

Mechanisms of action of lychee seed on skin photo-aging protection: an integrated analysis based on computational biology and network pharmacology

Wenjing Yan¹, Jiajia Yin¹, Tengyu Ma¹, Yu Tian¹ and Haixin Sun^{1,*}

¹ College of Life Sciences, Qingdao University, Qingdao, Shandong, 266071, China

Corresponding authors: (e-mail: ywjqddx@126.com).

Abstract Skin photoaging is a common skin problem characterized by degradation of skin structure function and collagen damage. Litchi chinensis seed, a traditional Chinese medicine, contains a variety of bioactive components and shows potential value in the treatment of various diseases. In this study, we investigated the protective mechanism of lychee seed against skin photoaging based on computational biology and network pharmacology approaches. Eight major active constituents of lychee seed, including mannitol, β -sitosterol, ghrelin, stigmasterol, stigmasterol, epicatechin, and quercetin, were obtained through the screening of the Traditional Chinese Medicine (TCM) Systematic Pharmacology Database (TCMSPD). GeneCards and OMIM databases were used to search for targets related to skin photoaging, and 71 common targets were obtained by intersecting with the active ingredients of lychee seed to construct a network of “traditional Chinese medicine-active ingredient-gene target-disease”, and the GO functional enrichment analysis showed that these targets were involved in 101 biological processes, which were mainly related to the activities of transcription factors, nuclear receptors and neurotransmitter receptors, etc. Western Blot experiments confirmed that these targets were involved in the activities of transcription factors, nuclear receptors and neurotransmitters. Western Blot assay confirmed that lychee seed could reduce skin collagen destruction by inhibiting the expression of $I\kappa B\alpha$, $IKK\alpha$ and $NF-\kappa B65$ proteins in the $NF-\kappa B$ pathway. Microarray data analysis showed that GSE181022 and GSE107361 gene chips identified 671 and 3158 differentially expressed genes, respectively, and five core targets were obtained after taking the intersection with drug targets. The results showed that lychee seed could effectively reduce skin tissue aging, mainly through regulating the $NF-\kappa B$ signaling pathway, which provided a scientific basis for lychee seed to combat skin photoaging.

Index Terms litchi seed, skin photoaging, network pharmacology, computational biology, $NF-\kappa B$ signaling pathway, differentially expressed genes

1. Introduction

Overexposure to ultraviolet light from sunlight can cause sunburn, inflammation, erythema, photoaging and skin tumors [1]. The mechanism of UV-induced skin photodamage is not fully understood. Currently, excessive generation of oxygen radicals is considered to be the main cause of skin photodamage, and UV irradiation can induce skin cells to produce reactive oxygen species (ROS), and the accumulation of large amounts of reactive oxygen species can damage cellular lipids, proteins, DNA, etc., which leads to the occurrence of skin photodamage [2]-[5]. Under normal conditions, the skin has protective abilities against UV radiation, such as epidermal thickening, pigmentation, apoptosis and DNA repair [6], [7]. In addition there are a series of intracellular antioxidant systems including non-enzymes and enzymes that scavenge intracellular ROS and prevent oxidative cellular damage [8], [9]. When UV-induced ROS production is excessive, the intracellular oxidative and antioxidant balance is disrupted, resulting in oxidative stress pressure leading to cellular damage [10], [11].

In recent years, it has been found that the application of antioxidants can scavenge some of the ROS, thus reducing the occurrence of skin photoaging and skin tumors, so antioxidants with anti-inflammatory, anti-aging, and anticancer effects have gradually become the focus of research [12]-[14]. And lychee seeds contain a large number of phenolic substances, which can neutralize free radicals in the body and reduce free radicals to stabilizing substances, thus effectively preventing free radical chain reaction, which is a natural antioxidant or free radical terminator [15]-[17]. The study of the activity and mechanism of lychee seed on skin damage repair can provide a theoretical research basis for the development and application of lychee in skin health products.

Skin photoaging is a process of degenerative changes in skin structure and function induced by ultraviolet radiation, which is mainly characterized by symptoms such as loss of skin elasticity, wrinkle formation and

pigmentation. The current global anti-aging market is expanding and there is a growing demand for safe and effective natural anti-aging ingredients. Plant-derived bioactive compounds have become the object of much attention in the field of anti-aging research due to their high safety, low side effects, and diverse mechanisms of action. Litchi seeds, as a by-product of litchi fruit, are widely used in traditional medicine for the treatment of various diseases, and their rich bioactive components show potential medicinal value. Existing studies have confirmed that lychee seed possesses a variety of pharmacological activities, including cardiovascular protection, nervous system modulation, gastrointestinal function improvement, antimicrobial, antidiabetic, immunomodulatory and antitumor effects. However, the protective effects of lychee seed against skin photoaging and its potential molecular mechanisms have not been systematically investigated. The traditional drug development model is time-consuming, costly and inefficient, which is difficult to meet the current needs of drug development. Network pharmacology, as an emerging research method, can reveal the molecular mechanism of drug action at the system level by integrating technologies such as systems biology, network analysis and computational biology. This method can efficiently predict the interactions between drugs and targets, providing a new idea for the study of the mechanism of action of the complex system of traditional Chinese medicine. By establishing mathematical models and algorithms, computational biology can simulate and predict the behavior and changes of biological systems, providing theoretical basis and direction guidance for experimental research. Combining network pharmacology with computational biology can reveal the protective mechanism of lychee seed against skin photoaging from multiple levels and perspectives.

Based on the above background, the present study integrates the methods of network pharmacology and computational biology to systematically investigate the protective mechanism of lychee seed against skin photoaging. Firstly, we screened the active chemical components and their targets of lychee seed through the systematic pharmacology database of traditional Chinese medicine (TCM); secondly, we searched the GeneCards and OMIM databases for the targets related to skin photoaging, and intersected with the targets of lychee seed to identify the potential therapeutic targets; and then, we constructed a network of TCM-active components-gene targets-diseases, and performed protein interaction network analysis, GO function enrichment analysis, and KEGG pathway analysis. Then, the "TCM-active ingredient-gene target-disease" network was constructed, and protein interactions network analysis, GO functional enrichment analysis and KEGG pathway enrichment analysis were performed to predict the molecular mechanism of lychee seed in preventing skin photoaging; finally, the predicted results were verified by gene microarray data analysis and Western Blot experiments, with a focus on the role of the NF- κ B signaling pathway in the process of lychee seed's anti-skin photoaging. This study aims to elucidate the mechanism of protection against skin photoaging by lychee seed at the molecular level, and to provide scientific basis and theoretical support for the development of anti-aging products based on lychee seed.

II. Mechanisms of action of skin photoaging protection based on network pharmacology

II. A. Information and Methods

II. A. 1) Screening of effective chemical components of lychee kernel and their target points of action

The Chinese medicine systematic pharmacology database [18] and analytical platform were recorded, and the keyword "lychee kernel" was used to search for the active chemical components of lychee kernel by setting the screening criteria of oral bioavailability (OB) $\geq 30\%$ and drug similarity (DL) ≥ 0.18 . Then, we used the Traditional Chinese Medicine Systematic Pharmacology Database and Analysis Platform to retrieve the corresponding targets of action of the active chemical components. Finally, in the Uni Prot database, the qualifying species was set to human and all target names were converted to standard gene names.

II. A. 2) Acquisition of common targets for protection against skin photoaging by lycopene nuclei

"gastric cancer" and "liver cancer" were used as keywords, and the targets related to skin photoaging were searched in the GeneCards® database and OMIM® database, and then the "Relevancescore ≥ 15 " was set for screening. The final screened targets were imported into an Excel sheet for standardization, including the removal of duplicate targets. The common target of litchi nucleus in the treatment of skin photoaging was intersected by using the micro-biotech platform, which was the common target of litchi nucleus in the treatment of skin photoaging, and the common target name was converted into the standard gene name by using the Uni Prot database.

II. A. 3) Chinese herbal medicine-active ingredient-gene target-disease construction

The screened effective chemical components of Litchi chinensis and their target points were imported into CytoScape 3.7.2 software to construct a network diagram of "traditional Chinese medicine-components-targets" of Litchi chinensis. The common target information was imported into CytoScape 3.7.2 software to draw the network of "traditional Chinese medicine-common target-disease" for the treatment of skin photodamage with lychee kernel.

II. A. 4) Construction of protein-protein interaction networks

The common targets of lychee nuclei for the treatment of skin photoaging were imported into the STRING platform, the restricted species was set to human, and the interactions leveled correlation was set to ≥ 0.40 , the free nodes were hidden, and the interaction targets were not expanded additionally, and the protein-protein interaction network diagram was produced using Cyto Scape 3.7.2 software. In CytoScape 3.7.2 software, click CytoHubba and select degree, filter the top 20 core targets, and reconstruct the PPI network of core targets using the same method.

II. A. 5) Functional enrichment and pathway enrichment analysis of common targets

The common targets were uploaded to the Metascape platform, and the restricted species was set as human, and gene ontology (GO) functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed. $P < 0.01$ was set as the screening condition, and then the enrichment analysis results were ranked from largest to smallest according to the $-L_g p$ value, and the top 10 entries were selected and then visualized by using the Microbiome platform.

II. B. Results and Analysis

II. B. 1) Main effective active components of lychee kernel

The TCMSP platform was utilized to retrieve 70 active ingredients of lychee kernel, which were screened according to the set OB and DL, and a total of 8 effective active ingredients of lychee kernel were obtained as shown in Table 1.

Table 1: The main active components of the lychee nucleus

MolID	Compound name	OB(%)	DL
MOL010690	Uniflex BYO	31.09	0.26
MOL001494	Mannitol	44.16	0.21
MOL002883	Ethyl oleate	34.05	0.21
MOL000358	Beta-sitosterol	39.11	0.77
MOL000359	Sitosterol	39.11	0.77
MOL000449	Stigmastero	45.63	0.79
MOL000073	Epicatechin	51.85	0.26
MOL000098	Quercetin	44.28	0.31

II. B. 2) Litchi chinensis nucleus - a target for skin photoaging

Seventy-nine targets for the action of the main effective active ingredients of lycopodium were obtained, as well as 6,825 targets related to liver fibrosis, and the intersection of the two was taken, resulting in 71 lycopodium-skin photodamaged targets as shown in Fig. 1. Including prostatic endoperoxide synthase 1 (PTGS1), progesterone receptor (PR), muscarinic acetylcholine receptor (CHRM) 3, CHRM1, CHRM2, adrenergic receptor α 1A (ADRA1A), nicotinic acetylcholine receptor α 1 subunit (CHRNA2) and so on.

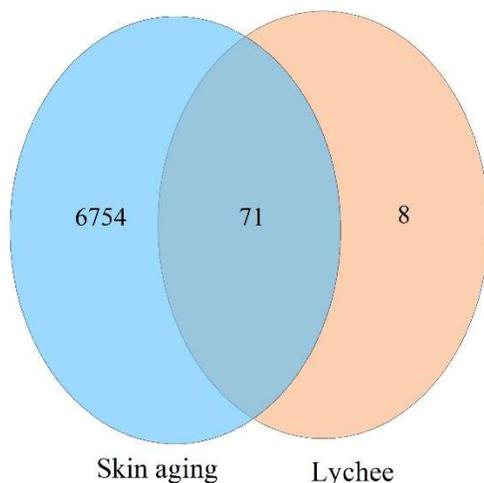


Figure 1: Lychee core - Wayne diagram of the skin light aging target

II. B. 3) “TCM-Active Ingredient-Gene Target-Disease” network

The network of “herbal medicine-active ingredient-gene target-disease” is shown in Figure 2, in which green represents skin photoaging, purple represents lycopene, blue represents the main active ingredient of lycopene, and yellow represents lycopene-hepatic fibrosis target. From the figure, it can be seen that the lychee nucleus mainly acts on 79 lychee nucleus-skin photoaging targets through six active ingredients (mannitol, β -sitosterol, glutosterol, stigmasterol, epigallocatechin, and quercetin) to intervene in the photoaging of the skin.

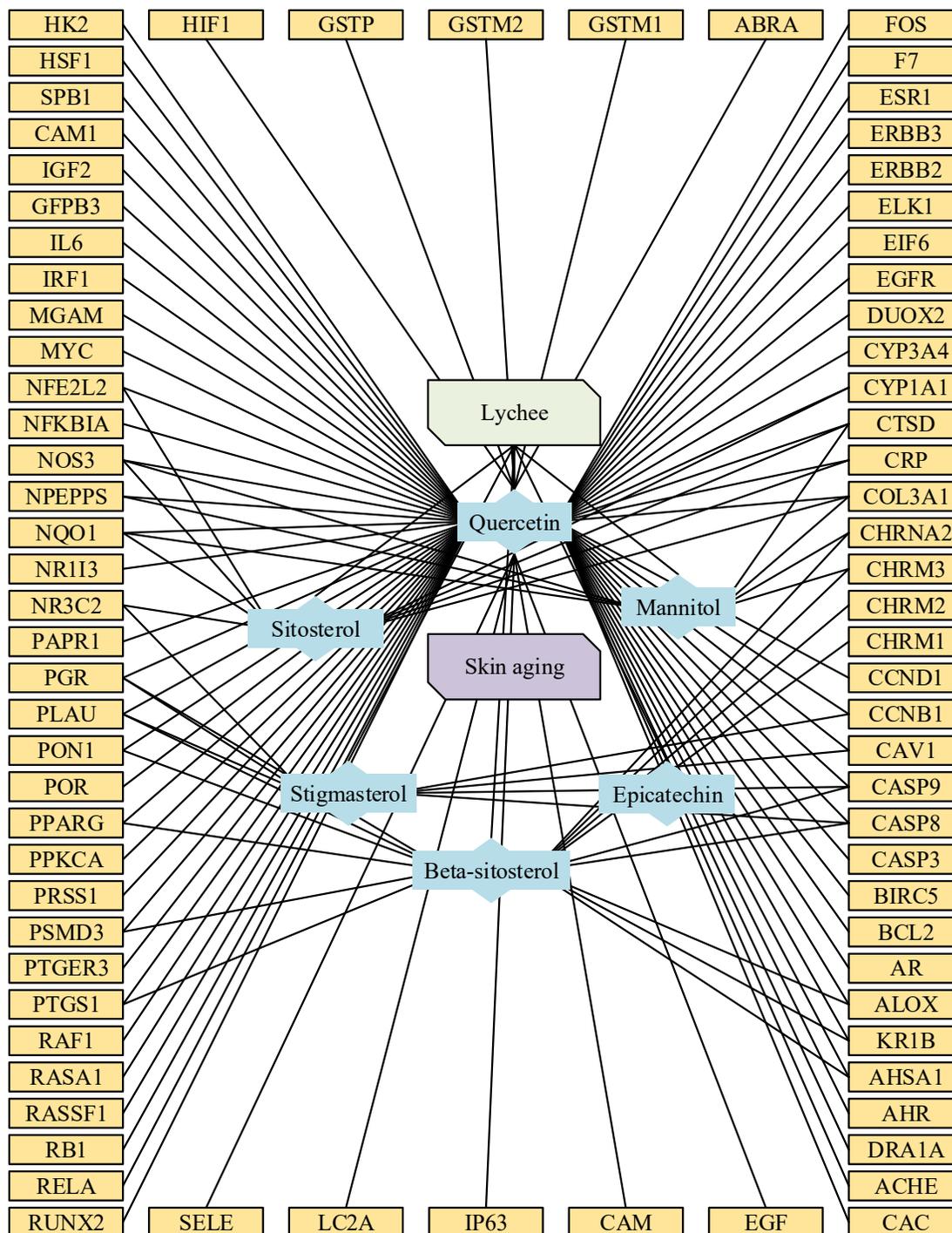


Figure 2: Online map of the genetic target disease of traditional Chinese medicine

II. B. 4) Results of GO enrichment analysis

GO functional enrichment analysis histograms are shown in Figure 3 for DNA-binding transcriptional activation fieldon activity, RNA polymerization specificity (A1), DNA-binding residual transcriptional activation pressor activity

(A2), nuclear receptor activity (A3), ligand-activated mounted transcriptional pressor activity (A4), steroid hormone receptor activity (A5), DNA-binding transcriptional in-binding (A6), HSAP90 quantum leuco binding (A7), activating transcription factor binding (A8), acetylcholine receptor activity (A9), RNA polymersol II-specific wall DNA-in-combination transcription factor binding (A10), steroid binding (A11), ubiquitin-like protein ligase binding (A12), glutathione binding (A13), postsynaptic neurotransmitter receptor aptitude (A14), oligopeptide binding (A15), NAD(P)-based H, and hemosiderin yellow-white as receptors for oxidoreductase activity (A16), integrin binding (A17), heme binding (A18), cysteine-type peptidase activity involved in apoptotic processes (A19), and kinase regulator activity (A20). A total of 101 biological processes are involved in lytic nuclear-hepatic fibrosis targets, mainly RNA polymerase II specificity, DNA-binding transcriptional activator activity, nuclear receptor activity, ligand-activated transcription factor activity, steroid hormone receptor activity, activated transcription factor binding, acetylcholine receptor activity, steroid binding, ubiquitin-like protein ligase binding, glutathione binding, and postsynaptic neurotransmitter receptor activity, etc.

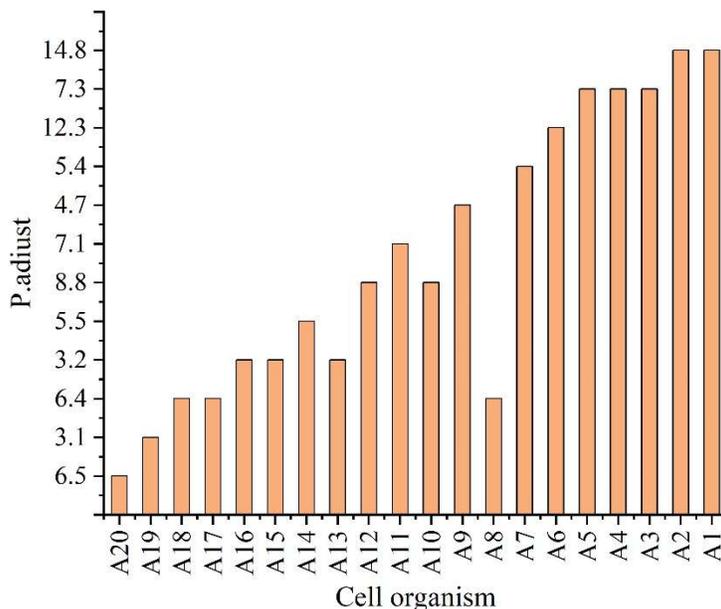


Figure 3: Go function enrichment analysis bar diagram

III. Experimental studies based on network pharmacology

III. A. Materials and Methods

1. Screening of active ingredients of lychee nucleus

TCMSP, a systematic pharmacological analysis platform for traditional Chinese medicines, was utilized to retrieve the main active ingredients of mannitol, β -sitosterol, ghrelin, stigmasterol, epicatechin, and quercetin. According to the ADME screening criteria provided by TCMSP database, bioavailability (OB) $\geq 30\%$ and drug-like properties (DL) ≥ 0.18 , were used as valid parameters, which were appropriately supplemented by reviewing literature methods. The above mentioned work platform was used to screen the active ingredients of each Chinese medicine in the formula of Litchi chinensis nucleus.

2. Corresponding target genes of drug active ingredients

Using TCMSP database to query the action targets of the main active ingredients, and standardize the target protein information obtained through Uniprot database to get the gene number of the key target corresponding to each active ingredient of traditional Chinese medicine in Litchi chinensis.

3. Acquisition of skin photoaging-related gene data

Jointly use GeneCards database and NCBI Gene database to screen skin photoaging related genes, and take the results of both of them into concatenation to get the related gene targets of skin photoaging.

4. Protein-protein interaction network and MCODE analysis

Take the intersection of lychee nucleus main active ingredient regulation target and skin photoaging target genes to get the core target, and use online Venn diagramming software to visualize the diagram. The core target PPI network was constructed through STRING database, and the obtained TSV format network file was imported into Cytoscape 3.7.2 software to continue the analysis, and the core target proteins were clustered and analyzed through

the MCODE plug-in in the software, and the functional modules were constructed to explore the mechanism of action.

5. Drug-compound-target network

Cytoscape 3.7.2 software was used to construct the “drug-compound-target” network, and according to the network topology algorithm, we screened out the effective active ingredients with the degree of value, and calculated the number of core targets contained in the 8 active ingredients, and drew the diagram.

III. B. Results

III. B. 1) Computational Biology Predicts Anti-Skin Aging Targets and Related Pathways of Lycium Nucleatum

The GSE181022 GeneChip raw data were normalized as shown in Figure 4, with yellow dots indicating lowering, blue dots indicating as change, and green dots indicating elevation. The figure obtained 671 differentially expressed genes, 312 up-regulated genes and 319 down-regulated genes.

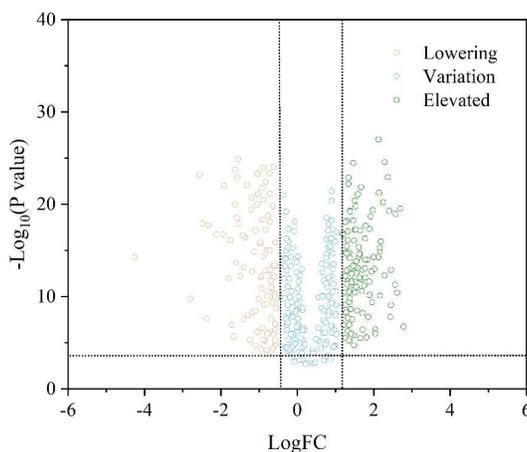


Figure 4: The volcanic analysis of the gene of the GSE181022 chip

The GSE107361 GeneChip data were analyzed as shown in Figure 5, and 3,158 differentially expressed genes, 2,113 up-regulated genes and 1,045 down-regulated genes were obtained.

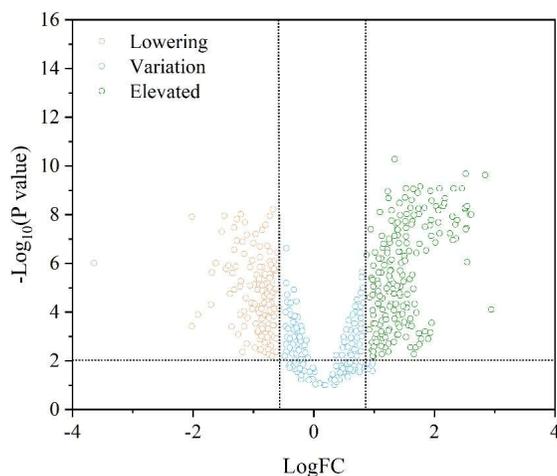


Figure 5: The volcanic analysis of the gse107361 chip difference gene

Drug target and chip differences as shown in Figure 6. CMSP database analysis obtained 17 active ingredients of lychee nucleus, 9 of which are fat-soluble, removing the duplicate targets, a total of 99 drug targets, which will be intersected with the above chip results to get a total of 5 core targets.

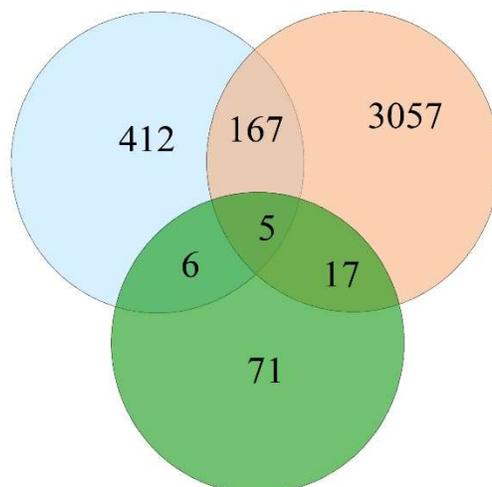


Figure 6: The drug target points to the DNA expression gene's Wayne diagram

III. B. 2) Effect of lychee kernel extract on the expression of major proteins in skin photoaging

Western Blot method was used to detect the expression levels of the main proteins of NF- κ B pathway in the skin tissues of each group, and the results are shown in Figure 7. It was found that the expression of IkBa, IKKa, and NF-kBP65 proteins increased in the aging model group ($P < 0.05$), and the expression was down-regulated after lycopodium intervention and gradually decreased with the increase of lycopodium intervention dose ($P < 0.05$).

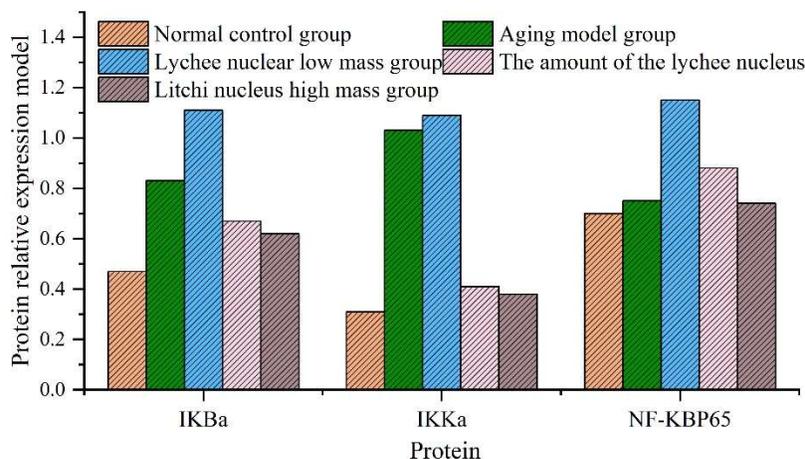


Figure 7: Lichee checks the regulation of the aging NF-kb pathway of the skin

It has been shown that there is phosphorylation in the NF- κ B signaling pathway regulating the expression of mannitol, and therefore it is hypothesized that the expression of its protein level is related to the phosphorylation of this process. Therefore, the present study demonstrated that mannitol is the target molecule of lychee nucleus intervention in aging skin tissues and that the NF- κ B pathway is closely related to this process by detecting the expression of mannitol and the major NF- κ B proteins in which it is located in skin tissues after lychee nucleus intervention.

In conclusion, lychee nucleus can effectively reduce the aging of skin tissues by inhibiting the expression of IKBa, IKKa, and NF- κ B P65 proteins in the NF- κ B pathway, thus reducing skin collagen destruction and resisting skin aging, which provides a scientific basis for the mechanism of action of lychee nucleus against skin aging.

IV. Discussion

Plant-derived bioactive compounds have attracted considerable attention in the treatment of a wide range of diseases due to their established medicinal properties. Litchi chinensis kernel is one of the few plants that are widely

used in the traditional treatment of various diseases. The alkaloids are recognized as β -carboline alkaloids due to their structural backbone. Among them, lychee kernel has been focused by researchers for its wide range of pharmacological activities and potential therapeutic effects. According to pharmacological findings, most of the studies related to lychee kernel in the field of bioactive compounds and phyto-origin research are based on the presence of β -carboline alkaloids as the basis of pharmacological efficacy. Studies have shown that lychee kernel has great efficacy in a wide range of diseases and possesses a variety of pharmacological activities such as cardiovascular, neurological, gastrointestinal, anti-microbial, anti-diabetic, immunomodulatory, circulatory and anti-tumor activity. Despite its reported toxic side effects, lychee nucleus deserves sustained attention due to its pharmacokinetic profile of low bioavailability and rapid renal clearance and pharmacodynamic profile of prominent bioactivity and is expected to be a potential drug candidate through modification by modern medicinal chemistry techniques. Therefore, based on this research objective, the present study utilized computational chemistry and bioinformatics techniques at the micromolecular level in an attempt to explore the potential medicinal value of lychee nuclei and to lay a solid foundation for the development of drugs with well-defined targets and pharmacological activities.

A total of seven candidate protein targets were obtained by screening in this study. By reviewing the relevant literature, it was found that some of the protein targets have been supported by relevant experimental data and have been focused as drug candidates for development. It was found that mannitol, β -sitosterol, glutathione, stigmasterol, epigallocatechin, and quercetin were found to be the targets involved in the regulation of signaling between nerve cells in skin tissues. In addition, in several models, mannitol significantly improved the ability of the skin to indicate smoothness. These effects appeared to be mediated by inhibition of monoamine oxidase or acetylcholinesterase, up-regulation of glutamate transporter proteins, reduction of reactive oxygen species, increase of neurotrophic factors, and anti-aging effects. These findings suggest that the target proteins obtained in this study are similar to the results of related laboratories, indicating that the protein targets obtained using the studies presented herein have some credibility. The functional enrichment analysis and signaling pathway enrichment analysis of the target proteins further explained the pharmacological effects and molecular mechanisms of *L. lycopersicum*. In the results of this study, it can be found that the target proteins of mannitol are mainly involved in the functions of some amino acid metabolism, neurotransmitter secretion, and enzyme activity regulation. This suggests that mannitol can exert pharmacological effects in skin protection, psychopharmacology and substance metabolism in vivo.

In order to further obtain the core regulatory targets and to further verify the accuracy of the predicted results, this study constructed the regulatory network using the candidate target proteins and the enriched signaling pathways as the entry points and analyzed the regulatory network in depth. The results suggested that the target protein genes playing core regulatory roles in the obtained regulatory network were mainly MAPK1 and MDM2. MAPK is an important transmitter of molecular signals from the cell surface to the interior of the nucleus. This signaling pathway plays a central role in the control of mammalian cell cycle progression, metabolism, differentiation, survival, migration, and senescence. Dysregulation or over-activation of the MAPK pathway usually leads to various pathologies. Alterations in the MAPK pathway have been reported to be significantly associated with the development of melanoma, breast, esophageal, colon, gastric, and hepatocellular carcinomas, among other tumors. MDM2 is a key negative regulator of the p53 gene and plays a critical role in the control of its transcriptional activity, protein stability, and nuclear localization through p53 ubiquitylation. The upregulation of MDM2 expression in many cancers leads to the loss of p53-dependent activities, such as apoptosis and cell cycle arrest. It has been reported in the literature that lychee nucleus induces apoptosis in MCF-7 cells. In addition, lychee nuclei effectively inhibited the migration and invasive ability of breast cancer cells and significantly promoted the expression of epithelial calreticulin and PTEN, while suppressing the protein expression levels of N-calreticulin, poikilodulin, PI3K, p-mTOR and AKT. These results seem to be suggesting that lychee nuclei may also play an important role in cancer-related diseases. To verify the accuracy of the predicted results, this study first calculated the binding free energies of lychee nuclei and MAPK1 and MDM2 proteins using molecular docking technique. The results showed that the lychee nucleus had good binding free energies with MAPK1 and MDM2 proteins, suggesting that the antitumor pharmacological activity of lychee nucleus might be closely related to these two targets. In addition, this study also used the database to analyze the expression levels of MAPK1 and MDM2 in different cancer diseases.

V. Conclusion

In this study, eight major active constituents in lychee seeds, including mannitol, β -sitosterol, glutenol, stigmasterol, stigmasterol, epigallocatechin, and quercetin, which exerted their anti-skin photoaging effects by acting on 71 common targets, were identified through computational biology and network pharmacology analysis.

Functional enrichment analysis showed that these targets were involved in 101 biological processes, mainly involving the regulation of transcription factor activity, nuclear receptor activity and neurotransmitter receptor function.

The experimental results confirmed that lychee seed could effectively attenuate skin tissue aging, and its mechanism mainly reduced skin collagen degradation by inhibiting the expression of I κ B α , IKK α and NF- κ Bp65 proteins in the NF- κ B signaling pathway.

Gene chip data analysis showed that 671 and 3158 differentially expressed genes were identified in GSE181022 and GSE107361, respectively, and five core targets were obtained after intersecting with drug targets, which further corroborated the mechanism of action of lycopodium.

Molecular docking technique calculations showed that lychee seed has good binding free energy with MAPK1 and MDM2 proteins, suggesting that lychee seed may exert anti-aging effects by regulating these targets.

The comprehensive data suggest that lychee seed can effectively counteract skin photoaging by regulating skin cell growth, differentiation and metabolism through the synergistic action of multiple targets and pathways. These findings provide a scientific basis for the application of lychee seed in anti-aging products, and also lay the foundation for the further development of natural anti-aging drugs with clear molecular targets.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

References

- [1] Awad, F., Assrawi, E., Louvrier, C., Jumeau, C., Giurgea, I., Amselem, S., & Karabina, S. A. (2018). Photoaging and skin cancer: Is the inflammasome the missing link?. *Mechanisms of ageing and development*, 172, 131-137.
- [2] Huang, A. H., & Chien, A. L. (2020). Photoaging: A review of current literature. *Current Dermatology Reports*, 9, 22-29.
- [3] Gromkowska - Kępa, K. J., Puścion - Jakubik, A., Markiewicz - Żukowska, R., & Socha, K. (2021). The impact of ultraviolet radiation on skin photoaging—review of in vitro studies. *Journal of cosmetic dermatology*, 20(11), 3427-3431.
- [4] Asyi, M. S., Syahrizal, D., Sary, N. L., & Husna, F. (2023). The Impact of Photoaging on Skin: A Systematic Review Analysis. *Journal of Social Research*, 3(1), 209-215.
- [5] Salminen, A., Kaarniranta, K., & Kauppinen, A. (2022). Photoaging: UV radiation-induced inflammation and immunosuppression accelerate the aging process in the skin. *Inflammation Research*, 71(7), 817-831.
- [6] Song, S., Li, F., Zhao, B., Zhou, M., & Wang, X. (2025). Ultraviolet light causes skin cell senescence: from mechanism to prevention principle. *Advanced Biology*, 9(2), 2400090.
- [7] Brand, R. M., Wipf, P., Durham, A., Epperly, M. W., Greenberger, J. S., & Faló Jr, L. D. (2018). Targeting mitochondrial oxidative stress to mitigate UV-induced skin damage. *Frontiers in Pharmacology*, 9, 920.
- [8] De Jager, T. L., Cockrell, A. E., & Du Plessis, S. S. (2017). Ultraviolet light induced generation of reactive oxygen species. *Ultraviolet light in human health, diseases and environment*, 15-23.
- [9] Ryšavá, A., Vostálová, J., & Rajnochova Svobodova, A. (2021). Effect of ultraviolet radiation on the Nrf2 signaling pathway in skin cells. *International Journal of Radiation Biology*, 97(10), 1383-1403.
- [10] Pourang, A., Tisack, A., Ezekwe, N., Torres, A. E., Kohli, I., Hamzavi, I. H., & Lim, H. W. (2022). Effects of visible light on mechanisms of skin photoaging. *Photodermatology, photoimmunology & photomedicine*, 38(3), 191-196.
- [11] Chen, X., Yang, C., & Jiang, G. (2021). Research progress on skin photoaging and oxidative stress. *Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii*, 38(6), 931-936.



- [12] Petruk, G., Del Giudice, R., Rigano, M. M., & Monti, D. M. (2018). Antioxidants from plants protect against skin photoaging. *Oxidative medicine and cellular longevity*, 2018(1), 1454936.
- [13] Papaccio, F., Caputo, S., & Bellei, B. (2022). Focus on the contribution of oxidative stress in skin aging. *Antioxidants*, 11(6), 1121.
- [14] Nisa, R. U., Nisa, A. U., Tantray, A. Y., Shah, A. H., Jan, A. T., Shah, A. A., & Wani, I. A. (2024). Plant phenolics with promising therapeutic applications against skin disorders: A mechanistic review. *Journal of Agriculture and Food Research*, 101090.
- [15] Huang, D., Gu, Q., Sun, Z., Soeberdt, M., Kilic, A., Abels, C., & Xu, J. (2020). Litchi Products as Dermatological Agents and Their Active Components. *ACS Food Science & Technology*, 1(1), 66-76.
- [16] Sathya, R., Arasu, M. V., Ilavenil, S., Rejiniemon, T. S., & Vijayaraghavan, P. (2023). Cosmeceutical potentials of litchi fruit and its by-products for a sustainable revalorization. *Biocatalysis and Agricultural Biotechnology*, 50, 102683.
- [17] Yan, W., Yin, J., Ma, T., Tian, Y., & Sun, H. (2025). Network Pharmacology and Integrated Molecular Docking Study on the Mechanism of the Protective Effect of Litchi Seed in Skin Photoaging. *J. COMBIN. MATH. COMBIN. COMPUT*, 127, 7435-7458.
- [18] Zhang Run-Zhi, Yu Shao-Jun, Bai Hong & Ning Kang. (2017). TCM-Mesh: The database and analytical system for network pharmacology analysis for TCM preparations. . *Scientific reports*, 7(1-4), 2821.