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"The Key to *Ganoderma lucidum* Fermentation Broth Alleviating Skin Care: Ganoderic Acid"

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1. Introduction

As the largest human body organ, skin offers protection against external factors and is involved in physiological activities like temperature regulation and immune response[1]. However, skin health is increasingly challenged by environmental pollution, ultraviolet radiation, microbial infections, and chronic stress, leading to a rise in skin diseases like acne, eczema, psoriasis, and skin cancer, which significantly impact quality of life. Therefore, investigating mechanisms for maintaining skin health and developing safe and effective strategies for preventing and treating skin diseases is of great practical significance.

Ganoderma lucidum (*G. lucidum*), a well-known medicinal fungus with a history of over 2000 years in traditional medicine, is widely used for its health-promoting effects such as prolonging life, enhancing physical strength, and strengthening the immune system[2]. Research has shown it can benefit skin health, but most studies have focused on individual components[3-4][5]. However, current research on the skin health benefits of *G. lucidum* mainly focuses on the effects of individual components, lacking systematic exploration of its overall efficacy and mechanisms of action, especially for complex systems like *G. lucidum* fermentation broth.

Tumor necrosis factor-alpha (TNF-α) is a key inflammatory cytokine involved in various physiological processes, including cell proliferation, differentiation, apoptosis, immune regulation, and inflammation induction[6]. Targeted TNF-α drugs have been effective in treating inflammatory diseases but have potential side effects[7][8][9]. This highlights the broad market potential for developing a natural and safe TNF-α inhibitor.

Network pharmacology, which studies drug actions through a multi-component, multi-target approach, can enhance our understanding of G. lucidum fermentation broth's skin benefits. LC-MS is a powerful tool for analyzing complex samples. This study combines these approaches to explore the skin benefits of G. lucidum fermentation broth, providing a basis for developing new skin-care products[10][11]. The findings could advance the application of G. lucidum in skin health and offer new ideas for TCM modernization.

This study aims to comprehensively elucidate the skin benefits and mechanisms of action of Ganoderma lucidum mycelium fermentation broth using LC-MS/MS combined with network pharmacology. First, the active components in the *G. lucidum* fermentation broth are detected

and identified using LC-MS/MS to clarify its chemical composition. Then, through network pharmacology analysis, the active components in the fermentation broth are predicted to interact with skin-related targets, and a "compound-target-pathway" network is constructed to reveal the mechanisms of action of the *G. lucidum* fermentation broth on the skin. Finally, the skin benefits of the *G. lucidum* fermentation broth are verified through cell experiments, providing a scientific basis for the development of novel skincare products based on *G. lucidum* fermentation broth. This study not only helps to further explore the application value of *G. lucidum* in the field of skin health but also offers new ideas and methods for the modernization of traditional Chinese medicine research and application, with significant theoretical and practical significance.

2. Materials and Methods

2.1 Experimental Materials and Databases

This study utilized multiple resources, including Web of Science for retrieval, PubChem for compound 3D structures, PDB for target prediction and validation, UniProt and GeneCards for skin-related protein information, and Super-PRED for target prediction. Cytoscape was used for network analysis.

2.2 Determination of Metabolites in *G. lucidum* Fermentation Broth

A 200 mg sample of freeze-dried G. lucidum fermentation broth was placed in a 15 mL centrifuge tube, and 10 mL of 50% methanol-water solution (methanol:water = 50:50) was added. After 30 minutes of ultrasonication, 11 mL of the supernatant was transferred to another tube and centrifuged at 14,000 rpm for 5 minutes. The supernatant was filtered through a 0.22 μm membrane and collected for UHPLC-MS/MS analysis. Blank samples were treated similarly.

2.3 Network Pharmacology Analysis of *G. lucidum* Fermentation Broth's Skin Effects

2.3.1 Collection of Skin-Related Targets

Skin-related genes were retrieved from UniProt and GeneCards using the keyword “skin”. After removing duplicates, targets with a relevance score >1.0 were retained.

2.3.2 Prediction and Calculation of *G. lucidum* Compound Targets

Compounds identified via LC-MS/MS were analyzed on Super-PRED to predict their targets. Venny software was used to find the intersection between these targets and skin-related targets, with detailed information retrieved from UniProt.

2.3.3 Protein-Protein Interaction (PPI) Network of Potential Targets

A PPI network was constructed using STRING (Homo sapiens), visualizing interactions between potential targets. Results were analyzed in Cytoscape.

2.3.4 GO and KEGG Enrichment Analysis

KEGG and GO enrichment analyses were performed on potential targets using DAVID. Targets with $p<0.05$ were selected for further analysis.

2.3.5 Construction of Active Components and Target Network

A "compound-target-pathway" network was built using Cytoscape, with key compounds and targets identified by network degree values.

2.4 Characterization of G. lucidum Fermentation Broth's Skin Benefits

2.4.1 Determination of Cellular TNF-α Content

Ana-1 cells were seeded in a 96-well plate (4000 cells/well) and cultured for 24 hours. Samples were added at different concentrations, and TNF-α levels were measured by ELISA after 24 hours, with differences analyzed using one-way ANOVA ($P<0.05$).

2.4.2 Cell Scratch Healing Experiment

HaCat cells were seeded in a 6-well plate with a culture-insert 2 well. After 24 hours, the insert was removed, and drugs were administered. Images were taken at 0h and 24h post-treatment, and scratch healing percentages were calculated using Image J.

3. Results

3.1 Screening and Prediction of Active Components and Effective Targets in *G. lucidum* Fermentation Broth

Through LC-MS/MS, 81 organic active components were detected, mainly including various amino acids, sugars, and *G. lucidum* triterpenes. These 81 active components were imported into the Super-PRED website to calculate possible compound targets. The targets of the 81 components were then merged and de-redundant, and targets with a possibility of over 80% were selected, resulting in a total of 162 predicted targets. Using the keyword "Skin" to search the GeneCards database, 9331 skin-related target genes (Relevance score>1) were obtained, excluding duplicate genes.

The intersection of the 162 *G. lucidum* fermentation broth docking targets and the 9331 skin targets was analyzed using a Venn diagram, revealing 141 targets that *G. lucidum* fermentation broth may act on to affect the skin (Figure 1). Furthermore, these 141 *G. lucidum*-skin targets were imported into the String database to construct a target interaction network, as shown in Figure 2.

3.2 Enrichment Analysis of Targets

The potential targets were subjected to KEGG signaling pathway enrichment analysis and GO biological process enrichment analysis in the human gene annotation database DAVID. By setting the significance level P value to less than 0.05 and combining the roles of these targets in the skin, target genes were selected to analyze the skin effects of *G. lucidum* fermentation broth, as well as the signaling pathways and biological processes involved.

Based on the DAVID database, GO enrichment analysis was performed on 141 potential skin targets of *G. lucidum* fermentation broth mycelium fermentation broth. The results showed that in the biological process (BP), cellular component (CC), and molecular function (MF), 216, 54, and 88 significant entries were obtained, respectively ($P<0.05$). The top twenty entries with the most enriched genes were selected and sorted to draw an enrichment analysis bubble chart (Figure 3A). The results indicate that the biological processes involved in the action of *G. lucidum* fermentation broth mainly include phosphorylation, signal transduction, protein phosphorylation, inflammatory response, and G protein-coupled receptor signaling pathways, among other key activities. In the molecular function aspect, the *G. lucidum* fermentation broth is primarily involved in important functions such as protein binding, ATP binding, identical protein binding, metal ion binding, protein serine/threonine kinase activity, and protein serine kinase activity. The cellular components affected by the *G. lucidum* fermentation broth mainly include various cellular and membrane components such as cytoplasm, plasma membrane, nucleus, and nuclear protoplasmic membrane. Furthermore, the KEGG pathway enrichment analysis was conducted on these targets using the DAVID database, resulting in the enrichment of 134 significant KEGG pathways ($P<0.05$). Through literature research, 19 pathways related to the skin were selected (Figure 3B), with PI3K-Akt signaling pathway, MAPK signaling pathway, estrogen signaling pathway, neurotrophic factor signaling pathway, and platelet activation pathway ranking high among them, as detailed in Table 1.

3.3 Construction of Active Component-Target-Pathway Network

Utilizing the results of KEGG pathway enrichment analysis and the Cytoscape software, a network model of *G. lucidum* fermentation broth components-targets-pathways was constructed to observe the interactions between the active components of *G. lucidum* fermentation broth, target proteins, and related pathways. As shown in Figure 4, the network model includes 65 active components (represented by red square nodes), corresponding to

141 potential target points (represented by blue circular nodes), and involving 19 related signaling pathways (represented by yellow diamond nodes). In this network, the size of the nodes represents their connectivity, with larger nodes indicating higher network degree. According to the analysis results of the component-target-pathway network model, it can be determined that the active components of *G. lucidum* fermentation broth might act on multiple targets and correspond to multiple pathways. In the network, the top 10 active components with the highest connectivity are Valylproline, Schaftoside, Leucylproline, L-Saccharopine, Glycyl-L-leucine, Glycoursodeoxycholic acid, Ganoderic acid C2, Ganoderic acid B, Ganoderic acid A, and gamma-Glutamylleucine. Among these nodes, the top 10 nodes with the highest connectivity are Q99714 (HSD17B10), O15164 (TRIM24), Q9HAZ1 (CLK4), Q9NUW8 (TDP1), P27695 (APEX1), P19838 (NFKB1), Q9Y345 (SLC6A5), P54132 (BLM), P07339 (CTSD), and P28482 (MAPK1). Among the 19 skin-related pathways, the pathways with more than 10 connections are PI3K-Akt signaling pathway, MAPK signaling pathway, estrogen signaling pathway, neurotrophic factor signaling pathway, platelet activation, FoxO signaling pathway, Apelin signaling pathway, and Rap1 signaling pathway.

3.4 Cellular Benefits of *G. lucidum* Fermentation Broth

The results of the cell experiments demonstrated that the TNF-α content in the negative group (NG) was 194.59 ± 32.95 ng/mL, whereas in the positive control (PG), it was 4211.41 ± 45.41 ng/mL. The TNF-α content in samples adding 1mg/L GAA, GAB, GAC2, GSA, SCH and 0.1% FB were reduced to 3027.4 ± 36.17, 3505.86 ± 18.14, 3505.09 ± 29.73, 3443.32 ± 8.77, 3441.27 ± 2.73, 3487.73 ± 24.27, respectively (Figure 5A). The results showed that 1mg/L of five components reduced the intracellular TNF-α content by 16.77% - 18.29%, While 0.1% FB reduced the intracellular TNF-α content by 28.11%. The TNF-α content in samples adding 0.1mg/L GAA, GAB, GAC2, GSA, SCH and 0.01% FB were reduced to 3498.14 ± 30.86, 3575.55 ± 25.27, 3677.91 ± 28.09, 3440.77 ± 33.23, 3529.86 ± 2.86, 3646.23 ± 26.77, with a decrease of 12.67% - 18.30% (Figure 5B).

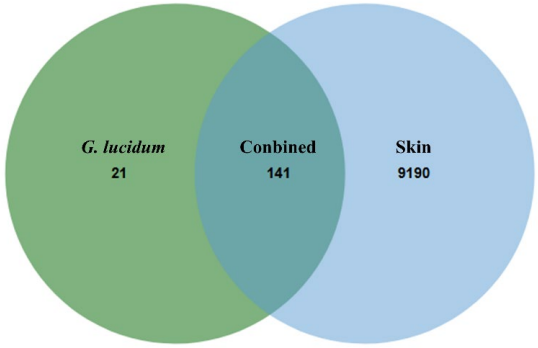
The results of the cell scratch healing experiment showed that the scratch healing of the untreated control group was 6.78% ± 1.57% at 24 hours. The scratch healing ratio in samples adding 1mg/L GAA, GAB, GAC2, GSA, SCH and 0.1% FB rose to 38.48% ± 1.95%, 31.21% ± 1.28%, 11.37% ± 1.10%, 33.06% ± 0.53%, 37.61% ± 2.05%, 35.86% ± 1.15%, respectively (Figure 6A&B). The scratch healing ratio increased to 1.67 times to 5.68 times that of the negative control group (NG). The scratch healing ratio in samples adding 0.1mg/L GAA, GAB, GAC2, GSA, SCH and 0.01% FB increased by 1.27 times to 4.50 times (Figure 6C&D).

1.1. Figures, Tables and Schemes

Table 1. Pathways associated with skin problems in KEGG enrichment analysis

Pathway	Count	Ratio	PValue	Genes	Skin efficacy
PI3K-Akt signaling pathway	16	10.12	6.35E-05	O00329, P07900, P11229, P29474, Q9Y243, O15111, P28482, P19838, P17252, P17948, P24941, P49841, P48736, P27986, P42338, P08238	Wound healing
MAPK signaling pathway	15	9.49	0.0003	Q9H2K8, P30305, Q9Y243, O15111, Q15418, P28482, P51812, P17612, P19838, P17252, Q99683, P17948, Q16584, P01375	Inflammation
Estrogen signaling pathway	14	8.86	2.90E-07	O00329, P07339, P07900, P29474, Q9Y243, P28482, P17612, Q05655,	Photoaging

				P35372, P27986, P42338, P08238, Q13255	
Neurotrophin signaling pathway	12	7.59	3.03E-06	O00329, Q9Y243, Q15418, P19838, Q05655, Q99683, P28482, Q16288, P51812, P49841, P27986, P42338	Wound healing
Platelet activation	12	7.59	4.52E-06	P17612, O00329, Q9Y243, P29474, P23219, P00734, P28482, P48736, P27986, P42338, Q9H244	Inflammation[12]
FoxO signaling pathway	11	6.96	4.61E-05	O00329, Q9Y243, O15111, O95977, Q99873, P28482, P24941, P27986, P42338, Q13255, P40763	Oxidative stress
Apelin signaling pathway	10	6.33	0.0004	P17612, P56524, Q9NYA1, Q9Y243, P29474, P28482, Q13370, P48736, P19634	Wound healing
Rap1 signaling pathway	10	6.33	0.0068	O00329, Q9Y243, P17252, P28482, P17948, Q05586, P21462, P27986, P42338, P21554	Inflammation
TNF signaling pathway	10	6.33	0.0001	O00329, Q9Y243, O15111, P19838, Q99683, P28482, P35354, P27986, P42338, P01375	Wound healing Inflammation



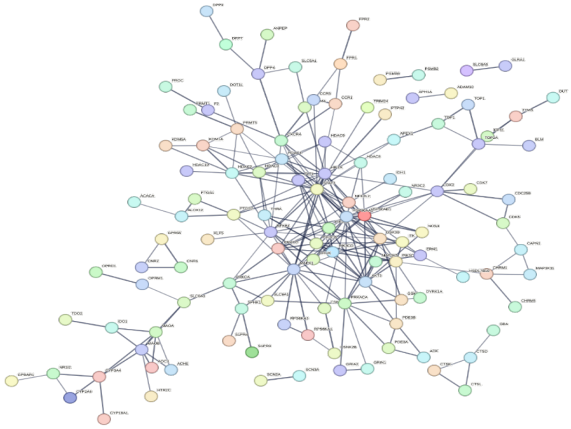


Figure 1. The Venn diagram of *G. lucidum* fermentation broth targets and skin targets.
Figure 2. The PPI interaction network of intersecting targets.

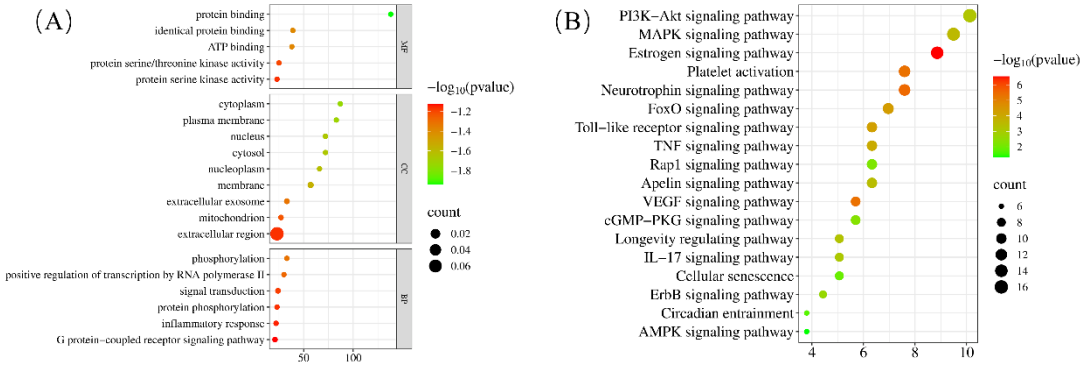


Figure 3. The enrichment analysis of *G. lucidum* fermentation broth targets (A) GO enrichment analysis; (B) KEGG enrichment analysis.

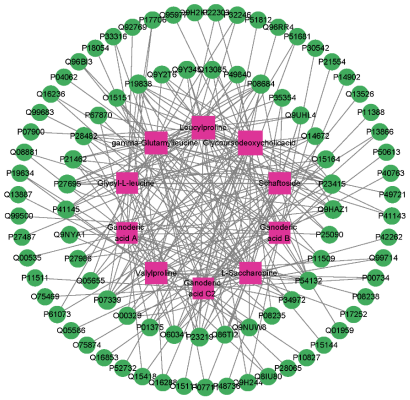


Figure 4. Part ingredients-skin potential target gene network. The size of each node in the network represents the size of its degree value. The gray connecting lines indicate that each node is interconnected.

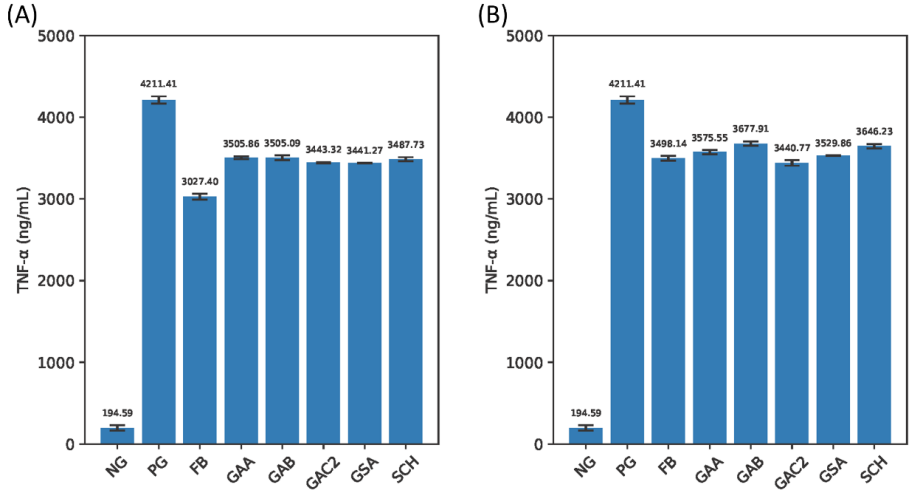


Figure 5. TNF-α content of the Ana-1 cells. (A) adding 1mg/L GAA, GAB, GAC2, GSA, SCH and 0.1% FB; (B) adding 0.1mg/L GAA, GAB, GAC2, GSA, SCH and 0.01% FB. GAA, GAB, GAC2, GSA, SCH, and FB correspond to ganoderic acid A, ganoderic acid B, ganoderic acid C2, glycoursodeoxycholic acid, schaftoside, and *G. lucidum* fermentation broth, respectively.

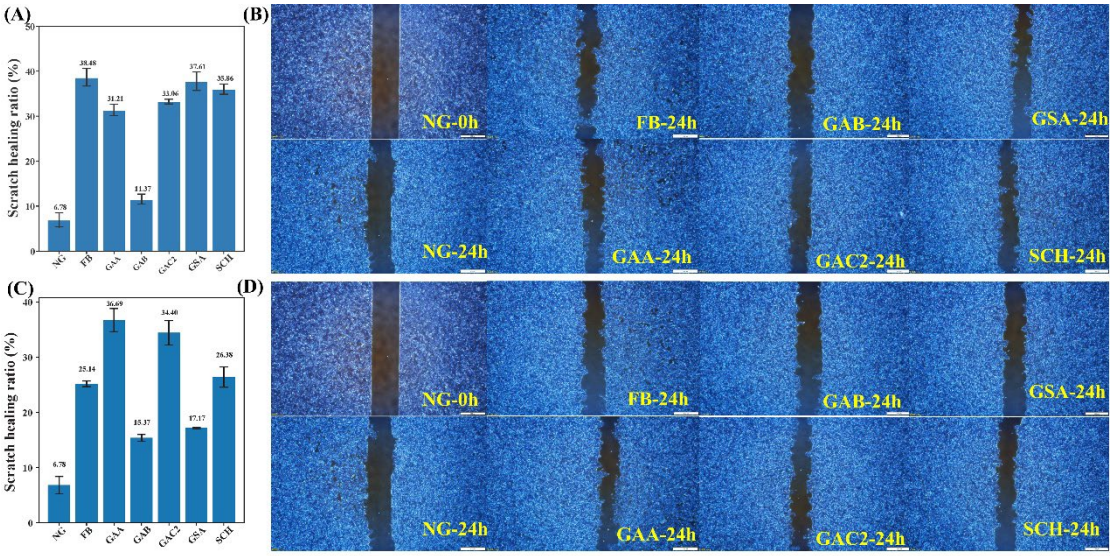


Figure 6. Effect on scratch healing of HaCat cells. (A) Scratch healing ratio after adding 1mg/L GAA, GAB, GAC2, GSA, SCH and 0.1% FB; (B) Scratch healing fluorescent image of samples adding 1mg/L GAA, GAB, GAC2, GSA, SCH and 0.1% FB; (C) Adding 0.1mg/L GAA, GAB, GAC2, GSA, SCH and 0.01% FB; (D) Scratch healing fluorescent image of samples adding 0.1mg/L GAA, GAB, GAC2, GSA, SCH and 0.01% FB. GAA, GAB, GAC2, GSA, SCH, and FB correspond to ganoderic acid A, ganoderic acid B, ganoderic acid C2, glycoursodeoxycholic acid, schaftoside, and *G. lucidum* fermentation broth, respectively.

4. Discussion

As the largest organ of the human body, the skin is frequently exposed to various external irritants, resulting in frequent skin inflammation. Consequently, a pivotal aspect of skincare is determining how to alleviate skin inflammation. The occurrence of skin inflammation is closely related to various inflammatory factors, such as TNF-α and NF-κB1. In this study, it was found that ten active components in *G. lucidum* fermentation broth play an important role in alleviating skin inflammation and are related to multiple proteins and signaling pathways, indicating that these active components have potential research and application value.

G. lucidum is a very valuable edible and medicinal fungus and has been proven to have beneficial effects on inflammation and immunity. The results of cell experiments indicate that *G. lucidum* fermentation broth can significantly reduce the content of the inflammatory factor TNF-α in skin cells and can effectively accelerate the healing of skin damage tissue, proving that *G. lucidum* fermentation broth is an excellent cosmetic raw material. Sajjad Ahmadi-Renani found that the addition of *G. lucidum* extract can significantly downregulate the expression of proteins such as nitric oxide synthase and TNF-α in cells, thereby showing good anti-inflammatory effects[13]. Research by Liu has shown that Ganoderic acid C1 can inhibit the production of TNF-α and other pro-inflammatory cytokines by PBMC, blocking the activation of the NF-κB pathway and alleviating the inflammation of the colonic mucosa in Crohn's disease[14]. In early research, Xie analyzed the active components in *G. lucidum* fruiting bodies and fermentation broth, identifying a variety of polysaccharides, nucleosides, peptides, triterpenes, and alkaloids from 9559 metabolites[15]. In this study, 81 organic compounds were identified from *G. lucidum* fermentation broth through high-performance liquid chromatography-mass spectrometry, among which *G. lucidum* triterpenes, *G. lucidum* polysaccharides, sterols, and *G. lucidum* peptides have been proven to have anti-inflammatory and antioxidant pharmacological effects[14,16-19]. These findings indicate that the multiple active components in *G. lucidum* work synergistically to exert anti-inflammatory and antioxidant effects.

From the *G. lucidum*-skin target network (Figure 4), it can be seen that many skin-related targets can be regulated by various compounds in *G. lucidum* fermentation broth. These genes include, but are not limited to, Q99714 (HSD17B10), O15164 (TRIM24), Q9HAZ1 (CLK4), Q9NUW8 (TDP1), P27695 (APEX1), P19838 (NFKB1), Q9Y345 (SLC6A5), P54132 (BLM), P07339 (CTSD), P28482 (MAPK1), and P01375 (TNF-α). These results indicate that the skin care effects of *G. lucidum* fermentation broth have the biological attributes of multiple components and multiple targets. In addition, the PPI results show that the 141 target proteins are not independent of each other, but are interconnected and interact with each other (Figure 2). *G. lucidum* fermentation broth can participate in skin protection by regulating various proteins. As shown in Figure 2, NFKB1, MAPK1, STAT3, and HSP90AB1 are important target genes in the PPI network. The GO and KEGG enrichment results of the 141 action targets were analyzed to select 19 skin-related pathways (Figure 3B), including the PI3K-Akt signaling pathway, MAPK signaling pathway, estrogen signaling pathway, neurotrophic factor signaling pathway, platelet activation pathway, and TNF signaling pathway, indicating that *G. lucidum* fermentation broth may exert its anti-inflammatory, soothing, and repair skin care effects

through these pathways. Previous studies have shown that the inhibition of the PI3K/Akt pathway can reduce the activation of Akt, thereby reducing the phosphorylation and degradation of NF-κB inhibitory protein IκB kinase, inhibiting the activation of NF-κB, and thus alleviating systemic inflammation[20]. Bozena Kaminska summarized previous studies, proving that the inhibition of the MAPK pathway reduces the synthesis of pro-inflammatory cytokines and their intracellular signal transduction, thereby effectively inhibiting the occurrence of inflammation[21]. The MAPK signaling pathway includes extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38, which are closely related to T cell activation, proliferation of fibroblast-like synoviocytes (FLS), production of inflammatory cytokines, and induction of cellular inflammation[22]. TNF-α is a common pro-inflammatory cytokine that plays a dominant role in the pathogenesis of inflammatory diseases[23]. Inhibiting TNF-α expression and TNF-α antibody treatment can effectively alleviate skin inflammation[24]. Toll-like receptors have a significant impact on immune responses and are involved in the proliferation, survival, and apoptosis of inflammatory cells[25]. The endogenous activation of Toll-like receptor signaling pathways exacerbates the body's inflammatory response. Previous research has revealed that the activation of the IL-17 pathway can stimulate keratinocytes (epidermal cells of the skin) to produce inflammatory mediators such as IL-6, IL-8, and G-CSF, which further attract neutrophils and other immune cells to the site of inflammation, exacerbating the inflammatory response and becoming key participants in the inflammatory response, especially when skin inflammation is prominent[26]. Therefore, *G. lucidum* fermentation broth may alleviate skin cell inflammation through the synergistic regulation of the above multiple pathways.The results of cell experiments proved that components such as Ganoderic acid A, B, and C2 do have good scratch repair effects and anti-inflammatory effects, and can significantly reduce the content of TNF-α in cells.

However, the limitation of this study is that it does not consider the interactions between active components. In addition, it is unknown whether these compounds can pass through the human epidermal barrier and be absorbed, and further research is needed for experimental verification. Considering these findings, they provide a theoretical basis for the further development of natural TNF-α inhibitors and the development of novel anti-inflammatory and soothing cosmetic raw materials based on *G. lucidum* fermentation broth.

5. Conclusion

This study has thoroughly explored the skincare benefits and mechanisms of action of G. lucidum mycelium fermentation broth using LC-MS and network pharmacology. LC-MS accurately identified 81 organic active components in the G. lucidum fermentation broth, including amino acids, sugars, and G. lucidum triterpenes. Network pharmacology analysis revealed its multi-component, multi-target, and multi-pathway characteristics, screening out 141 potential skin-related targets and constructing a "compound-target-pathway" network model. It was found that the active components of G. lucidum are involved in 19 skin signaling pathways such as PI3K-Akt and MAPK, playing a key role in anti-inflammatory, soothing, and skin damage healing. Cell experiment results confirmed that G. lucidum fermentation broth significantly reduced the content of the inflammatory factor TNF-α in skin cells, with an inhibition rate of 90.86%, and effectively accelerated skin damage healing, with the scratch healing rate increasing nearly four times in 24 hours. This study provides a scientific foundation for the development of G. lucidum fermentation broth as a novel raw material for skincare products and broadens the application potential of traditional Chinese medicine in the realm of skin health.

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