Proceedings of ICBioMed 2025 Symposium: Computational Modelling and Simulation for Biology and Medicine
DOI: 10.54254/2753-8818/2025.LD26430

Multi-Target Mechanisms and Translational Challenges of Traditional Chinese Medicine Active Components in Anti-Skin Photoaging

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Abstract. Ultraviolet radiation (UVA/UVB) induces skin photoaging through mechanisms including oxidative stress, extracellular matrix degradation, chronic inflammation, and DNA damage. In contrast, conventional chemical sunscreens carry safety hazards such as dermal penetration toxicity and endocrine disruption. Traditional Chinese Medicine (TCM) active components rely on the characteristics of multi-component and multi-target synergistic intervention; for example, baicalin scavenging reactive oxygen species (ROS) and repairing DNA damage, astragaloside IV promoting collagen synthesis, and asiaticoside enhancing barrier function. This study systematically explores the core mechanism of ultraviolet (UV)-induced skin photoaging, analyzes the multi-target regulatory effects of TCM components, such as baicalin, astragaloside IV, and asiaticoside, and compares them with conventional sunscreen agents to reveal the multi-target advantages in antioxidant, anti-inflammatory, collagen protection, and DNA repair pathways. At the same time, it clearly points out that their clinical translation of TCM components faces core bottlenecks. Such as low transdermal delivery efficiency, high batch-to-batch variability, and inadequate clinical sample sizes. In response to these limitations, transformative strategies such as developing novel delivery systems, optimizing strict quality control standards, and conducting large-sample, multi-center randomized controlled trials (RCTs) have been proposed from the perspectives of formulation technology, component standardization, and clinical research. These approaches establish a preliminary framework for developing TCM-based anti-photoaging products.

Keywords: Traditional Chinese medicine, anti- skin photoaging, UV, baicalin, astragaloside IV, asiaticoside.

1. Introduction

Ultraviolet radiation (UVA/UVB) is the main driving factor for skin photoaging. It leads to the deepening of skin wrinkles and the fragmentation of elastic fibers through mechanisms such as inducing oxidative stress (e.g., via depletion of reduced nicotinamide adenine dinucleotide phosphate (NADPH)), inducing the upregulation of matrix metalloproteinase-1/-3 (MMP-1/MMP-3), promoting the secretion of Tumor Necrosis Factor-α (TNF-α), and forming Cyclobutane

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pyrimidine dimers (CPDs) [1]. Clinical data show that the depth of wrinkles in chronically UV-exposed individuals increases by 0.12mm annually [1]. Furthermore, UVA penetrates into the dermis and continuously activates the Mitogen-activated protein kinase pathway (MAPK) through mitochondrial ROS, thereby further accelerating matrix destruction [2].

Although conventional chemical sunscreen agents such as oxybenzone can absorb UV, their transdermal absorption may cause endocrine disruption and allergic contact dermatitis, the incidence of which reaches 5.6% to 10.1% [3]. Additionally, their protective spectrum against UVA is often limited [3]. In contrast, the active components of TCM exhibit multi-target advantages. Astragaloside IV downregulates MMP-1 and promotes collagen synthesis by inhibiting the nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [4]; Baicalin scavenges ROS and reduces DNA damage [5]; Asiaticoside promotes collagen synthesis and eliminates ROS by inhibiting TNF-α-mediated inflammatory response [6]; Total flavonoids from Lycium barbarum leaves regulate the MAPK/MMP pathway [7]. However, approximately 90% of current mechanism studies are limited to cellular or animal models, and the sample size of RCTs is mostly less than 50 cases [8]. Furthermore, the variability in active component standardization can reach up to 30%. These factors jointly restrict the clinical translation of the TCM sunscreen system [2]. Therefore, it is particularly important to systematically analyze the mechanism of photoaging and TCM intervention targets, in order to provide a scientific basis for product development.

Based on this, this article aims to systematically explore the core mechanism of UV-induced skin photoaging and analyze the multi-target regulatory effects of three active components in TCM—baicalin, astragaloside IV, and asiaticoside—on counteracting oxidative stress, suppressing inflammatory responses, promoting collagen synthesis, and repairing DNA damage. It also makes a comparison of these TCM components advantages and disadvantages with conventional sunscreens. This comparison will clarify the unique value of their multi-target synergistic effects and highlight critical bottlenecks in clinical translation. Through the above research, it is expected to provide deeper scientific insights and a theoretical foundation for the development of safe and efficacious TCM-based anti-photoaging products.

2. Pathological mechanisms of ultraviolet-induced photoaging

The core mechanisms of UV-induced skin photoaging include oxidative stress, inflammatory response, matrix degradation, and melanin dysregulation. Firstly, UVB can directly damage DNA and activate mitochondria to produce ROS [5]. After UVB irradiation, ROS levels increase by 65% in HaCaT cells, while nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) decreases by 40% and superoxide dismutase (SOD) activity declines by 30% [8]. Excessive ROS activates key kinases in the MAPK pathway-p38 and c-Jun N-terminal kinase (JNK), leading to phosphorylation of c-Jun and c-Fos, constituent protein of the activator protein-1 (AP-1) transcription complex, and subsequently upregulating MMP-1 expression by 2- to 5-fold. This establishes a self-amplifying cycle where oxidative stress induces matrix degradation, further impairing skin barrier function [2, 7]. Although UVA does not directly damage DNA, it can stimulate the production of ROS by endogenous photosensitizers, leading to an increase in the mutation rate of mitochondrial DNA (mtDNA) [1]. Notably, TCM active components demonstrate significant potential for counteracting these mechanisms. For example, total flavonoids from Lycium barbarum leaves regulate the Nrf2/heme oxygenase-1 (HO-1) pathway, inhibit the expression of MMP-1/-2, and increase collagen synthesis [7]; flavonoids from the aerial parts of Astragalus membranaceus dose-dependently inhibit phosphorylation of stress response mediator JNK, thereby suppressing MMP-1 secretion [4].

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In addition, ROS activates the NF-κB pathway by phosphorylating the key kinase IκB kinase (IKK), which then phosphorylates the NF-κB inhibitor protein (IκB), leading to its degradation. This leads to IκB degradation and nuclear translocation of the NF-κB dimer, inducing a significant 2.5-fold increase in the secretion of pro-inflammatory cytokines including TNF-α and interleukin-1β (IL-1β) [2]. Concurrently, suppression of the transforming growth factor-beta/Smad(TGF-β/Smad) pathway reduces the synthesis of type I collagen by 30%-50% [8]. Experimental studies in mouse models show that 24 hours after UVB irradiation, the NF-κB activity in skin tissue increases threefold, significantly accelerating the degradation of extracellular matrix (ECM) [1]. In response to this, Ginsenoside Rb1 activates the Nrf2/Keap1/HO-1 pathway, reducing malondialdehyde (MDA) and TNF-α levels to improve photoaged skin cell viability [9]; flavonoids from Astragalus membranaceus aerial parts inhibit TNF-α-induced IL-6 secretion [4]; total flavonoids from Lycium barbarum leaves increase superoxide dismutase (SOD) activity by 40% and reduce collagen degradation [7].

In terms of matrix degradation imbalance, UVB induces MMP-1 expression by activating the extracellular signal-regulated kinases 1/2(ERK1/2) pathway, a key mitogen-activated protein kinase subpathway regulating cell proliferation. After fibroblasts were irradiated with 20 mJ/cm²UVB, MMP-1 mRNA levels increased fivefold, leading to specific cleavage of type I collagen fibers [1]. UVA reduces procollagen mRNA synthesis by 40% through AP-1 activation while enhancing MMP-1 activity twofold, ultimately leading fragmentation of dermal elastic fibers and the deposition of amorphous substances [2]. TCM intervention can effectively reverse this imbalance. The total flavonoids of Lycium barbarum leaves suppress ERK1/2 phosphorylation, reducing MMP-1 expression by 55% and increasing type I collagen content by 30% [7]. Flavonoids from Astragalus membranaceus aerial parts inhibit the secretion of MMP-1 and promote collagen synthesis in a dose-dependent manner (median inhibitory concentration IC50=25 μM) [4].

As for the aberrant melanin regulation, UVB increases melanin synthesis 2.5-fold by activating the cyclic adenosine monophosphate/protein kinase A pathway (cAMP/PKA pathway), inducing phosphorylation of the key transcription factor microphthalmia-associated transcription factor (MITF), and upregulating tyrosinase expression [8]. UVA inhibits ubiquitination-mediated tyrosinase degradation via mitochondrial ROS regulation, leading to hyperpigmentation [1]. For instance, salidroside suppress MITF phosphorylation and reduces tyrosinase activity by 40% [9]. Lycium barbarum leaf total flavonoids inhibit tyrosinase mRNA expression by 50% through suppression of the PKA/MITF pathway [7]; flavonoids from Astragalus membranaceus aerial parts reduce pigment deposition by modulating mitochondrial antioxidant enzyme activities [4].

3. Multi-target anti-photoaging effects of TCM bioactive components

3.1. Scutellaria baicalensis and its active component (baicalin)

Scutellaria baicalensis Georgi, the dried root of a plant from the Lamiaceae family, is bitter-cold in nature and enters Lung, Gallbladder, Spleen, Large Intestine, Small Intestine meridians [10]. It clears heat, drying dampness, purging fire and detoxifying. As a key heat-clearing and damp-drying herb, its dried root is rich in flavonoid active components, with baicalin as the core bioactive compound.

Baicalin, the primary bioactive constituent of Scutellaria baicalensis, exhibits a triple mechanism in the protection against skin photoaging. In terms of antioxidant defense, HaCaT keratinocyte assays confirm it eliminate 65% of UVB-induced ROS while increasing SOD activity by 40% and

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glutathione peroxidase(GSH-Px) activity by 35% via Nrf2 pathway activation [5]. Mechanism studies show baicalin binds Nrf2 to promote nuclear translocation, upregulates the expression of antioxidant effector molecules heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1), forming dual "scavenging-repair" protection [5]. At the level of DNA damage repair, baicalin reduces the formation of CPDs by 70%, and simultaneously upregulate the expression of the DNA helicase complex XPB/ERCC3 involved in nucleotide excision repair (NER) by 2.3-fold, significantly reversing the base damage induced by UVA [5]. Inflammation suppression experiments demonstrated that baicalin inhibits the nuclear translocation of NF-κB in a half-maximal inhibitory concentration (IC50=25 μM), reducing the secretion of IL-1β and TNF-α by 40%, and blocking the phosphorylation of the JNK/p38 MAPK pathway [5]. An ethanol-induced lymphocyte model further confirmed that 100μM baicalin reduce inflammation-associated DNA damage by 52% [5]. Clinical application has confirmed that the topical formulation containing 5% baicalin can significantly ameliorate photoaging manifestations, including reducing UV-induced erythema, enhancing skin barrier function and accelerating the repair of micro-damage. Its nanocarrier technology significantly enhances transdermal efficiency, especially demonstrating breakthrough effects in UVC protection. These advances support baicalin's translational potential in photoaging prevention and treatment.

3.2. Astragalus membranaceus and its active component (astragaloside IV)

Astragalus membranaceus (Fisch.) Bge., the dried root of Astragalus membranaceus (Fisch.) Bge. or Astragalus membranaceus var. mongholicus (Bge.) Hsiao (Fabaceae family). It is sweet and warm in property, and it enters the Lung and Spleen meridians. The Pharmacopoeia of The Pharmacopoeia of the People's Republic of China(2020 Edition) records its functions in tonifying qi and lifting yang, stabilizing the exterior to stop sweating, promoting diuresis and repairing sores [10]. It has been traditionally used in the repair of sores and ulcers. In recent years, the application of Astragalus membranaceus in skin diseases has received attention, providing a new direction for the protection and repair of photoaging. The effective components of Astragalus membranaceus can reduce the photodamage to the skin caused by ultraviolet rays, improve the hyperpigmentation caused by photoaging to a certain extent and delay skin aging. It has important application potential in photoaging protection and repair products. Astragaloside IV, as the core active component of Astragalus membranaceus demonstrates dual anti-inflammatory and immunomodulatory functions. Demonstrating its broad anti-inflammatory potential, astragaloside IV reduces the release of TNF-α by 50% in a diabetic rat wound model by inhibiting the phosphorylation of the NF-κB/p65 subunit, while enhancing macrophage phagocytic function by up to 30% [2]. It blocks the degradation of NF-κB inhibitor protein α(IκBα) to prevent nuclear translocation of the NF-κB dimer, thereby inhibits the release of IL-1β and IL-6 [2]. Furthermore, astragaloside IV upregulates the expression of COL1A1, a key gene for fibroblast collagen synthesis, and inhibits MMP-9 activity by 35% [2]. Clinical data show that the continuous use of topical preparations containing 3% to 5% Astragalus extract for 8 weeks can reduce the depth of fine lines on the skin by approximately 18% and increase the density of collagen fibers by 22% [2]; this effect is closely related to the TGF-β/Smad pathway [2]. In terms of microcirculation repair, Astragaloside IV promote the secretion of vascular endothelial growth factor (VEGF), increasing the rate of dermal angiogenesis by 40% after UV damage [2]. Experiments confirm that it regulates VEGF receptor phosphorylation through the PI3K/Akt pathway, accelerating endothelial cell migration and lumen formation [2]. These findings provide experimental evidence supporting astragaloside IV's multi-faceted potential in anti-

DOI: 10.54254/2753-8818/2025.LD26430

photoaging strategies, targeting key processes like inflammation, collagen preservation, and vascular remodeling.

3.3. Centella asiatica and its active component (asiaticoside)

Centella asiatica refers to the dried whole plant of the Apiaceae family. It is bitter, pungent and cold in property, and enters the liver, spleen and kidney meridians, with functions of clearing heat and promoting diuresis, detoxifying and reducing swelling. Recent studies have found that Centella asiatica exerts multi-dimensional protective effects in the field of anti-skin photoaging [10]. Its active component, asiaticoside, delays the process of photodamage through synergistic mechanism of collagen remodeling, oxidative stress suppression, and stratum corneum barrier restoration. Asiaticoside targets collagen regeneration as its core mechanism. Fibroblast experiments confirm that asiaticoside (25–100 μM) dose-dependently increases type I collagen synthesis by 62% and suppresses MMP-1 mRNA expression by 55% [11]. By activating TGF-β/Smad pathway, it upregulates COL1A1 gene transcription, blocks AP-1 binding to MMP-1 promoter, and accelerates keratinocytes migration, forming a dual regulation of "pro-synthesis and anti-degradation" [11]. At 24 hours post-UVB injury, asiaticoside increased re-epithelialization by 40%, the expression of tight junction protein ZO-1 increased by 2.3 times, and the transepidermal water loss (TEWL) of the epidermis decreased by 35% [12]. Notably, ROS clearance was synergistically enhanced when combined with vitamin C (CI=0.8), suggesting a synergistic effect of the antioxidant network [8]. Clinical data showed that topical 2% asiaticoside applied for 8 weeks increased collagen density by 28% vs. baseline and restored epidermal barrier thickness to 92% of normal levels [13].

Certain active components such as paeoniflorin can activate the Nrf2/HO-1/NQO1 pathway to scavenge ROS, inhibit UVA-induced fibroblast apoptosis (with 40% reduced apoptosis rate vs. untreated controls) and ameliorating murine skin damage [8]. Luteolin suppresses the MAPK pathway, downregulating MMP-1 expression by 55% and thereby reducing collagen degradation [9].

This section summarizes the mechanistic basis for the application of TCM active components (e.g., baicalin, astragaloside IV, and asiaticoside) in combating skin photoaging through multi-target synergy, encompassing antioxidant defense, inflammation suppression, collagen homeostasis regulation, and barrier function restoration. An integrated photoaging intervention system of "prevention and restoration" has been established. Although its multi-target synergy demonstrates significantly superior efficacy to the unidimensional photoprotection of conventional sunscreens at the mechanism level, its clinical translation nevertheless faces core bottlenecks, such as transdermal delivery efficiency, constituent standardization and large-scale clinical validation studies.

4. Comparative advantages and translational bottlenecks: TCM vs. conventional sunscreens

In contrast to conventional sunscreens, the multi-target advantages of TCM active components are evident. Physical sunscreens e.g., titanium dioxide(TiO_2), primarily block UVB radiation through ultraviolet reflection and scattering [3], whereas chemical sunscreens such as oxybenzone(BP-3) absorb UV radiation but exhibit incomplete UVA protection and carry risks of endocrine disruption and hypersensitivity reactions [1, 3]. Leveraging multi-target synergistic mechanisms, TCM active components thus demonstrate distinctive advantages in intervening photoaging cascade reactions.

However, the clinical translation of TCM-based anti-photoaging preparations faces three major bottlenecks in transdermal delivery efficiency, constituent standardization, and clinical evidence robustness. The transdermal efficiency of TCM formulations(e.g., decoctions and ointments) is only 5% to 10%, thus limiting drug delivery to the dermis. The oral bioavailability remains low. For

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instance, the oral bioavailability of Astragalus polysaccharides is less than 20%, and they are easily destroyed by enzymatic hydrolysis in the gastrointestinal tract [4, 8]. The novel nanodelivery systems increase the transdermal rate threefold, such as liposome-encapsulated baicalin. Microneedle technology enhances polysaccharide delivery efficiency 4-6-fold, while lipid nanoparticle-encapsulated Phlai oil increases zingiberene penetration flux 4.63-fold [8]. These techniques achieve spatiotemporally controlled release by regulating particle size and surface charge [4, 8], but they have engineering challenges such as poor formulation stability (particle size increases by 50% after 3 months of storage at 4 ℃) and high cost [4]. In terms of constituent standardization, batch-to-batch variation of Astragalus polysaccharides reaches up to 30%, resulting in an IC50 fluctuation range of 20-45 μM [4, 12]. The alkaloid composition of different primordia uncaria varies by more than 40%, and the quality control technology needs to be optimized [12]. In terms of clinical evidence, currently 90% of the research is limited to cell or animal models, and the sample size of human trials is generally less than 50 cases and lacking multicenter RCT validation. The sole Phase III clinical trial showed that TCM-containing sunscreens increased epidermal moisture content by 18% but showed no significant improvement in gold-standard endpoints such as wrinkle depth (-0.05mm) and elasticity value (+5%) [7, 8].

These challenges reflect the key gap in the research on anti-photoaging of TCM between "mechanism validation" and "clinical translation" - while demonstrating efficacy in in vitro assays (e.g., antioxidant and anti-inflammatory activities), its large-scale application is constrained by underdeveloped pharmaceutical technologies, rudimentary quality control, and insufficient clinical evidence [3, 8].

5. Future translational strategies and development prospects

The active components of TCM demonstrate significant advantages of multi-mechanism synergistic intervention in the field of anti-skin photoaging. They establish a protective chain covering the entire process of ultraviolet damage through multiple pathways such as anti-oxidative stress, inhibition of inflammatory responses, and promotion of collagen synthesis, and its overall toxicity risk is significantly lower than that of conventional chemical sunscreens. Compared with the single physical barrier or chemical absorption mechanisms of conventional sunscreens, the multi-target regulation mode of TCM has prominent advantages in compensating for the limitations of the protective spectrum and repairing skin damage. However, there are still some transformation bottlenecks, such as insufficient standardization of components, stability and cost control problems of nanopreparation, small sample size of clinical research, and lack of multi-center RCT verification. Based on the current research progress, future transformation strategies should focus on multi-dimensional breakthroughs. By applying network pharmacology and multi-omics technologies, the synergistic mechanism among the active components of TCM is deeply analyzed, especially the interaction targets of core components such as baicalin and asiaticoside in the antioxidant and anti-inflammatory pathways. New delivery technologies such as exosome-based drug delivery systems and microneedle arrays develop to significantly improve transdermal efficiency and ensure long-term stability of preparations [14]. Establish strict quality control standards for the fingerprint-based of active components, verify the therapeutic effect through multi-center large-sample clinical trials, and focus on monitoring key indicators such as wrinkle depth and skin barrier function; At the same time, by integrating the theory of TCM pattern differentiation, personalized compound preparations are developed for different photoaging patterns, such as a collagen metabolism regulation plan with asiaticoside as the main component, and ultimately a high-efficiency translational pathways from mechanism research to clinical application is constructed [14].

DOI: 10.54254/2753-8818/2025.LD26430

6. Conclusion

This review examines the mechanisms through which ultraviolet radiation drives skin photoaging—including oxidative stress induction, extracellular matrix degradation, and DNA damage—and proposes replacing conventional sunscreens with TCM active components. In addition, this study shows that baicalin can scavenge ROS and repair DNA damage, astragaloside IV can inhibit MMP-9 while promote angiogenesis, and asiaticoside enhances collagen synthesis to strengthen barrier function. These active components of TCM construct a prevention-repair system through multi-target synergy, which is mechanistically superior to the single mechanism of chemical sunscreens. However, its clinical translation remains constrained by low transdermal efficiency, significant batch-to-batch variation in components and insufficient clinical evidence. In the future, it is necessary to achieve a breakthrough from the mechanism advantage to clinical efficacy of TCM's anti-photoaging through the development of novel delivery systems, the optimization of quality control standards and large-scale validation.

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