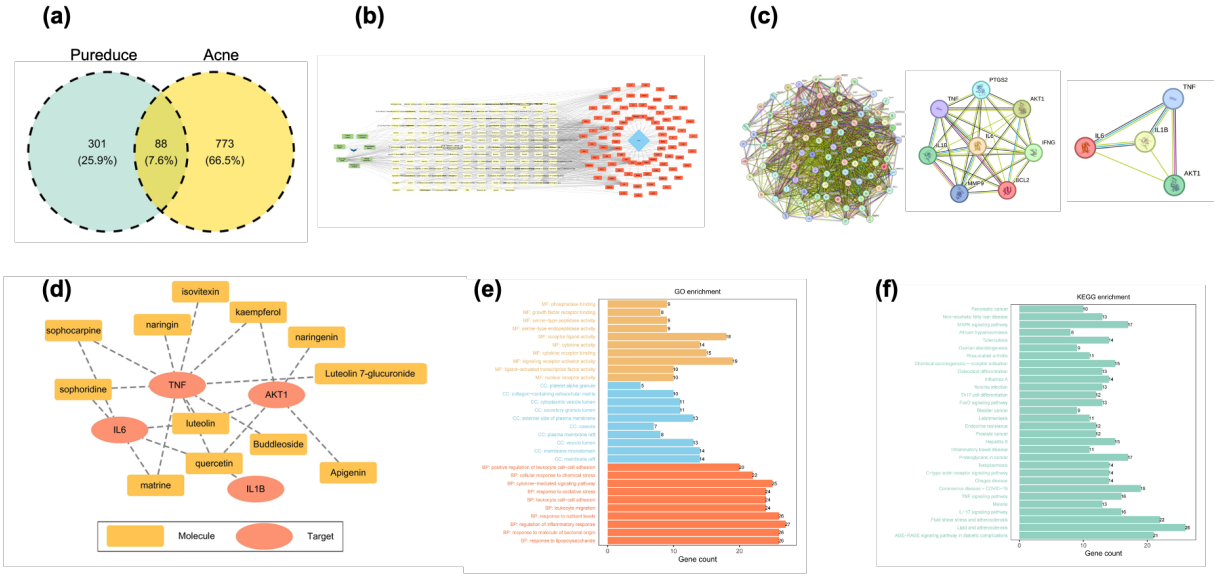

Figure 1 Network pharmacology analysis of Pureduce on acne. (a) Veen diagram and candidate targets of Pureduce and acne. (b) "Drug-Active Component-Common Target" of Pureduce ameliorating acne (green rectangle: Pureduce composition; yellow rectangle: the active ingredients of Pureduce; red rectangle: overlapping targets of Pureduce and acne.) (c) PPI network of targets of Pureduce on acne. (d) "Core Target-Active Component" of Pureduce ameliorating acne. (e) GO enrichment analysis of targets of Pureduce. (f) Analysis of KEGG enrichment in 30 pathways as targets of Pureduce.

Constructing of the "Drug-Active Component-Common Target" network and PPI networks

A "drug–active component–common target" network was constructed using Cytoscape based on the 153 active ingredients of Pureduce, 88 common targets, and 7 medicinal herbs (Figure 1B). The 88 targets were further analyzed using the STRING database to build a protein–protein interaction (PPI) network. Using the cytoHubba plugin, eight hub genes were identified: TNF, IL6, IL1B, AKT1, MMP9, IFNG, PTGS2, and BCL2, based on multiple topological algorithms including MNC, Degree, EPC, Closeness, and Radiality. Among them, TNF, IL6, IL1B, and AKT1 were selected as core targets due to their high significance (Figure 1C).

To further investigate the interaction between active components and core targets, an "active ingredient–core target" network was constructed. A total of 12 active compounds, including quercetin, luteolin, sophocarpine, kaempferol, sophoridine, matrine, naringin, isovitexin, naringenin, luteolin 7-glucuronide, apigenin, and buddleoside, were found to interact with the core targets. Notably, quercetin showed interaction with all four core targets (Figure 1D).

GO and KEGG analysis

GO enrichment analysis of the 88 common targets yielded 2182 significant terms, primarily associated with biological processes such as inflammatory response regulation, leukocyte migration, and response to oxidative or bacterial stress (Figure 1E). KEGG pathway analysis identified 151 enriched pathways, including IL-17, TNF, AGE-RAGE, MAPK, and FoxO signaling, suggesting that Pureduce exerts anti-acne effects by modulating inflammation and lipid metabolism (Figure 1F).

Molecular docking

Molecular docking analysis was performed between the 4 core targets (TNF, IL6, IL1B, AKT1) and 12 active compounds of Pureduce using AutoDock. Seven target-ligand pairs exhibited binding affinities < –5 kcal/mol, indicating strong spontaneous binding (Figure 2).

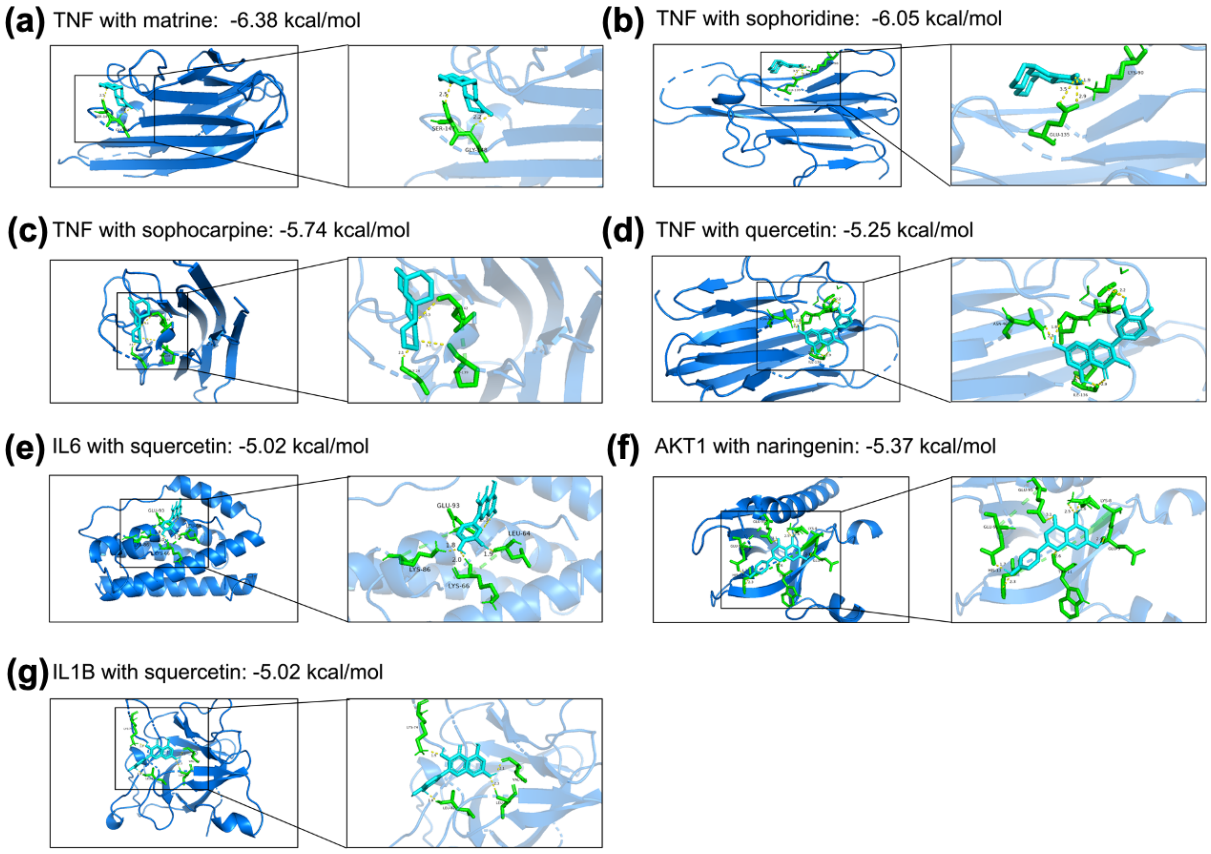

Figure 2 Molecular docking diagram. (a) TNF with matrine. (b) TNF with sophoridine; (c) TNF with sophocarpine. (d) TNF with quercetin. (e) IL6 with quercetin. (f) AKT1 with naringenin. (g) IL1B with quercetin.

Pureduce has anti-*C. acnes* activity

Pureduce exhibited potent antibacterial activity against *C. acnes* ATCC 6919, with both MIC and MBC values of 2.4 μg/mL (Figure 3).

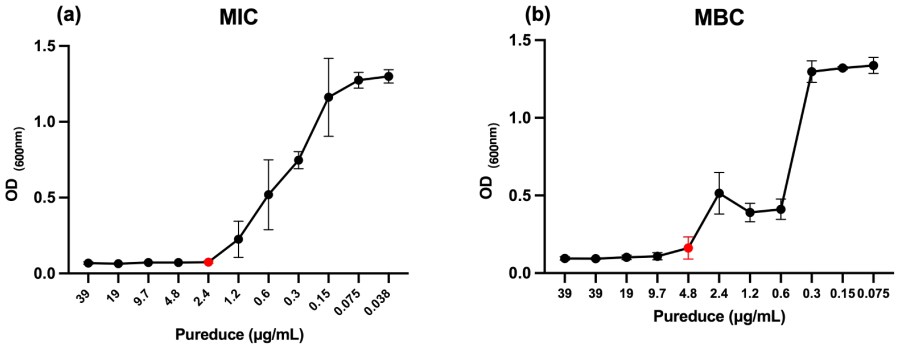

Figure 3 Anti-*C. acnes* activity of Pureduce. (a) MIC value of Pureduce against *C. acnes*. (b) MBC value of Pureduce against *C. acnes*. MIC, minimal inhibi- tory concentration; MBC, minimal bactericidal concentration.

Pureduce suppressed the production of inflammatory factor in LPS induced RAW 264.7 cells

CCK-8 assay showed that Pureduce had no significant cytotoxicity below 78 μg/mL (Figure 4A). At this concentration, Pureduce significantly reduced LPS-induced secretion of TNF-α, IL-1β, and IL-6 in RAW264.7 cells, as measured by ELISA (Figure 4B–D), confirming its anti-inflammatory efficacy.

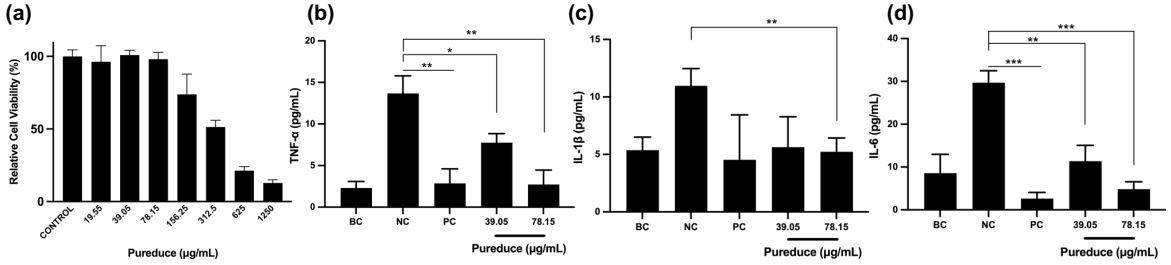

Figure 4 Anti-inflammatory activity of Pureduce. (a) Cytotoxicity of Pureduce towards RAW 264.7 cells. (b-d) Effects of Pureduce on TNF-α (B), IL-1β (C) and IL-6 (D) levels stimulated LPS. *p < 0.05, **p < 0.01, ***p < 0.001 were significantly different compared with the negative control group with LPS but without Pureduce.

Pureduce reduced the lipogenesis and AKT phosphorylation in SZ95 cells

Pureduce showed no significant cytotoxicity on SZ95 cells at concentrations below 250 ng/mL (Figure 5A). ORO staining revealed that Pureduce dose-dependently inhibited OA/PA-induced lipogenesis, with near-complete suppression at 40 ng/mL (Figure 5B&C). It is published that AKT and AKT phosphorylation are involved in lipogenesis of various cell lines, e.g., sebocytes, hepatocytes, adipocytes[25-27]. Western blot analysis further showed that Pureduce reduced AKT phosphorylation (Ser473) in a dose-dependent manner (Figure 5D&E), suggesting an AKT-mediated mechanism for its anti-lipogenic effect.

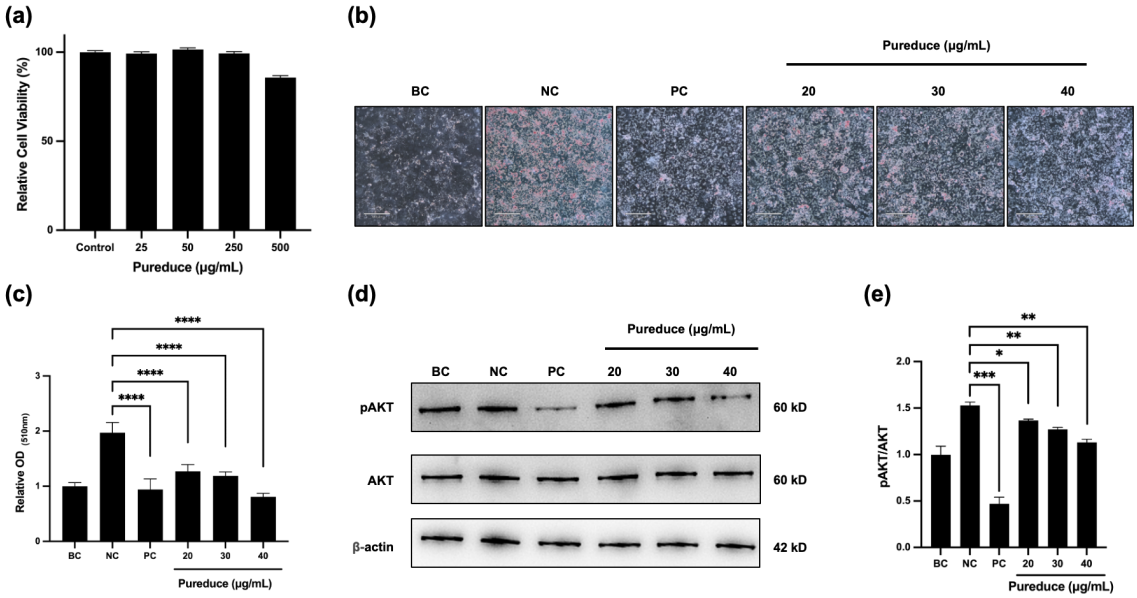

Figure 5 Anti-lipogenic activity of Pureduce. (a) Cytotoxicity of Pureduce towards SZ95 cells. (b) ORO staining of lipid accumulation in SZ95 cells. (c) Quantification of ORO staining intensity in SZ95 cells. (d) pAKT and AKT protein levels in SZ95 cells. (e) Quantification of pAKT/AKT protein levels in SZ95 cells. ORO, Oil Red O. *p < 0.05, **p < 0.01, ***p < 0.001 were significantly different compared with the negative control group with OA/PA but without Pureduce.

4. Discussion

Acne is a prevalent dermatological disorder that affects both physical appearance and psychosocial health. Despite the widespread use of conventional treatments, their side effects and the growing issue of antibiotic resistance underscore the need for safer, multi-targeted alternatives. Herbal medicines, with their favorable safety profiles, have emerged as promising candidates [28]. In this study, the therapeutic potential of the multi-herbal TCM formulation Pureduce was explored via network pharmacology and in vitro experiments. Pureduce was found to be associated with 88 acne-related targets, involving pathways related to bacterial recognition, inflammation, and lipid metabolism.

C. acnes is a major contributor to acne pathogenesis by activating Toll-like receptors (TLRs), which trigger downstream inflammatory cascades leading to hyperseborrhea and follicular hyperkeratinization [29]. Pureduce exhibited potent antibacterial activity against *C. acnes* ATCC 6919, with an MIC and MBC of 2.4 μg/mL, comparable to common antibiotics (Figure 3), supporting its potential as an antimicrobial agent.

Key inflammatory mediators such as TNF-α, IL-1β, and IL-6, known to be upregulated in acne lesions and correlated with disease severity [30, 31]. were significantly suppressed by Pureduce in LPS-stimulated RAW 264.7 macrophages (Figure 4B–D), confirming its anti-inflammatory efficacy. AKT1, another core target identified, is involved in lipogenesis regulation [32]. Pureduce significantly inhibited lipid accumulation in SZ95 sebocytes in a dose-dependent manner (Figure 5B&C), and suppressed AKT phosphorylation (Ser473) (Figure 5D&E), indicating that its anti-lipogenic effects may be mediated via the AKT1 pathway. Notably, lipid accumulation was nearly reversed at 40 μg/mL, although AKT phosphorylation

was only partially reduced, suggesting additional pathways may contribute to the lipogenesis inhibition.

Molecular docking further supported the involvement of TNF, IL6, IL1B, and AKT1 as targets of active compounds in Pureduce, including matrine, sophoridine, sophocarpine, quercetin, and naringenin. These phytochemicals have documented anti-inflammatory and anti-lipogenic activities[33-35]. For instance, matrine has shown promise in enhancing azelaic acid delivery through microneedles [36], and sophoridine has demonstrated therapeutic potential in chronic inflammatory conditions [37]. Quercetin and naringenin also exhibit broad bioactivities, with recent formulations improving acne outcomes through enhanced delivery and AKT modulation [38-42]. In summary, Pureduce exerts its anti-acne effects via antimicrobial, anti-inflammatory, and anti-lipogenic activities, likely through modulation of TNF-α, IL-6, IL-1β, and AKT1. Future studies should quantify its active constituents via LC-MS or HPLC to better understand the dose-effect relationships and standardize clinical applications.

5. Conclusion

In this study, network pharmacology analysis identified key active molecules and potential therapeutic targets of a novel multi-herbal extract Pureduce in acne treatment. The in vitro experiments further validated its pharmacological effects, demonstrating that Pureduce exerts anti-acne activity through multiple mechanisms, including inhibiting *C. acnes* growth, suppressing pro-inflammatory cytokine secretion, and reducing sebocyte lipogenesis via AKT1 inhibition. These findings provide mechanistic insights into the therapeutic potential of Pureduce and establish a theoretical foundation for further in-depth studies, including in vivo validation and clinical application exploration.

Refernce

1. Vos, T., et al., *Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010.* The Lancet, 2012. **380**(9859): p. 2163-2196.

2. Wang, Y., et al., *Analysis of the epidemiological burden of acne vulgaris in China based on the data of global burden of disease 2019.* Frontiers in Medicine, 2022. **9**: p. 939584.

3. Otlewska, A., W. Baran, and A. Batycka-Baran, *Adverse events related to topical drug treatments for acne vulgaris.* Expert Opinion on Drug Safety, 2020. **19**(4): p. 513-521.

4. Reynolds, R.V., et al., *Guidelines of care for the management of acne vulgaris.* Journal of the American Academy of Dermatology, 2024. **90**(5): p. 1006. e1-1006. e30.

5. Li, Y., et al., *Acne treatment: research progress and new perspectives.* Front Med (Lausanne), 2024. **11**(2296-858X (Print)): p. 1425675.

6. Hede, Q., Z. Yong, and D. Xin, *Observation on the clinical efficacy of Longdan Xiaocuo Fang in treating 540 cases of acne.* Chinese Journal for Clinicians, 2014. **42**(03): p. 70-71.

7. Zhouhong, Y., *A Brief Discussion on the Clinical Efficacy of Treating Infant Eczema with Eczema Powder.* Contemporary Medicine Forum, 2014. **12**(07): p. 281-282.

8. Chiu, Y.J., et al., *Chinese Herbal Medicine Glycyrrhiza inflataReduces Abeta Aggregation and Exerts Neuroprotection through Anti-Oxidation and Anti-Inflammation.* Am J Chin Med, 2018(1793-6853 (Electronic)): p. 1-25.

9. Jingjing, L., C. Shaoying, and L. Wei, *Research Progress on Chemical Constituents and Pharmacological Effects of Matricaria chamomilia L. and Predictive Analysis of Quality Markers.* Chinese Pharmaceutical Journal, 2024. **59**(08): p. 664-675.
10. Kang, N.J., et al., *Cinnamomum camphora Leaves Alleviate Allergic Skin Inflammatory Responses In Vitro and In Vivo.* Toxicol Res, 2019. **35**(3): p. 279-285.
11. Kwak, H.G. and H.B. Lim, *Inhibitory effects of Cnidium monnieri fruit extract on pulmonary inflammation in mice induced by cigarette smoke condensate and lipopolysaccharide.* Chin J Nat Med, 2014. **12**(9): p. 641-7.
12. Li, Z., et al., *Total flavonoids of Sophora flavescens and kurarinone ameliorated ulcerative colitis by regulating Th17/Treg cell homeostasis.* J Ethnopharmacol, 2022. **297**(1872-7573 (Electronic)): p. 115500.
13. Si, Y., et al., *Isolation and characterization of phellodendronoside A, a new isoquinoline alkaloid glycoside with anti-inflammatory activity from Phellodendron chinense Schneid.* Fitoterapia, 2021. **154**(1873-6971 (Electronic)): p. 105021.
14. Yang, B., et al., *Gentiana scabra Bunge roots alleviates skin lesions of contact dermatitis in mice.* J Ethnopharmacol, 2019. **233**(1872-7573 (Electronic)): p. 141-147.
15. Chengzhi, Z., et al., *Study on Antibacterial and Anti-Inflammatory Effects of Extracts from Salvia Miltiorrhiza and Licorice.* Yunnan Journal of Traditional Chinese Medicine and Materia Medica, 2023. **44**(07): p. 68-71.
16. Hede, Q. and Z. Yong, *The clinical efficacy of Longdan Xiaocuo Fang on acne vulgaris and its effect on sebum secretion.* Chinese Journal for Clinicians, 2010. **38**(05): p. 47-48.
17. Jianfan, Z. and S. Changjie, *Clinical application of Kushen capsules in dermatology hospitals.* Massage and Rehabilitation Medicine, 2021. **12**(12): p. 78-81.
18. ZHU Jin-fang, et al., *Optimization Herbal Prescriptions and Study on Formulation and Technology of Compound Horse Oil Acne Cream.* Research and Practice on Chinese Medicines, 2020. **34**(03): p. 48-51.
19. Alhamhoom, Y., et al., *Synergistic Antihyperglycemic and Antihyperlipidemic Effect of Polyherbal and Allopolyherbal Formulation.* Pharmaceuticals (Basel), 2023. **16**(10): p. 1368.
20. Sinan, K.I., et al., *Multiple online-HPLC methodologies and biological properties of leaves and stem barks extracts of Chrysanthellum indicum.* Microchemical Journal, 2024. **197**: p. 109847.
21. Shannon, P., et al., *Cytoscape: a software environment for integrated models of biomolecular interaction networks.* Genome Res, 2003. **13**(11): p. 2498-504.
22. Wu, T., et al., *clusterProfiler 4.0: A universal enrichment tool for interpreting omics data.* Innovation (Camb), 2021. **2**(3): p. 100141.
23. Morris, G.M., et al., *AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility.* J Comput Chem, 2009. **30**(16): p. 2785-91.
24. Wu, J., et al., *The protective effects of Cath-MH with anti-Propionibacterium acnes and anti-inflammation functions on acne vulgaris.* Frontiers in Pharmacology, 2021. **12**: p. 788358.
25. Choi, J.J., et al., *TNF-α increases lipogenesis via JNK and PI3K/Akt pathways in SZ95 human sebocytes.* Journal of dermatological science, 2012. **65**(3): p. 179-188.
26. Hagiwara, A., et al., *Hepatic mTORC2 activates glycolysis and lipogenesis through Akt, glucokinase, and SREBP1c.* Cell metabolism, 2012. **15**(5): p. 725-738.

27. Hussain, N., et al., *Effects of PKB/Akt inhibitors on insulin-stimulated lipogenesis and phosphorylation state of lipogenic enzymes in white adipose tissue.* Biochemical Journal, 2020. **477**(8): p. 1373-1389.
28. Cristani, M. and N. Micale, *Bioactive Compounds from Medicinal Plants as Potential Adjuvants in the Treatment of Mild Acne Vulgaris.* Molecules, 2024. **29**(10): p. 2394.
29. Dréno, B., et al., *Cutibacterium acnes (Propionibacterium acnes) and acne vulgaris: a brief look at the latest updates.* Journal of the European Academy of Dermatology and Venereology, 2018. **32**: p. 5-14.
30. Kistowska, M., et al., *IL-1β drives inflammatory responses to propionibacterium acnes in vitro and in vivo.* Journal of Investigative Dermatology, 2014. **134**(3): p. 677-685.
31. Nagy, I., et al., *Propionibacterium acnes and lipopolysaccharide induce the expression of antimicrobial peptides and proinflammatory cytokines/chemokines in human sebocytes.* Microbes and infection, 2006. **8**(8): p. 2195-2205.
32. Roy, T., et al., *The PI3K-Akt-mTOR and associated signaling pathways as molecular drivers of immune-mediated inflammatory skin diseases: update on therapeutic strategy using natural and synthetic compounds.* Cells, 2023. **12**(12): p. 1671.
33. Chen, X., et al., *Research advancements in pharmacological activities and mechanisms of matrine.* Pharmacognosy Magazine, 2024. **20**(1): p. 189-205.
34. Chen, Y., et al., *Research progress of sophoridine's pharmacological activities and its molecular mechanism: an updated review.* Frontiers in Pharmacology, 2023. **14**: p. 1126636.
35. Gao, Y., et al., *Anti-nociceptive and anti-inflammatory activity of sophocarpine.* Journal of ethnopharmacology, 2009. **125**(2): p. 324-329.
36. Xing, M., et al., *Acid-base combination principles for preparation of anti-acne dissolving microneedles loaded with azelaic acid and matrine.* European Journal of Pharmaceutical Sciences, 2021. **165**: p. 105935.
37. Rong, Z., et al., *Sophoridine alleviates hyperalgesia and anxiety-like behavior in an inflammatory pain mouse model induced by complete freund's adjuvant.* Molecular Pain, 2023. **19**: p. 17448069231177634.
38. Yang, B., et al., *Naringenin ameliorates hyperuricemia by regulating renal uric acid excretion via the PI3K/AKT signaling pathway and renal inflammation through the NF-κB signaling pathway.* Journal of agricultural and food chemistry, 2022. **71**(3): p. 1434-1446.
39. Lim, H.-J., et al., *Inhibitory effect of quercetin on propionibacterium acnes-induced skin inflammation.* International immunopharmacology, 2021. **96**: p. 107557.
40. Cheng, H., et al., *Naringin inhibits colorectal cancer cell growth by repressing the PI3K/AKT/mTOR signaling pathway.* Experimental and therapeutic medicine, 2020. **19**(6): p. 3798-3804.
41. Zhao, M., et al., *Naringenin ameliorates LPS-induced acute lung injury through its anti-oxidative and anti-inflammatory activity and by inhibition of the PI3K/AKT pathway.* Experimental and Therapeutic Medicine, 2017. **14**(3): p. 2228-2234.
42. Fang, F., et al., *A novel regulatory mechanism of naringenin through inhibition of T lymphocyte function in contact hypersensitivity suppression.* Biochemical and Biophysical Research Communications, 2010. **397**(2): p. 163-169.