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Exploring the mechanism of *Glycyrrhiza glabra* and *Curcuma domestica* against skin photoaging based on network pharmacology

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ABSTRACT Excessive exposure to UV radiation results in skin photoaging, which may be prevented or treated using natural plant compounds. Herbal cosmetics and medicines have grown in popularity due to the abundance of relatively safe compounds. This research aims to explore the network pharmacology of *Glycyrrhiza glabra* (GG) and *Curcuma domestica* (CD) against skin photoaging. Active compounds from GG-CD were sourced from databases including TCSMP, KnapSack, TCMID, and published literature, while disease targets were collected from GeneCards and OMIM databases. The STRING database was utilized to construct the protein-protein interaction (PPI) network. Enrichment analyses for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway were performed using Metascape. The herb-compounds-target-pathway-disease (H-C-T-P-D) network was visualized using Cytoscape software. A total of 529 compounds, 2,335 active compound targets, and 120 skin aging targets were obtained. GO enrichment revealed 1,635 biological processes, 67 cellular components, and 121 molecular functions. The study suggests that GG and CD have the potential to treat skin photoaging by targeting multiple targets, such as TP53, TNF, AKT1, IL6, and IL-1B, as well as multiple pathways, such as those in cancer, apoptosis, TNF, IL-17, and the AGE-RAGE signaling pathway. Experiment validation is necessary to confirm the preliminary network pharmacology results.

KEYWORDS *Curcuma domestica*; *Glycyrrhiza glabra*; Network pharmacology; Skin photoaging

1. Introduction

Aging is often associated with wrinkles due to decreased skin elasticity caused by reduced fibroblasts and extracellular matrix (ECM) components in the dermal layers (Salminen et al. 2022). Aging can occur due to genetic (intrinsic aging) and environmental conditions (extrinsic aging), such as ultraviolet (UV) radiation, which has become the most harmful cause of skin aging, especially UVA and UVB rays that can penetrate the skin layer, causing dermal tissue damage, resulting in skin photoaging (Chen et al. 2021). Furthermore, UV radiation overexposure may lead to DNA damage and skin photoaging. This triggers interaction with skin cells such as keratinocytes and fibroblasts. Excessive skin exposure to UVA may also causes direct damage to skin cells through inflammatory reactions and oxidative stress pathways (Gromkowska-Kępka et al. 2021). Du et al. (2022) conducted a study with 419 women in Jakarta, Indonesia, found that pigmentation and skin conditions caused uneven skin tone and aging features as they aged. Moreover, melasma, seborrheic keratosis, and post-inflammatory hyperpigmentation were common in their twenties and thirties, while melasma was found in all participants aged 41 and older.

Recently, natural resources have been widely favored and explored due to their benefits in preventing skin photoaging. They work by enhancing skin elasticity and reducing wrinkles, reducing skin oxidative stress, inhibiting skin pigmentation, improving skin hydration, and inhibiting other signaling pathways related to aging, such as activator protein-1 (AP-1) and p65 nuclear factor-κB (NF-κB) (Costa et al. 2022). Previous studies suggested the benefits of polyherbal in antiaging formulations. *In vitro* study on NIH3T3 fibroblast cells showed that polyherbal formulation containing leaves of Nyctanthes arbor-tristis, unripe and ripe fruit pulp of *Aegle marmelos*, and the terminal meristem of *Musa paradisiaca* flower in the ratio of 6:2:1:1 exhibited great anti-oxidant and anti-elastase properties (Sundaram et al. 2018). Anti-aging properties are also demonstrated by Harak herbal formula (HRF) extracts, which consist of the combination of roots from five plants, including *Ficus racemosa*, *Capparis micracantha*, *Clerodendrum petasites*, *Harrisonia perforata*, and *Tiliacora triandra*. HRF extracts are mitigated by UVA-induced photoaging in rats by increasing nuclear factor erythroid 2-related factor 2 (Nrf2) expression alongside their capacity to decrease reactive oxygen species (ROS)

generation and oxidative harm (Lohakul et al. 2021). Recently, the ethanolic extract of *Zingiber cassumunar* Roxb. has been reported to have protective effects against skin-photoaging induced by UVB in a rat model via modulations of ROS, matrix metalloproteinase-1 (MMP-1), and tyrosinase (Tyas et al. 2024). Similarly, the extract of Robusta coffee beans also possesses anti-skin photoaging by modulating MMP-1 expression (Mariati et al. 2021). All of these natural-based materials serve as a good anti-aging agent.

The combination of licorice (*Glycyrrhiza glabra*) and turmeric (*Curcuma domestica*) could potentially enhance the effectiveness of polyherbal cosmetic formulations for anti-aging. Licorice is known for its rich phytoconstituents that possess excellent properties, including antioxidant, anti-inflammatory, and skin-lightening, which may be effective in inhibiting skin aging process Cerulli et al. (2022). It is an abundant natural resource in tropical countries, including Indonesia, that has been utilized as an ethnomedicine against skin aging (Ho et al. 2024). Turmeric, on the other hand, has also been found to have a positive effect on skin photoaging and has been widely used in Indonesia as an authentic ethnomedicine to prevent skin aging (Elhawary et al. 2024). Excessive exposure to UVB rays leads to photoaging, a process in which ROS are overproduced. This, in turn, activates the mitogen-activated protein kinase (MAPK) pathway, leading to an increase in MMP-1, an enzyme that breaks down type 1 collagen. This UV radiation-induced external aging is marked by a reduction of type 1 collagen expression (Threskeia et al. 2023). Previous *in vivo* studies demonstrated that *Curcuma domestica* and curcumin significantly reduced proinflammatory cytokines and enhanced type 1 collagen in the skin tissue in UVB-irradiated mice (Zheng et al. 2020a; Threskeia et al. 2023). Glycyrrhetinic acid, an active component from licorice, and curcumin from turmeric extract are widely studied as anticancer agents. Glycyrrhetinic acid combined with curcumin could effectively inhibit phosphatase and tensin homolog/phosphoinositide 3-kinase/protein kinase B (PTEN/PI3K/Akt) signaling as a regulator of cell proliferation in tumor cell growth (Chang et al. 2017). This pathway is related to aging through skin senescence and self-renewal of skin-derived precursors. A dysregulated PI3K signaling pathway through PTEN downregulation increases ROS, which may exacerbate the photoaging effects (Teng et al. 2021). Therefore, unveiling the mechanism of *Glycyrrhiza glabra* and *Curcuma domestica* against skin photoaging requires further molecular approaches through network pharmacology.

Network pharmacology is a groundbreaking in silico method in the biotechnology and drug discovery area. It involves creating a network between proteins, compounds, and diseases to identify the mechanisms and therapeutic effects of various compounds (Noor et al. 2022). This approach has been used in another study to identify the molecular mechanism of herbal combination against skin photoaging (Han et al. 2022; Xu et al. 2023). Thus, this study aims to disclose the underlying mechanisms of *Glycyrrhiza glabra* and *Curcuma domestica*, two highly potential anti-aging agents, in the skin photoaging process.

2. Materials and Methods

2.1. Screening the active compounds of Glycyrrhiza glabra (GG) and Curcuma domestica (CD)

The study's flowchart is depicted in Figure 1. The active compounds of *Glycyrrhiza glabra* (GG) and *Curcuma domestica* (CD) were retrieved from various online databases. Firstly, the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) (https://tcmsp-e.com/tcmsp.ph/) was used. It is the largest Traditional Chinese Medicine (TCM) database for discovering drug from herbal medicines (Ru et al. 2014; Xu et al. 2023). KNApSAcK (http://www.knapsackfamily.com/KNApSAcK/) was also used, which is an extensive database for retrieving information on the relationship between metabolites and biological activities (Nakamura et al. 2014; Sadaqat et al. 2023). Additionally, the Traditional Chinese Medicines Integrated Database (TCMID) (https://bidd.group/TCMID/), a comprehensive database aimed at modernizing TCM, was also used (Huang et al. 2018; Que et al. 2021). Furthermore, literature that had been published beforehand was used to gather information on herb compounds (Ayati et al. 2019; Hasan et al. 2021). The PubChem (https://pubchem.ncbi.nlm.nih.gov/) database was used to identify the simplified molecular-input line-entry system (SMILES) structures of compounds after eliminating duplicate targets from both plants (Gan et al. 2019).

2.2. Screening the targets connected to the compounds

The compound targets were gathered using two tools, i.e. Swiss Target Prediction (STP) (http://www.swisstargetprediction.ch/) and the Similarity Ensemble Approach (SEA) (http://sea.bkslab.org/). The SMILES were inputted into the databases with the "*Homo sapiens*" configuration, and any duplicated compound targets from these two databases were removed (Oh et al. 2021). Both STP and SEA are computational tools for predicting the potential targets of small molecules. STP combines the ligand-based and target-based approaches (a hybrid method between 2D and 3D). In contrast, SEA assesses the similarity between the input 2D molecule and known ligand across many protein structures (Mayr et al. 2020).

2.3. Screening of skin photoaging disease targets

The disease targets were obtained using the keyword "skin photoaging" in GeneCards (https://www.genecards.org/) and Online Mendelian Inheritance in Man (OMIM) (https://www.omim.org/) (Han et al. 2022). GeneCards and OMIM provide comprehensive data on human genes and disease (Hamosh et al. 2005; Stelzer et al. 2016). The duplicated disease targets in the two databases were deleted. Subsequently, in order to determine the potential targets of

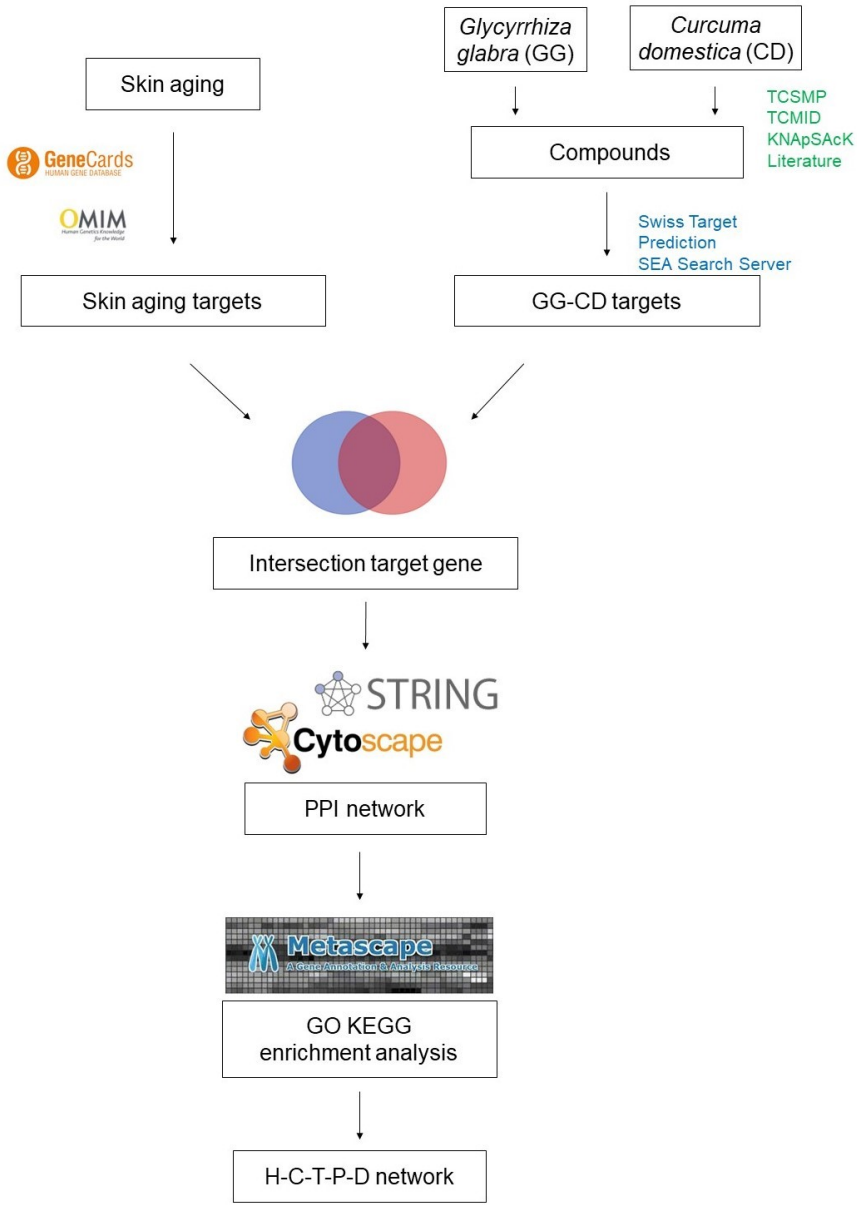

FIGURE 1 Flowchart of the study.

both *Glycyrrhiza glabra* and *Curcuma domestica* in treating skin photoaging, a Venn diagram between herb targets and disease targets was constructed using the Bioinformatic Evolutionary Genomic tool (http://bioinformatics.psb.ugent.be/webtools/Venn/).

2.4. Construction of protein-protein interaction (PPI) network

A PPI network of potential targets was constructed by employing the STRING tool (https://string-db.org/). The species was adjusted to "*Homo sapiens*" prior to the analysis, and only targets with a confidence score of ≥ 0.4 were included. This tool identifies the functional association of two proteins that contribute to a specific biological function (Szklarczyk et al. 2019). The PPI network map obtained in STRING was saved in a tab-separated value (.tsv) format and then imported into Cytoscape software (version 3.10.0) for network mapping and topology analysis with three topological features, including "degree", "betweenness", and "closeness" (Que et al. 2021). The Cytohubba plug-in was used to construct the regulatory network for the top 20 proteins with the greatest degrees, which were considered as the core targets of GG-CD (Xiang et al. 2022).

2.5. Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis

The primary mechanism and pathway of GG-CD against photoaging was identified using Metascape (https://metascape.org/) tool by analyzing the KEGG pathway and GO function. The analysis was carried out with a focus on

"*Homo sapiens*" organisms and a cut-off *p-value* of 0.01. Minimal overlap was adjusted as three enrichment analyses, including biological process (BP), cellular composition (CC), molecular function (MF), and KEGG pathway (Xiang et al. 2022). The top 20 items were graphed based on the number of targets involved.

2.6. Construction of herb-compound-target-pathway-disease (H-C-T-P-D) network

The network between herbs, compounds, targets, pathways, and disease was established using Cytoscape (version 3.10.0). The top 10 pathways were then used to establish the relationship between target and disease elements.

3. Results and Discussion

3.1. Active compounds of Glycyrrhiza glabra and Curcuma domestica

Our study yielded a total of 367 compounds in GG and 172 compounds in CD. Ten duplicate compounds of GG and CD were found, including acetic acid, malic acid, fumaric acid, citric acid, geraniol, alpha terpineol, inositol, arachidic acid, anethole, and sitosterol. The 529 compounds obtained after the duplicate compounds were eliminated are listed in Table S1.

3.2. Targets genes of Glycyrrhiza glabra and Curcuma domestica against skin photoaging

A total of 1,507 targets from STP and 1,258 targets from SEA found to be linked to herb compounds. After removing the duplicate entries from both databases, a total of 2,335 targets were obtained (Table S2). Skin photoaging-related targets were retrieved using GeneCards and OMIM, with a total of 292 and 171 targets, respectively. Following the elimination of the duplicates, both databases yielded 450 targets associated with skin photoaging (Table S3). The Venn diagram results showed that there were 120 overlapping targets between 2,335 compound targets and 450 disease targets (Figure 2a; Table S4). These 120 targets are considered as the potential targets that mediate the anti-aging properties of *Glycyrrhiza glabra* and *Curcuma domestica*.

3.3. PPI network of targets against skin photoaging

PPI analysis was carried out on previously identified potential targets. STRING analysis yielded 1765 edges and 119 protein nodes (Figure 2b), with an average node degree of 29.7 and a PPI enrichment *p-value* of less than 1.0e-16. Figure 2c depicts the top 30-degree value of the PPI network.

The obtained data was subsequently imported into Cytoscape software to create a PPI network. The network consists of 1,765 edges and 117 nodes, displaying the interaction of disease and compound targets (Figure 3a). Three topological attributes of these targets showing mean values of degree, node betweenness, and closeness at 30.17, 0.0073, and 0.57, respectively. Further details of the topological analysis are provided in Table S5. The core targets of *Glycyrrhiza glabra* and *Curcuma domestica* as anti-skin photoaging using CytoHubba plug-in was shown in Figure 3b. The top 20 targets were tumor protein p53 (TP53), tumor necrosis factor (TNF), AKT serine/threonine kinase 1 (AKT1), interleukin-6 (IL6), interleukin-1ß (IL1B), JUN, epidermal growth factor receptor (EGFR), mitogen-activated protein kinase 3 (MAPK3), caspase 3 (CASP3), matrix metalloproteinase-9 (MMP-9), transforming growth factor-ß1 (TGFB1), hypoxia-inducible factor 1 subunit α (HIF1A), NF-κB subunit 1 (NF-κB1), estrogen receptor 1 (ESR1), catenin-β1 (CTNNB1), peroxisome proliferator-activated receptor-γ (PPARG), prostaglandin-endoperoxide synthase 2 (PTGS2), Fos proto-oncogene (FOS), Toll-like receptor (TLR4), and fibronectin 1 (FN1).

3.4. GO KEGG enrichment analysis

Gene Ontology (GO) enrichment analysis is employed to detect disproportionately represented biological processes (BP), molecular functions (MF), and cellular components (CC) among a given set of genes or proteins. GO functional enrichment identified the 1,635 BP, 67 CC, and 121 MF associated with 117 targets (Table S6). Top 20 entries were plotted in the GO bar chart (Figures 4a-c). BP encompass a number of events, such as response to hormone, response to radiation, and response to UV (Figure 4a), which are carried out by MF, which are elemental activities of gene products at the molecular level, such as nuclear factor activity and transcription binding activity (Figure 4c). CC, on the other hand, refers to the physical structures within a cell or its extracellular environment where gene products are located, such as extracellular matrix, membrane raft (Figure 4b). Subsequently, the KEGG signaling pathway was performed, and 185 signaling pathways were discovered (Table S7). The top 20 signaling pathways were shown in Figure 4d. The targets of GG-CD for skin aging were mainly related to pathways in cancer, apoptosis, TNF signaling pathway, IL-17 signaling pathway, and AGE-RAGE signaling pathway in diabetic complication.

3.5. H-C-T-P-D network analysis

The complex relationship between GG-CD and skin photoaging is demonstrated in the H-C-T-P-D network (Figure 5), which consists of 676 total nodes (two herb GG-CD nodes, 533 compound nodes, 120 target nodes, 20 core pathway nodes, and one skin aging nodes) and 8,475 total edges. Potential therapeutic targets from each compound in GG-CD that related to skin aging were shown in Table S8. The pink diamonds, orange and blue hexagons, and pink ellipses represent herbs, compounds, and targets, respectively. Blue round rectangles represent pathways, while the purple V shape represents the disease. H-C-T-P-D network analysis revealed ten main compounds with the highest degree in the network, suggesting their pivotal role in the mechanism of GG and CD against skin photoaging.

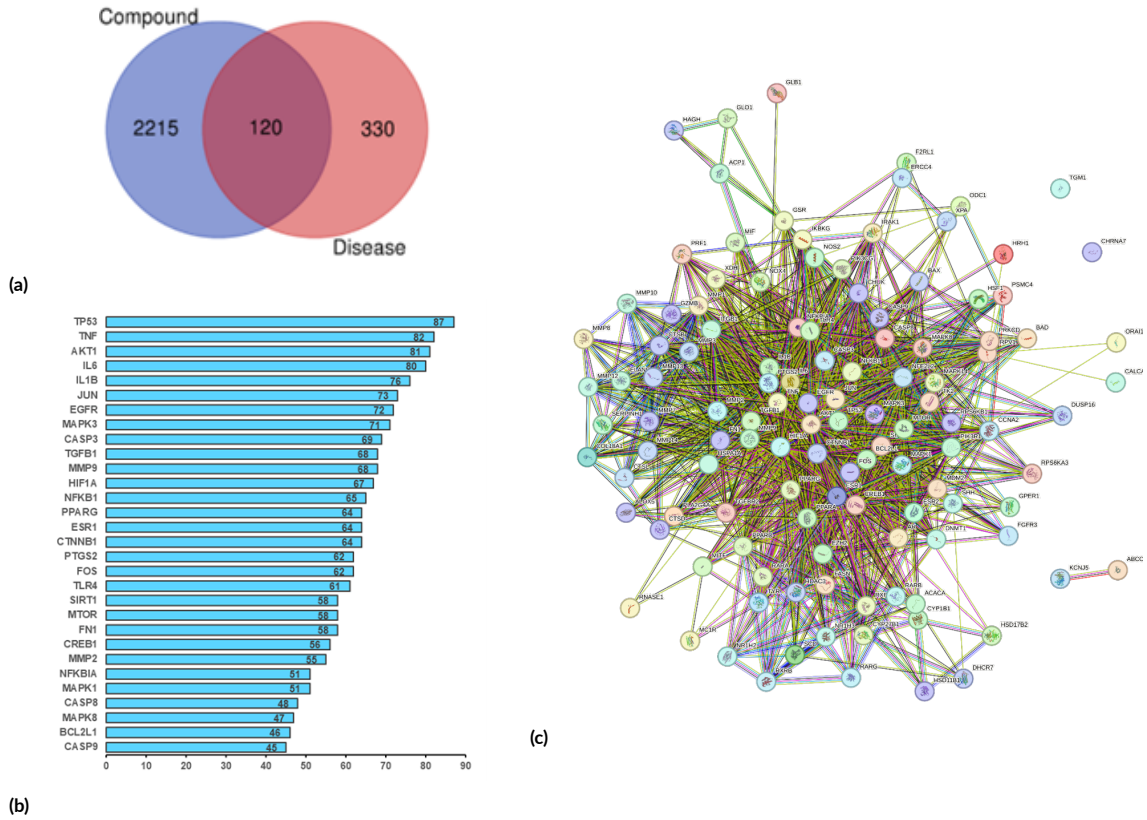

FIGURE 2 PPI network of *Glycyrrhiza glabra* and *Curcuma domestica* against skin photoaging. (A) Venn diagram showing the overlapping targets between compound and skin photoaging targets. (B) PPI network degree of the top 30 proteins. (C) PPI network of the 120 potential targets.

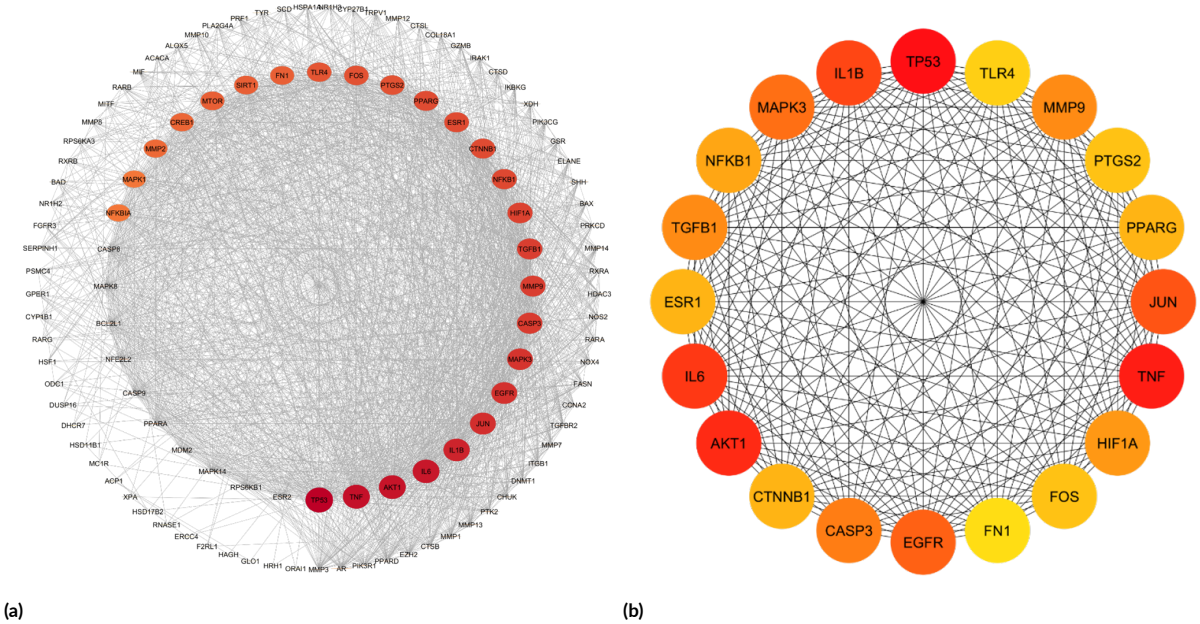

FIGURE 3 Molecular complex and core targets. (A) The protein network of overlapped targets underwent topology analysis on Cytoscape is arranged in a ring based on degree value. The size of the node indicates degree value, while the red color represents higher degree values. (B) Top 20 core targets obtained by Cytohubba plug-in.

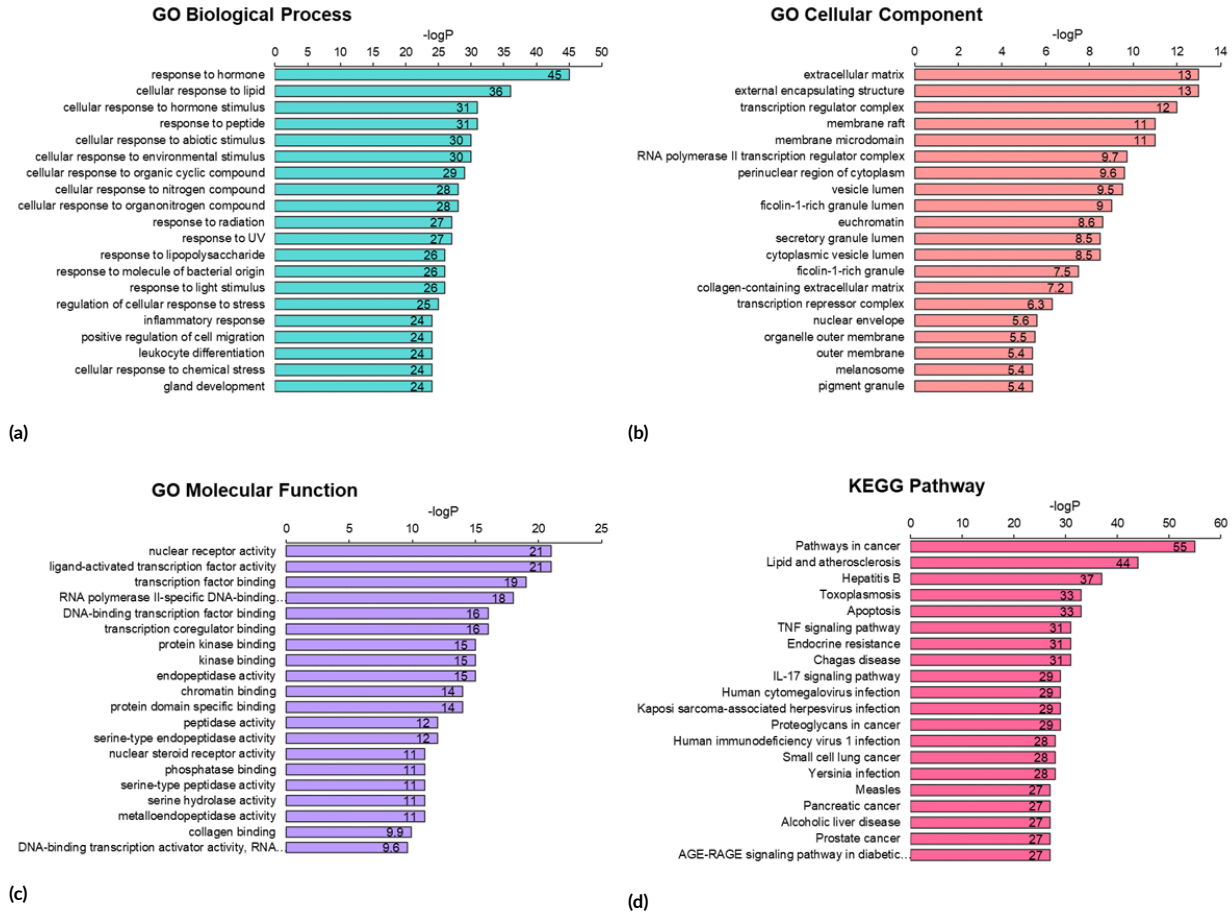

FIGURE 4 GO function and KEGG pathway enrichment analysis of herbs for skin photoaging. (A) Biological processes. (B) Cellular components. (C) Molecular functions. (D) KEGG.

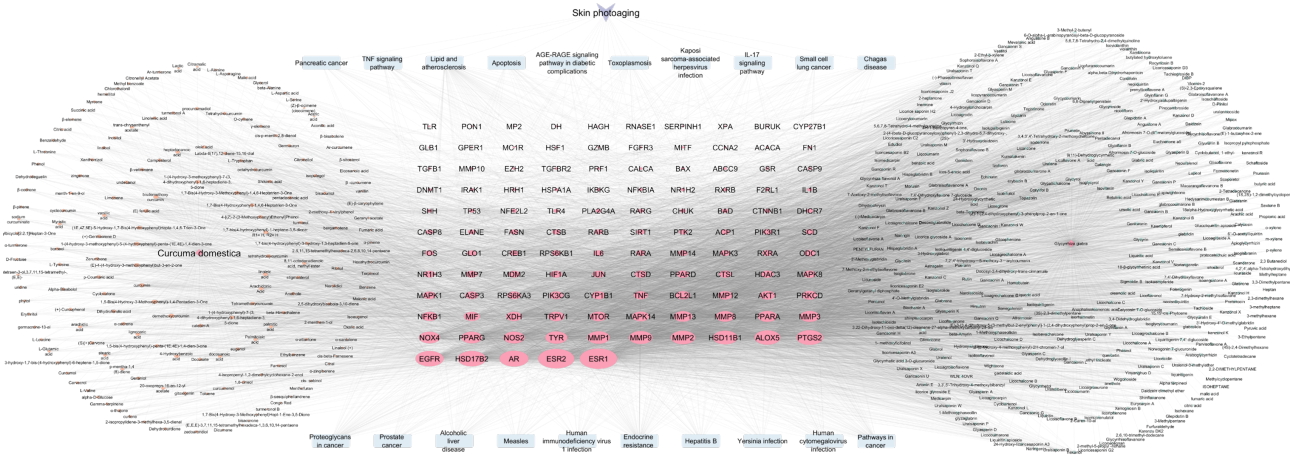

FIGURE 5 The herbs-compound-target-pathway-disease network showed the potential mechanism of *Glycyrrhiza glabra* and *Curcuma domestica* to treat skin photoaging.

Those compounds and their degrees, respectively, were demethoxycurcumin from CD (34), 1,5-bis(4-hydroxy-3-methoxyphenyl)-1,4-pentadien-3-one from CD (33), (3S)-2,3-dimethylpentane from GG (31), curcumin from CD (31), 1-(4-hydroxy-3-methoxyphenyl)-5-(4-hydroxyphenyl)-penta-(1E,4E)-1,4-dien-3-one from CD

(30), (E)-4-(4-hydroxy-3-methoxyphenyl)but-3-en-2-one from CD (30), (1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxyphenyl)hepta-1,4,6-trien-3-one from CD (29), isoliquiritigenin from GG (28), homobutein from GG (28), and liquoric acid from GG (28).

3.6. Discussion

Photoaging is characterized by the alteration of the skin due to exposure to UV that may lead to skin aging. Overexposure to UV radiation is associated with an excess of intracellular ROS, which causes lipid peroxidation, significantly impairing skin barrier function and promoting skin mutagenesis and carcinogenesis (Parisi et al. 2023). Current preventive management against skin photoaging, such as sunscreen with a specific sun protection factor (SPF) value, possesses several limitations. Individual variability, consumer misinterpretation, and overestimation of SPF value are the challenging hurdles yet to be overcome by current sunscreen technology. Concerns are also raised about the efficacy and safety of many sunscreen products around the world (Krutmann et al. 2020). Herbal sources for skin pathology therapy have continuously been prevalent for several points of interest, including the long history of utilization, lower cost, and lower adverse effects. Combining various herbal products may result in a synergistic effect and support in the dermatology pre- and clinical research (Sharma et al. 2022).

Several studies have investigated the antioxidant, anti-inflammatory, and anti-carcinogenic properties of active metabolites derived from *Glycyrrhiza glabra* and *Curcuma domestica* (Chang et al. 2017). However, most research focused on the isolated secondary metabolites of these herbs in photoaging treatment and were less systematic in their anti-aging mechanism. The development of bioinformatics enables researchers to utilize computer science for biological study through the in silico method. Among those methods is network pharmacology, an emerging and promising in silico approach that allows integrative and systemic analysis to uncover the complex mechanisms of drug compounds. Network pharmacology is widely used through computation and integrative approaches to discover the potential mechanisms of herbs and natural compounds in treating several diseases (Zhao et al. 2021). Therefore, this study employs a network pharmacology approach to systematically understand the mechanism of *Glycyrrhiza glabra* and *Curcuma domestica* as anti-skin photoaging.

The result of the PPI network illustrates the abundant interactions among targets. According to degree ranking in the PPI network, the potential therapeutic targets in the treatment of skin aging were TP53, TNF, AKT1, IL6, IL-1B, JUN, EGFR, MAPK3, CASP3, MMP-9, TGFB1, HIF1A, NF-κB1, ESR1, CTNNB1, PPARG, PTGS2, FOS, TLR4, and FN1. Previous study utilizing network pharmacology and molecular docking approach showed that TP53, AKT1, IL-6, JUN, MAPK3, CASP3, and PTGS2 may be the main regulators in the treatment of photoaging of Ba Zhen Tang, a herbal formula that consists of ginseng, *Atractylodes macrocephala*, poria, angelica, chuanxiong, white peony, *Radix Rehmanniae Preparata*, and licorice (Han et al. 2022). TP53 is a multifunctional protein that is related to cancer signaling pathways. It plays a crucial role in both skin aging and tumor formation. Therefore, it could be used as an indicator of the functional state of skin cells in anti-aging cosmetics (Gritsenko et al. 2017). A study found that blocking TNF-α inhibited the recruitment of inflammatory cells to the dermis in the UVB-irradiated mice (Sharma et al. 2020). Caspase 3 is an important regulator and activator of apoptosis during UVB-induced photoaging (You et al. 2021). The activation of the PI3K-Akt pathway increases NADPH oxidase activity and results in excessive production of ROS. ROS are mainly generated by oxidative cell metabolism and are involved in skin photoaging (Noh et al. 2016). UV exposure increases the production of prostaglandin E2 (PGE2) and causes disruption of the TGF signaling pathway. IL-1β plays an essential role in activating the synthesis of both fibroblast-derived IL-6 and collagenase/MMP-1, which has a role in breaking down dermal collagen in photoaging. MMP-9 is formed in response to solar UV radiation exposure to human skin (Csekes and Račková 2021).

EGFR has been widely studied as a potential target for cancer therapy. Previous study showed that inhibition of EGFR activity may disrupt skin homeostasis process that leads to keratinocytes alteration and premature skin aging (Gerber et al. 2016). A previous study shows that MAPK3 downregulation results in the decrease of proinflammatory response (Zheng et al. 2020b). This suggests the pivotal role of MAPK3 in skin photoaging process.

HIF-1α was found to be responsible in maintaining tissue homeostasis and neovascularization, thus possessing a central role in the regeneration of collagen and elastin in skin. Modulation of HIF-1α activity was proven to be effective to control skin aging process (Pagani et al. 2018). Another key regulator in skin photoaging and general inflammation process is NF-κB. Prior study explained that UV light exposure may result in the surge of NF-κB through IκB kinase (IKK)-mediated and independent pathway, thus becoming a core component in skin aging process (Haga and Okada 2022). ESR1 protein also poses as a component in core skin aging pathway. Previous study elucidated the role of fatty acid synthase (FASN)-activated ESR1 to promote cell regeneration (Yeh et al. 2021). CTNNB1 protein was proven to inhibit mitochondrial activity, particularly by inducing skin mitochondrial respiratory deficiency and dysfunction (Lee 2021). PPARG in the epidermis was shown to play an important role to dampen inflammatory process of the skin. Downregulation of PPARG activity might result in structural alteration and increase of inflammatory responses, inducing skin aging (Konger et al. 2021).

PTGS2, mRNA of cyclooxygenase-2 enzyme, was studied for its significant role in skin inflammation process. Previous research discovered that suppression of PTGS2 expression result in the reduction of carcinogen-

induced tumorigenic potential and tumor formation in the Krt14-Cre^{+} epidermal basal cells of UV-irradiated mouse, which correlate with the findings from KEGG enrichment analysis potential pathways (Moon et al. 2020). Fos and Jun proto-oncogene were proven to possess a significant link to skin inflammation process. JUN triggers the formation of AP-1 transcription complex through the forming of heterodimer with FOS, which main function is to control cell proliferation and differentiation (Cammayo-Fletcher et al. 2023). TLR4 modulation exhibit a beneficial role in skin photoaging pathophysiology. Inhibition of TLR4 suppress the secretion of anti-inflammatory mediators, such as MMP-9 and IL-8 triggered by UV ray exposure (Kumar 2021). Similarly, FN1 was studied as a candidate for skin aging biomarkers. A negative correlation was found between FN1 expression and both skin roughness and age. In addition, aged fibroblasts also demonstrate diminished FN1 level, indicating the pivotal role of FN1 in skin aging process (Kim et al. 2022).

Through GO functional enrichment analysis of overlapping targets, we discovered that potential targets of GG-CD to treat skin aging were closely associated with certain biological process, such as response to hormone, response to radiation and UV. Prolonged and repetitive exposure to UV radiation (UVR) causes changes in the skin that are similar to those found in chronological aging, leading to an accelerated aging process known as photoaging. UVR treatment and photoaging not only expose the skin to carcinogenesis, but also affect various systemic processes, such as attenuation of autoimmune diseases (Salminen et al. 2022). Hormones also have an influence on the skin aging process. Estrogen, for example, plays a beneficial role in skin physiology, while skin aging can be significantly delayed by the administration of estrogen (Stevenson and Thornton 2007).

According to KEGG enrichment analysis, GG-CD regulates numerous pathways. The putative primary mechanisms of GG-CD against skin photoaging include several pathways, such as cancer, apoptosis, TNF, and IL-17, and AGE-RAGE signaling pathways. Skin photocarcinogenesis and photoaging are highly correlated. Both diseases are mostly caused by UV radiation, which causes DNA alteration. UV exposure induces oxidative stress, which disrupts signal transduction pathways like MAPK and NF-κB (Bosch et al. 2015). TGF signaling has a significant role in the pathogenesis of photoaging and UV-induced skin cancer. TGF/Smad3 signaling in the dermis is activated by chronic UV exposure. This activation may cause a fibrotic reaction, which may be linked to premature collagen formation in photoaged skin. Increased levels of TGF stimulate keratinocytes and endothelial cells in the tumor microenvironment of UV-induced skin cancer, encouraging the development of cancer-associated fibroblasts and suppressing immune cell activities (Ke and Wang 2021).

AGE-RAGE signaling pathway in diabetic complications is also implicated in the aging process of the skin. AGEs impact various layers of the skin, inducing inflammation and aging. In the dermis, AGEs stimulate fibroblast apoptosis and disrupt the extracellular matrix by enhancing MMP-1, MMP-2, and MMP-9 activity, thereby impairing skin homeostasis. Additionally, AGEs impair the skin barrier function in the epidermis by reducing ceramide and cholesterol content. Furthermore, AGE-RAGE signaling leads to the destruction of keratinocyte cell structure and increased melanin production (Chen et al. 2022). Elevated IL-17 signaling also plays a significant role in the chronic inflammation observed in aged skin. In aged skin, there is a notable increase in the expression of IL-17 by various immune cells. IL-17 activates NF-κB in epidermal cells, altering homeostatic functions and causing inflammation. Consequently, targeting this pathway could potentially mitigate age-associated skin conditions (Solá et al. 2023).

The H-C-T-P-D network illustrated ten core compounds that exhibit the highest degree during the preliminary analysis. In summary, four compounds were the phytoconstituents for GG, while the other six were found in CD. Demethoxycurcumin (DMC), a derivate from curcumin that showed the highest degree, was widely studied for its excellent antioxidant potential. Previous study showed that DMC can protect the skin against excessive ROS exposure, furtherly confirmed by its exceptional 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging ability *in vitro* (Rohman et al. 2020; Solá et al. 2023). In agreement with the potential mechanisms of CD and GG revealed by KEGG enrichment analysis, 1,5-bis(4-hydroxy-3-methoxyphenyl)-1,4-pentadien-3-one, a curcumin analogue, exhibited an apoptotic and antiproliferative effect against cancer cell lines *in vitro* (Ismail et al. 2020).

Curcumin, one of CD main biomarkers, was broadly explored for its prominent pharmacological activities. This polyphenolic compound demonstrated its anti-aging effect through various mechanisms, including Nrf2/HO-1 signaling pathway activation, suppression of lipid peroxidation processes, and thioredoxin reductase (Trx Rs) activation, thus resulting in the inhibition of oxidative stress (Zia et al. 2021). The pre-clinical study showed that administration of curcumin encapsulated in elastic vesicle via topical could attenuate UV-induced photoaging in mice (Agrawal and Kaur 2010). Another diarylheptanoid, 1-(4-hydroxy-3-methoxyphenyl)-5-(4-hydroxyphenyl)-penta-(1E,4E)-1,4-dien-3-one, was identified as a core compound from CD. However, there is limited research available regarding the activity of this compound.

(E)-4-(4-hydroxy-3-methoxyphenyl)but-3-en-2-one, a sesquiterpene phytoconstituent of CD, was proven to suppress neutrophil ability to generate superoxide and elastase (Chen et al. 2010). In the skin photoaging process, excessive UV exposure triggers the migration of neutrophil and release of elastase, resulting in the degradation of elastase and upregulation of MMPs (Papaccio et al. 2022). Another phytoconstituent possessed by CD, (1e,4z,6e)-5-hydroxy-1,7-bis(4-hydroxyphenyl)hepta-1,4,6-trien-3-one, was proven to exhibit an antioxidant

activity through DPPH and ferric reducing antioxidant power (FRAP) assay, thus becoming a potential candidate for anti-aging agent (Chainoglou and Hadjipavlou-Litina 2020).

Isoliquiritigenin has been widely studied due to its anti-inflammatory, anticancer, and antiapoptotic attributes. This compound was proven to inhibit free radical, including ROS, and several anti-inflammatory mediators in UVB-exposed skin, becoming a potential agent for skin aging treatment (Park et al. 2021). Another compound extracted from GG, homobutein, was revealed to possess an excellent antioxidant property by capturing peroxyl radicals, thus inhibiting inflammatory cascade in UV-exposed skin (Pan et al. 2023). Liquoric acid, also derived from licorice, was revealed to possess anticancer activity by regulating EGFR (Mustafa et al. 2023). This result was in line with the discoveries from KEGG enrichment analysis, which shows potential activities from GG and CD bioactive in the pathway against cancer.

Network pharmacology serves as a preliminary study requiring several steps for drug development. Numerous studies have advanced network pharmacology research by integrating molecular docking and molecular dynamics studies (Que et al. 2021; Jiang et al. 2022; Zuhri et al. 2022). Molecular docking predicts the interactions between molecules, while molecular dynamics simulations analyze their movements over time (Aghajani et al. 2022). Network pharmacology study conducted by Xu et al. (2023) aims to delineate the molecular mechanism of MP gel, comprising Arnebiae Radix, Poria, Angelicae Sinensis Radix, Borneolum, and Cnidii Fructus, against skin photoaging. Following the network pharmacology study, they identified caspase-3, caspase-8, and caspase-9 as candidate proteins for molecular docking. Subsequent molecular docking results revealed that caspase-3 exhibited the highest binding affinity. Consequently, they formulated the MP gel and assessed its efficacy on UV-irradiated mice. The MP gel was proven to reduce caspase-3 expression, a key mediator in apoptosis associated with skin aging (Xu et al. 2023). These findings underscore the promising potential of network pharmacology in elucidating and developing therapeutic interventions for skin photoaging.

In summary, network pharmacology was utilized in our investigation to elucidate on the probable role of *Glycyrrhiza glabra* and *Curcuma domestica* in the photoaging treatment by targeting multiple proteins, including TP53, TNF, AKT1, IL-6, IL-1B, JUN, EGFR, MAPK3, CASP3, MMP-9, TGFB1, HIF1A, NF-βB1, ESR1, CTNNB1, PPARG, PTGS2, FOS, TLR4, and FN1. However, this study still has some limitations and further fundamental investigation is necessary to validate of these findings. Our study offered a novel perspective for future research on *Glycyrrhiza glabra* and *Curcuma domestica* in the treatment of skin photoaging. Further study could focus on developing a product formulation containing these extracts combination and evaluating its efficacy against skin photoaging. Additionally, molecular docking and molecular dynamic can be employed to prioritize potential targets for further *in vitro* or *in vivo* studies.

4. Conclusions

Based on network pharmacology, multiple compounds, targets, and pathways were involved in the effects of *Glycyrrhiza glabra* and *Curcuma domestica* on preventing skin aging. The core targets of GG-CD against skin aging include TP53, TNF, AKT1, IL-6, IL-1B, JUN, EGFR, MAPK3, CASP3, MMP-9. Meanwhile, demethoxycurcumin (DMC) and (3S)-2,3-dimethylpentane are the main compounds in GG and CD that contributed skin aging are, respectively. According to this viewpoint, a combination of *Glycyrrhiza glabra* and *Curcuma domestica* could be utilized as active ingredients for anti-aging products.

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Authors' contributions

ORA designed the study. ORA, FFF, CKJ carried out the computational work. ORA analyzed the data. ORA, FFF, CKJ wrote the manuscript. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare have no competing interests that relevant to the submitted work.

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