Natural Resources for Human Health

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Review

View Article online

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Received 11 November 2025
Revised 27 November 2025
Accepted 16 June 2026
Available Online 02 September 2026

Edited by Kannan RR Rengasamy

KEYWORDS:
Isoflavones
Photoaging
Oxidative Stress
Collagen
ROS

Natr Resour Human Health 2026; 6 (4): 419–435
https://doi.org/10.53365/nrfhh/224622
eISSN: 2583-1194

Isoflavones in the Prevention of Photoaging: Antioxidant and Collagen-Regulating Mechanisms—An Integrative Review

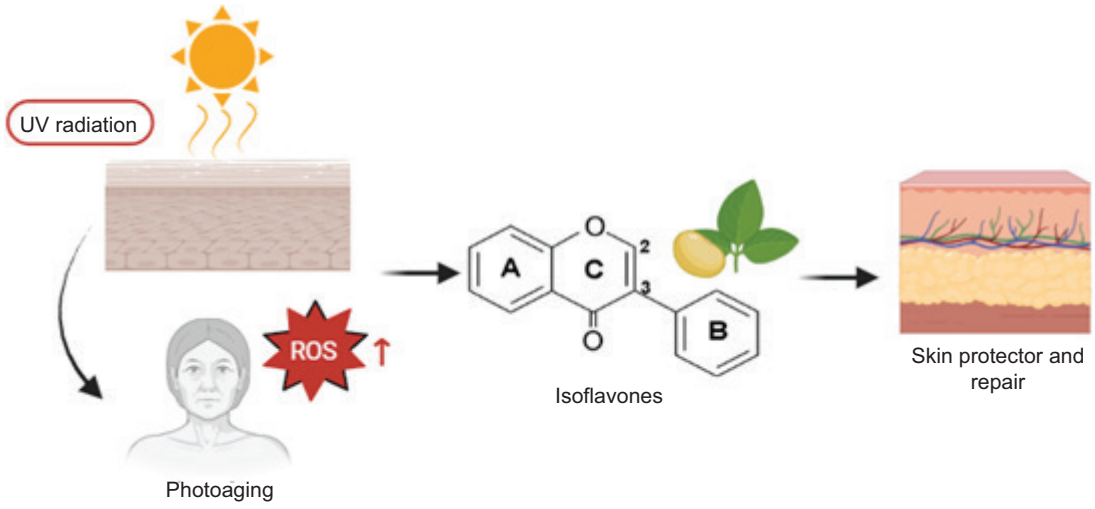
Yuri Amelia[1], Wahyu Widowati[2,*], Fen Tih[2], Rizky Pratama[3]

[1]Master Program of Skin Ageing and Aesthetic Medicine, Faculty of Medicine, Maranatha Christian University, Bandung, Indonesia
[2]Department of Pharmacology, Faculty of Medicine, Maranatha Christian University, Bandung, Indonesia
[3]Biomolecular and Biomedical Research Center, Aretha Medika Utama, Bandung, Indonesia

ABSTRACT: Skin aging due to ultraviolet (UV) light exposure, known as photoaging, is a form of extrinsic aging characterized by increased oxidative stress, collagen degradation, and structural changes in the dermis. Chronic UV exposure triggers the formation of reactive oxygen species (ROS), activation of matrix metalloproteinases (MMPs), inflammation, and decreased tissue regeneration. Soy isoflavones, as natural phytoestrogens, offer potential as antiphotoaging agents through potent antioxidant mechanisms and stimulation of collagen biosynthesis. This article aims to explore the scientific evidence regarding the potential of soy isoflavones, especially genistein and daidzein, in preventing and repairing skin damage due to photoaging. Although isoflavones are known to be antioxidants, integrative studies comparing their effects based on biological models are limited. A systematic literature search was conducted on three major databases (PubMed, Google Scholar, and Semantic Scholar) using the following keywords: soy isoflavone, photoaging, collagen, and MDA. Selection followed the PRISMA flow, from which eight articles were selected for thematic analysis. The findings showed that isoflavones effectively decreased ROS and MMPs activity, and increased COL1A1 expression in both *in vitro* and *in vivo* models. This molecular-level repair translated to human-level benefits, as clinical trials showed improved hydration, elasticity, and decreased wrinkles. Key biomarkers analyzed included ROS, MMP-1, IL-6, TEWL, and COL1A1. Soy isoflavones protect the skin from premature aging by reducing oxidative stress, inhibiting collagen degradation, and stimulating collagen synthesis. This makes isoflavones a promising ingredient in natural antiaging therapies.

* Corresponding author.
E-mail address: wahyu_w60@yahoo.com; wahyu.widowati@maranatha.edu (Wahyu Widowati)

GRAPHICAL ABSTRACT



1. INTRODUCTION

The phenomenon of global population aging has become a major focus of public health and social policy. According to reports from the National Institute on Aging (NIA) and the World Health Organization (WHO), the world is currently facing unprecedented demographic conditions, where the number of older people (aged ≥ 65 years) is expected to surpass the number of children aged below 5 years in the next few decades. In 2010, the global elderly population was estimated at 524 million, and this figure is projected to nearly triple to 1.5 billion by 2050, with the majority of the increase occurring in developing countries (World Health Organization, 2011). This increase in the elderly population is triggered by a decline in the birth rate and an increase in life expectancy due to advances in health technology and improved socioeconomic conditions. The research by Fernandes et al. emphasized population aging as a direct result of declining fertility and increasing life expectancy. In the periodic demographic model, the population will naturally age in the absence of births and migration, leading to the progressive increase in the elderly proportion over the years (Fernandes et al., 2023). In the Asia-Pacific region, including Indonesia, the dynamics of aging are faster than in developed countries. According to the HelpAge International report, Indonesia is experiencing a rapid demographic transition. In 2020, the number of elderly people reached more than 27 million, and it is projected to increase to more than 48 million by 2035. Indonesia is expected to become one of the countries with the largest elderly population in the world, which poses major challenges in the fields of health services, social protection, and economic development, including the elderly group (ESCAP, 2022). In addition to the quantitative growth of the elderly population, the quality of life of the elderly is now a major focus in the fields of health research and policy. A bibliometric study conducted by Zhang et al. showed a significant increase in scientific publications related to healthy aging since the beginning of the 21st century, signaling that global attention has shifted from mere longevity to healthy, active, and productive old age. Much of this research is directed toward chronic disease prevention strategies, enhancing functional capacity, developing lifestyle, and integrating molecular-based interventions in dermatology and skin regeneration. This emphasizes the importance of a multidisciplinary approach in addressing the broad implications of the aging process, including skin aging as an indicator of systemic health (Zhang et al., 2024)

Within this context of aging, skin health is a major focus. Skin aging is broadly classified into two distinct processes, intrinsic and extrinsic aging. Intrinsic aging is a natural degenerative process that occurs due to genetic and cellular metabolic changes over time. Meanwhile, extrinsic aging is triggered by environmental factors such as UV rays, pollution, and unhealthy lifestyles. Both mechanisms contribute to a decline in cell function, fragmentation of collagen fibers, and increased activity of destructive enzymes such as matrix metalloproteinases (MMPs). Aging also leads to decreased proliferative capacity of fibroblasts and increased senescent cells, which overall deteriorates skin structure and function (Kim & Park, 2016). Photoaging is a form of skin aging induced by long-term exposure to ultraviolet (UV) light. UV light induces biological and structural changes in the epidermis and dermis that are morphologically distinct from those of chronological or intrinsic aging. Photoaging is clinically characterized by coarse wrinkles, hyperpigmentation, loss of

skin elasticity, and thickening of the dermis due to abnormal accumulation of elastotic material, called solar elastosis (Kang, 2019). UV radiation, particularly UVA and UVB, penetrates the epidermis and dermis, generating free radicals or reactive oxygen species (ROS) such as superoxide, hydrogen peroxide, and hydroxyl radicals. These ROS induce the expression of MMPs, especially MMP-1 and MMP-9, which degrade collagen and elastin in the dermis. In addition, UV also increases the expression of inflammatory cytokines (Interleukin-1β [IL-1β], tumor necrosis factor-α [TNF-α]), as well as causes DNA damage and p53 activation, which accelerate cell senescence and apoptosis (Chen et al., 2021; Hussen et al., 2025; Tanveer et al., 2023).

In the context of skin aging, preventive and therapeutic strategies focus on the use of antioxidant compounds to neutralize ROS, reduce oxidative stress, and strengthen the cellular defense system. Antioxidants derived from endogenous and exogenous sources, including vitamins, polyphenols, flavonoids, and plant extracts, play important roles in protecting skin cells from UV-induced oxidative damage and inflammatory responses (Chen et al., 2021; Hussen et al., 2025). These bioactive compounds not only protect structural components of the skin but also modulate molecular pathways involved in inflammation, extracellular matrix degradation, and skin regeneration (Tanveer et al., 2023; Liu et al., 2024). Several natural compounds, including green tea polyphenols, resveratrol, curcumin, and isoflavones, have been investigated for their potential antiaging effects through antioxidant, anti-inflammatory, and collagen-protective mechanisms (Tanveer et al., 2023; Wójciak et al., 2024a). Isoflavones are a group of polyphenolic compounds naturally found in soybeans, tempeh, red clover, and *Pueraria lobata*. The main components of isoflavones include genistein, daidzein, and glycitein, which can bind to estrogen receptor-β in the skin. They exhibit antioxidant and anti-inflammatory activities and modulate collagen gene expression, including Collagen1A1 (COL1A1) (Desmawati & Sulastri, 2019; Liu et al., 2020). Considering the high prevalence of photoaging in tropical populations and the increasing demand for nature-based therapies, this review aims to present current scientific evidence on the antiaging mechanisms of isoflavones, especially their antioxidant and collagen-regulating properties, to enrich scientific understanding and provide a foundation for the development of isoflavone-based topical and oral therapies in antiaging dermatology.

2. METHOD

The literature search was conducted systematically through three main databases, namely PubMed, Google Scholar, and Semantic Scholar, using the following Boolean keyword combinations: "soy isoflavone" AND "collagen" AND "MDA" AND "skin photoaging." The literature selection process was carried out following the PRISMA guidelines (Figure 1).

2.1. Inclusion criteria

(1) *In vitro, in vivo, in silico*, or clinical study articles, (2) Published within the last 10 years (2015–2025), (3) In Indonesian or English, (4) Available on an open access basis, (5) Focus on the effects of soy isoflavones on skin photoaging.

2.2. Exclusion criteria

(1) Articles that are not available in open access, (2) Articles not in Indonesian or English language, (3) Not relevant to the skin photoaging or antiaging.

2.3. Google scholar

(1) Articles identified: 184, (2) Filter performed: 72, (3) Screening of titles and abstracts according to exclusion criteria: 5, (4) Full text: 3, (5) Final include: 3.

PubMed: (1). Article identified: 3, (2). Filter performed: 3, (3). Screening of titles and abstracts according to exclusion criteria: 2, (4). Full text: 1, (5). Final include: 1.

2.4. Semantic scholar

(1) Articles identified: 77, (2) Filtered: 36, (3) Title and abstract filtering according to exclusion criteria: 5, (4) Full text: 4, (5) Final include: 4.

3. MAIN CHEMICAL STRUCTURE OF ISOFLAVONES

Isoflavones are a group of phenolic compounds that are structurally included in phytoestrogens, due to their similarities with endogenous estrogens. They bind to estrogen receptors, especially Estrogen Receptor-β (ER-β), which is found in many skin tissues (Desmawati & Sulastri, 2019; Lephart & Naftolin, 2022).

The three most common and widely studied forms of isoflavones are genistein, daidzein, and glycitein (Figure 2). All three forms consist of a 3-phenylchromen-4-one basic skeleton that is responsible for their antioxidant and estrogenic activities. Genistein has hydroxyl groups at positions 5, 7, and

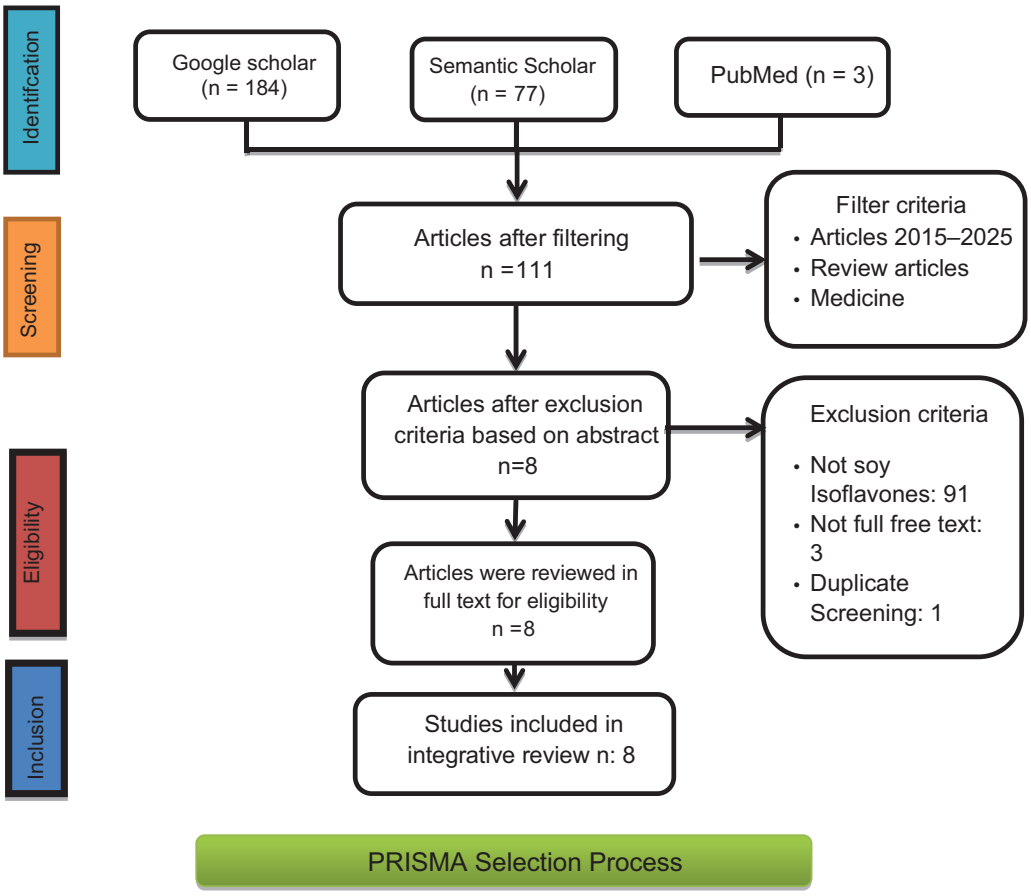


Figure 1. PRISMA literature selection process.

4', and is known to be the most biologically active isoflavone for increasing collagen expression (Liu et al., 2020; Wójciak et al., 2024a). Daidzein has a similar structure but without the hydroxyl group at position 5, while glycitein contains a methoxy group at position 6, which gives it slightly different chemical properties (Liu et al., 2020). These structural properties affect antioxidant activity, skin penetration ability, and interaction with estrogen receptors. The main source of isoflavones is the soybean plant (Glycine max), which has the highest content among all leguminosae. Besides soybean, other plants rich in isoflavones include red clover (Trifolium pratense), P. lobata (Kudzu), and lupin seeds (Desmawati & Sulastri, 2019; Kim, 2021). Soybean (G. max) is the main source of genistein, daidzein, and glycitein in glycoside form (Kim, 2021; Ubaid et al., 2023). Red clover (T. pratense) contains biochanin A and formononetin, which are precursors of daidzein and genistein (Desmawati & Sulastri, 2019; Wójciak et al., 2024a). P. lobata (Kudzu), rich in daidzein and puerarin, is mainly used in traditional Asian medicine (Liu et al., 2020; Ubaid et al., 2023). Other plants, such as lentils, mung beans, and chickpeas, also contain lower amounts of isoflavones, but still contribute as phytoestrogens (Desmawati & Sulastri, 2019; Kim, 2021).

Isoflavones are consumed mainly in the form of glycosides (sugar-bound), which are not biologically active. Once consumed, these compounds are hydrolyzed in the gut by β-glucosidase enzymes and gut microflora into aglycone forms, which are more absorbable and active (Liu et al., 2020; Ubaid et al., 2023). The aglycone form shows greater potency due to its smaller molecular size, lipophilic nature, and ability to penetrate the stratum corneum more efficiently than the glycoside form. Daidzein, for example, can be further converted to equol, which has a higher affinity for the ER-β receptor (Lephart & Naftolin, 2022; Ubaid et al., 2023). This metabolite can enter the systemic circulation and reach skin tissues, although levels depend on the individual's ability to produce equol (Lephart & Naftolin, 2022; Ubaid et al., 2023). Isoflavones in circulation undergo conjugation and convert to glucuronide or sulfate forms, which, although reduces their bioactivity, are reactivated by local

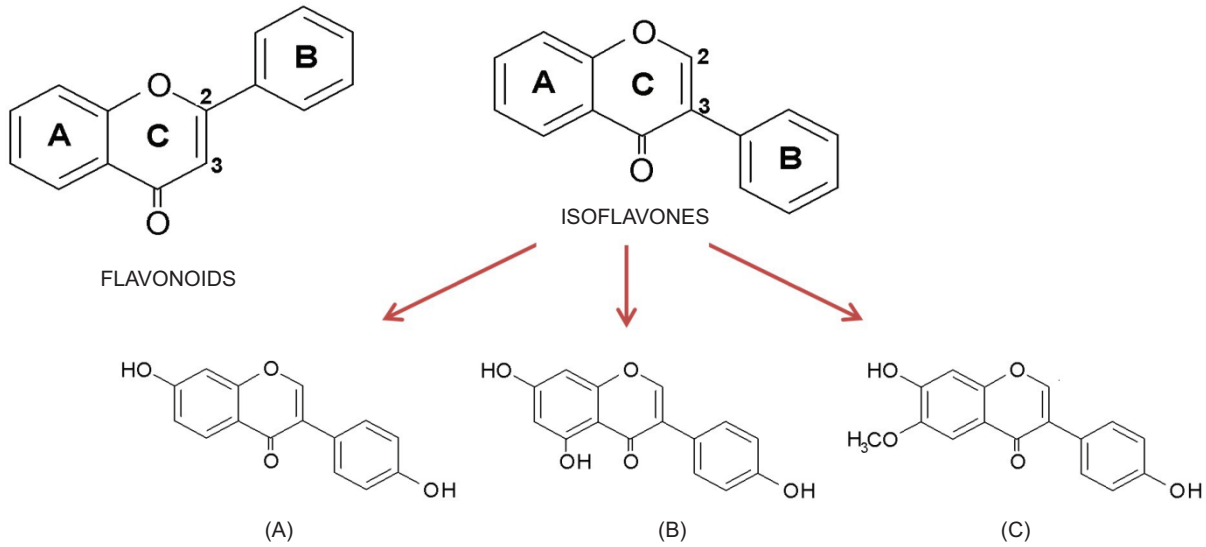


Figure 2. General structure of flavonoids and isoflavones and the chemical structure of aglycone forms of soy isoflavones: (A) daidzein, (B) genistein, and (C) glycitein (Wójciak et al., 2024a).

enzymes in target tissues, including the skin (Ubaid et al., 2023). In topical preparations, the aglycone form shows better skin penetration than the glycosidic form due to its smaller molecular size, higher lipophilicity, and non-requirement for activation enzymes (Liu et al., 2020; Wójciak et al., 2024a). Research shows that genistein in aglycone form can penetrate the stratum corneum and reach the dermis layer, allowing interaction with fibroblasts and thereby stimulation of collagen synthesis (Liu et al., 2020; Wójciak et al., 2024a).

4. MECHANISM OF SKIN PHOTOAGING

Photoaging is a process of premature skin aging caused by chronic exposure to UV radiation, especially UVA (320–400 nm) and UVB (290–320 nm). Such UV exposure can cause biological and structural changes in the skin, resulting in the appearance of aging skin, such as wrinkles, elastosis, uneven pigmentation, dryness, and decreased elasticity (Brar et al., 2025; Samantaray, 2024).

Exposure to UV radiation is a major factor in skin photoaging, primarily by inducing a swift and substantial rise ROS within cutaneous cells. This burst of highly reactive molecules, including superoxide anion (O_2), hydroxyl radicals (HO), and hydrogen peroxide (H_2O_2), overwhelms the skin's antioxidant capacity, leading to oxidative stress. The resultant oxidative damage is extensive enough that it promotes the degradation and cross-linking of collagen and elastin, which causes lipid peroxidation in cell membranes, disruption of cellular integrity, and, crucially, induces DNA damage, all of which drive the visible signs of premature aging (Augustyniak et al., 2016; Chen et al., 2021; Kang, 2019).

This UV-induced cellular injury includes significant DNA damage via a distinct mechanism. Specifically, UVB radiation is directly absorbed by the DNA molecule itself, forming photoproducts such as Cyclobutane Pyrimidine Dimers (CPDs), which physically distort the DNA helix and interfere with replication and transcription (Samantaray, 2024). Conversely, the longer wavelength UVA radiation penetrates deeper and causes indirect DNA damage, primarily by generating ROS that induce oxidative lesions such as 8-oxoguanine (Chen et al., 2021). If the cell's repair mechanisms, such as Nucleotide Excision Repair (NER), fail to correct this extensive DNA damage, it can trigger cell apoptosis (programmed cell death) to eliminate the compromised cell. However, if the damage persists and the cell survives, these unrepaired lesions can lead to crucial mutations in oncogenes and tumor suppressor genes, ultimately initiating the process that culminates in skin cancer (Chen et al., 2021; Samantaray, 2024).

Beyond direct molecular damage, this oxidative stress profoundly impacts gene expression by activating critical transcription factors, notably Activator Protein-1 (AP-1) (Hussen et al., 2025). The activation of AP-1 is directly responsible for the increased expression of various MMPs, which are the main destructive agents in photoaged skin. Among these, MMP-1 (collagenase), MMP-3 (stromelysin), and MMP-9 (gelatinase) actively target and degrade Type I and Type III collagen and elastin fibers. This fragmentation and the resultant decrease in the overall collagen severely compromise

the extracellular matrix, leading to wrinkles and loss of elasticity (Hussen et al., 2025; Liu et al., 2020; Tanveer et al., 2023). Simultaneously, UV exposure activates Nuclear Factor kappa-light-chain-enhancer of activated B (NF-κB). This activation drives a sustained proinflammatory response, stimulating synthesis and secretion of cytokines such as IL-1, IL-6, and Tumor Necrosis Factor-alpha (TNF-α) (Hussen et al., 2025). Chronic or repeated exposure to UV leads to persistent, chronic, low-grade inflammation within the skin, which creates a vicious cycle that accelerates photoaging. These inflammatory cytokines directly contribute to increased synthesis and activity of MMPs. The increased MMP activity intensifies the breakdown and fragmentation of existing collagen, and simultaneously, the inflammatory environment inhibits the ability of fibroblasts to synthesize new collagen. Consequently, this chronic inflammatory state rapidly depleted the skin's structural integrity, leading to severe and visible skin damage (Chen et al., 2021; Tanveer et al., 2023).

The entire process of UV-induced degradation is further exacerbated by intrinsic, age-related hormonal changes, particularly estrogen. Estrogen is critical for maintaining robust skin structure. Its sharp decline following menopause significantly accelerates aging process. Specifically, estrogen deficiency contributes to a marked reduction in epidermal thickness and dermal collagen content, which directly diminishes elasticity and slows wound healing. This hormonal shift amplifies the mechanisms of photoaging, as estrogen loss reduces natural antioxidant defenses and makes the skin more susceptible to UV-induced oxidative damage (Lephart & Naftolin, 2022; Tanveer et al., 2023).

Ultraviolet radiation also contributes to photoaging at a fundamental cellular level by inducing epigenetic changes. These modifications disrupt normal cellular function and gene expression. These detrimental modifications include widespread alterations to DNA methylation patterns and aberrant histone modifications. Most importantly, UV exposure accelerates the shortening of telomeres, which acts as a cellular clock. Once telomeres reach a critically short length, the cell is signaled to enter senescence (premature aging) or undergo apoptosis. These epigenetic disruptions and telomere damage drastically reduce the replicative lifespan of skin cells, undermining tissue maintenance and driving the visible signs of photoaging (Bao et al., 2023; Samantaray, 2024).

5. ROLE OF POLYPHENOLS AS ANTIOXIDANTS

Polyphenols found in food are regarded as potent antiaging agents because they possess strong antioxidant properties that allow them to effectively target key mechanisms of cellular damage. These compounds directly neutralize reactive oxygen species (ROS), protecting the skin from the oxidative stress that is exacerbated by chronic UV radiation exposure, a primary cause of photoaging characterized by DNA damage, MMP activation, and hormonal decline. By interfering with these destructive pathways, polyphenols help to reduce inflammation and slow down collagen degradation, thereby maintaining skin integrity. Therefore, incorporating polyphenols through supplementation is considered an essential part of preventative strategies against photoaging, alongside measures such as photoprotection and hormonal modification (Liu et al., 2024).

5.1. Delivery systems and formulation challenges of soy isoflavones

Soy isoflavones such as genistein and daidzein have great potential in the field of health, as antioxidants, and anti-inflammatory and antiaging agents. However, their clinical utilization is still limited due to low bioavailability, low water solubility, rapid metabolism, and poor gastrointestinal absorption (Chauhan et al., 2025; Yuan et al., 2024). Some of the major formulation challenges in the development of isoflavone-based products include low solubility, poor chemical stability, and high degradation rates during storage processes and in the gastrointestinal tract (Chauhan et al., 2025; Yuan et al., 2024). To overcome these challenges, various nanotechnology-based formulation approaches have been developed:

5.1.1. Liposome

Liposomes are phospholipid-based delivery systems with competitive skin penetration capacity, biocompatibility, nontoxicity, and nonimmunogenicity. Liposomes can encapsulate isoflavones either in the lipid bilayer or in their internal core, depending on the solubility properties of the active compound. Liposomes containing soy isoflavones have been successfully applied in commercial antiaging cosmetic formulations with improved delivery efficiency to the skin (Khan, 2018).

5.1.2. Nanoparticles and nanoformulations

Nanoparticle-based formulations such as polymeric nanoparticles, lipid nanocarriers, and self-emulsifying systems have been developed to improve the solubility, stability, and absorption of isoflavones. These nanodelivery systems can prolong the release of active substances, protect isoflavones from metabolic degradation, and significantly increase their bioavailability. Lipid nanoparticles (NLC) and micelles (using Pluronic F127 and Plasdone S630) were shown to increase

the bioavailability of isoflavones by several folds compared to conventional formulations (Chauhan et al., 2025).

5.1.3. Gelatin microspheres by spray drying technique

Spray-drying-based solid dispersion techniques have been applied to increase the solubility and bioavailability of daidzein, one of the main soy isoflavones. The spray-dried solid dispersions exhibited an amorphous state in most formulations, resulting in improved aqueous solubility, enhanced in vitro release, and increased oral bioavailability. This technique is promising for pharmaceutical and nutraceutical applications because it provides a simple and effective approach for improving the oral delivery of poorly soluble isoflavones (Panizzon et al., 2019).

The application of nanoformulation technology also faces challenges, including the complexity of the production process and high industrial cost, potential long-term toxicity of the carriers used in nanoparticles, and long-term stability of nanoformulations, especially liposomes, which tend to undergo aggregation or degradation (Dwivedi et al., 2023). Thus, the development of effective and safe soy isoflavone formulations requires the integration of innovative nanotechnologies with a deep understanding of the active compound characteristics, as well as continuous formulation optimization for clinical and cosmetic applications.

6. MOLECULAR MECHANISMS OF ISOFLAVONES IN PHOTOAGING PREVENTION

Isoflavones, especially from soybeans such as genistein and daidzein, are active compounds with antioxidant, anti-inflammatory, and photoprotective effects that have been shown to inhibit the process of skin photoaging due to UV exposure (Cho et al., 2019; Tang et al., 2022).

6.1. Antioxidant activity against ROS

Isoflavones, a class of polyphenols, are potent antiaging compounds recognized for their ability to significantly mitigate oxidative stress in the skin. Their primary mechanism involves strong antioxidant activity, which allows them to efficiently neutralize the various ROS produced following UV exposure, including superoxide anion (O_2), hydroxyl radicals (HO), and hydrogen peroxide (H_2O_2). Notably, the isoflavone genistein exhibits specific efficacy by directly acting to reduce the production of ROS in skin cells. This dual action of neutralizing existing radicals and suppressing the new generation effectively protects skin cells from widespread oxidative damage (Liu et al., 2020; Tang et al., 2022; Wójciak et al., 2024b).

6.2. Protection against DNA damage

The isoflavone genistein and broader soy extracts provide significant photoprotection by directly intervening in the molecular damage caused by UV radiation. Specifically, these compounds reduce DNA damage by actively suppressing the formation of UVB-induced cyclobutane pyrimidine dimers (CPDs), which are the primary photoproducts that distort DNA structure. By preventing the formation of these lesions, genistein and soy extracts help maintain genomic integrity, thereby safeguarding skin cells from the mutations that could otherwise initiate or promote the development of skin cancer. This protective mechanism is crucial for mitigating the long-term carcinogenic effects of chronic sun exposure (Tang et al., 2022).

6.3. Inhibition of inflammatory and matrix degradation pathways

Isoflavones exert powerful anti-inflammatory and structural protective effects by directly targeting the key signaling pathways activated by UV radiation. These compounds effectively suppress two proinflammatory transcription factors, NF-κB and AP-1. By inhibiting the activation of NF-κB, isoflavone reduces the expression and release of a broad spectrum of inflammatory cytokines, including IL-1, IL-6, CXCL1, and TNF-α. Simultaneously, the suppression of the AP-1 pathway directly interferes with the enzymatic breakdown of the skin's structure. AP-1 activation is the primary driver in the production of MMPs following UV exposure. By inhibiting AP-1, isoflavone in turn inhibits the activity of key MMPs, including MMP-1, MMP-3 and MMP-9. This dual-action mechanism, which suppresses both the master inflammatory switch (NF-κB/AP-1) and their destructive outputs (cytokines and MMPs), is essential for preserving the structural integrity and elasticity of the skin against UV damage (Tang et al., 2022).

6.4. Increased collagen production and synthesis

Isoflavones offer a dual benefit in maintaining the dermal structure by both stimulating the production of new collagen and protecting the existing fibers. Specifically, these compounds enhance Type I collagen synthesis by activating the TGF-β/Smad signaling pathway within dermal fibroblasts, thereby promoting tissue regeneration. Simultaneously, isoflavones provide a protective shield, which helps prevent collagen fragmentation induced by harmful environmental factors like UV radiation. This comprehensive action ensures both replenishment and preservation of the skin's essential structural protein (Cho et al., 2019).

6.5. Phytoestrogenic effects

Isoflavones are classified as phytoestrogens, and their chemical structure resembles that of natural estrogen, allowing them to exert beneficial phytoestrogenic effects on the skin. By successfully binding to estrogen receptors within the skin, isoflavones can help counteract the detrimental effects of hormonal aging. This binding action is particularly valuable in states of estrogen deficiency, such as during menopause, where they help maintain epidermal thickness, stimulate collagen production, and improve overall skin hydration. Therefore, isoflavones are effective substitutes for preservation of the structural and functional integrity of aging skin (Liu et al., 2020; Lephart & Naftolin, 2022; Rizzo et al., 2023).

6.6. Prevention of apoptosis

Isoflavones offer protective benefits by preventing apoptosis or programmed cell death in skin cells under stress. Specifically, these compounds, particularly genistein, have demonstrated activity in reducing oxidative stress-induced apoptosis by intervening directly in the cell death signaling cascade. This was achieved by suppressing the apoptotic pathway through two key actions: (1) inhibiting the activity of caspase-3, a crucial executioner enzyme of apoptosis, and (2) simultaneously increasing the expression of antiapoptotic proteins such as B-cell lymphoma 2 (BCL-2). By maintaining the viability of skin cells, isoflavones contribute to tissue homeostasis and overall skin health (Teixeira et al., 2019).

7. *IN VITRO*, *IN VIVO*, *IN SILICO*, AND CLINICAL EVIDENCE OF ISOFLAVONES IN PHOTOAGING

Various studies have been conducted to evaluate the antiphotoaging effects of isoflavones through *in vitro*, *in vivo*, *in silico*, and clinical approaches (Table 1). Each approach provides a deeper understanding of the mechanism of action, effectiveness, and potential therapeutic applications of isoflavones, especially genistein and daidzein.

7.1. *In Vitro* model

In vitro studies provide a deep molecular understanding of the mechanism of action of soy isoflavones, particularly genistein and daidzein, in the context of skin photoaging. These models, which typically utilize human dermal fibroblasts or keratinocytes, are instrumental because they allow for the isolation and dissection of specific molecular events on biological pathways, free from the systemic complexity of a living organism. A foundational mechanism confirmed by this evidence is the direct antioxidant capacity of these compounds. Specifically, Wójciak et al. demonstrated the potent ROS scavenging effect of selected isoflavones when skin fibroblasts and keratinocytes were subjected to various forms of provoked oxidative stress conditions (Wójciak et al., 2024b). This capability is crucial, as the UV-induced generation of ROS is the initial cascade trigger that leads to inflammation and subsequent cellular damage in the skin (Kim, 2021).

Beyond this direct neutralization of free radicals, isoflavones effectively intercept the more complex inflammatory and destructive signaling cascades. UV radiation initiates complex pathways, including the MAPK cascade, which in turn leads to the activation of key transcription factors (NF-κB and AP-1) that regulate gene transcription (Kim, 2021). These factors, upon activation, normally translocate from the cytoplasm into the nucleus, where they act as cellular "switches" to upregulate the genes for destructive enzymes. Studies such as those conducted by Shin et al. in human dermal fibroblasts showcase the functional outcome of this inhibitory action, a significant inhibition in the expression of MMP-1 (Matrix Metalloproteinase-1). MMP-1 is recognized as the major collagenase responsible for the enzymatic degradation of Type I collagen following UV exposure. By suppressing the NF-κB/MAPK/AP-1 axis and subsequently decreasing MMP-1 expression, the cellular environment shifts away from degradation. These combined inhibitory effects (decreasing ROS production and suppressing upstream signalling) ultimately favor an environment conducive to repair, resulting in increased collagen production and overall protection against oxidative stress-induced cell damage (Kim, 2021; Shin et al., 2017) (Figure 3).

Thus, the evidence confirms that isoflavones function as dual-action agents: as effective antioxidants and critical modulators of gene expression that play a central role in maintaining dermis structure and function. The main advantage of *in vitro* models lies in achieving this high level of mechanistic detail, although their physiological limitations must be carefully considered when extrapolating findings to an entire organism (Kim, 2021; Shin et al., 2017; Wójciak et al., 2024b).

7.2. *In Vivo* model

In vivo studies conducted in animal models, such as those by Shin et al., Duchnik et al., and Padmavathi et al., provide strong evidence of the biological effectiveness of isoflavones in a systemic and whole-tissue context, bridging the

Table 1
Soy isoflavone studies on photoaging, collagen, and oxidative stress.

No	Author & year	Title	Study design	Model	Intervention	Biomarkers	Main outcome	Notes
1	Shin et al., 2017	A combination of soybean and Haematococcus extract alleviates UVB-induced photoaging	Experimental	*In vitro* & *in vivo* (human & mouse cells)	Soybean + Haematococcus extract, 10 weeks	MMP-1, MAPK, AP-1, wrinkles, skin thickness	↓ MMP-1, MAPK, AP-1, wrinkles; ↑UVB protection	The combination of extracts is more effective than monoextracts
2	Natarelli et al., 2023	Clinical efficacy of topical or oral soy supplementation in dermatology	Systematic review	Clinical (15 human studies)	Topical & oral isoflavones (4-24 weeks)	Hydration, elasticity, collagen, TEWL, pigmentation	↑hydration, collagen; ↓TEWL, wrinkles, pigmentation	Oral + topical is more effective than either method
3	Duchnik et al., 2019	Effects of the soy isoflavones, genistein and daidzein, on male rats' skin	Experimental	*In vivo* (Wistar male rats)	Genistein & daidzein doses of 2 mg/kg & 20 mg/kg, total prenatal adult duration	Collagen, fibroblasts, skin thickness, MDA, catalase	↑collagen, fibroblasts ↓MDA, catalase	Improved skin structure and antioxidant activity
4	Padmavathi et al., 2020	Efficacy of topical soy isoflavonoid extract on UVB-induced photoaging in Guinea pig model	Experimental	*In vivo* (guinea pig)	Topical isoflavones versus tretinoin 0.05%, 4 weeks of therapy after 8 weeks of UVB irradiation	Erythema score (0–3)	↓ Significant erythema, equivalent or better than tretinoin	No irritating effect like tretinoin
5	Kim, 2021	Current perspectives on the beneficial effects of soybean isoflavones	Narrative review	*In vitro*, *in vivo*, clinical (review)	Genistein, daidzein, equol (various doses)	ROS, NF-κB, collagen, ER	↓ ROS & inflammation ↑collagen, estrogenic effects	Focus on molecular mechanisms
6	Ubaid et al., 2023	Daidzein from dietary supplement to a drug candidate: An evaluation of potential	Narrative review	*In vitro*, *in vivo*, clinical (review)	Daidzein (various doses & routes)	ROS, IL-6, NF-κB, collagen	↓inflammation, ROS; ↑collagen, cell protection	Daidzein is a potential anti-aging drug candidate
7	Wójciak et al., 2024a	Protective, anti-inflammatory, and antiaging effects of soy isoflavones	Narrative review	*In vitro* & *in vivo*	Genistein & daidzein (In extract/topical/ oral form)	SOD, GPx, MMP-1, IL-1β, TNF-α	↑antioxidant, collagen; ↓MMP-1, inflammation	Skin protective molecular mechanisms elucidated
8	Rizzo et al., 2023	Soy protein containing isoflavones improves facial signs of photoaging	Double-blind RCT	Clinical (postmenopausal women)	Soy protein supplement 160 mg isoflavones, 24 weeks	Wrinkles, pigmentation, skin hydration	↓wrinkles, pigmentation; ↑skin hydration	Effects increased from Week 12

Symbol description:
↑ = increase.
↓ = decrease.

gap between molecular findings and physiological outcomes (Figure 4). These models are crucial as they account for the complex processes of compound absorption, metabolism, distribution to the skin, and interaction within an intact tissue environment (Duchnik et al., 2019; Padmavathi et al., 2020; Shin et al., 2017).

The core protective mechanism is demonstrated through the enhancement of the skin's natural antioxidant defense system. Specifically, soy isoflavones were shown to directly combat photo-oxidative stress, leading to a significant reduction in malondialdehyde (MDA) levels (Padmavathi et al., 2020). MDA is a harmful marker of lipid peroxidation in cell membranes, and decreased levels confirm the compound's ability to inhibit this destructive process. This effect is correlated with an increased activity of key endogenous antioxidant enzymes, such as Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPx) (Duchnik et al., 2019). By boosting the activity of these enzymes in the cytoplasm and

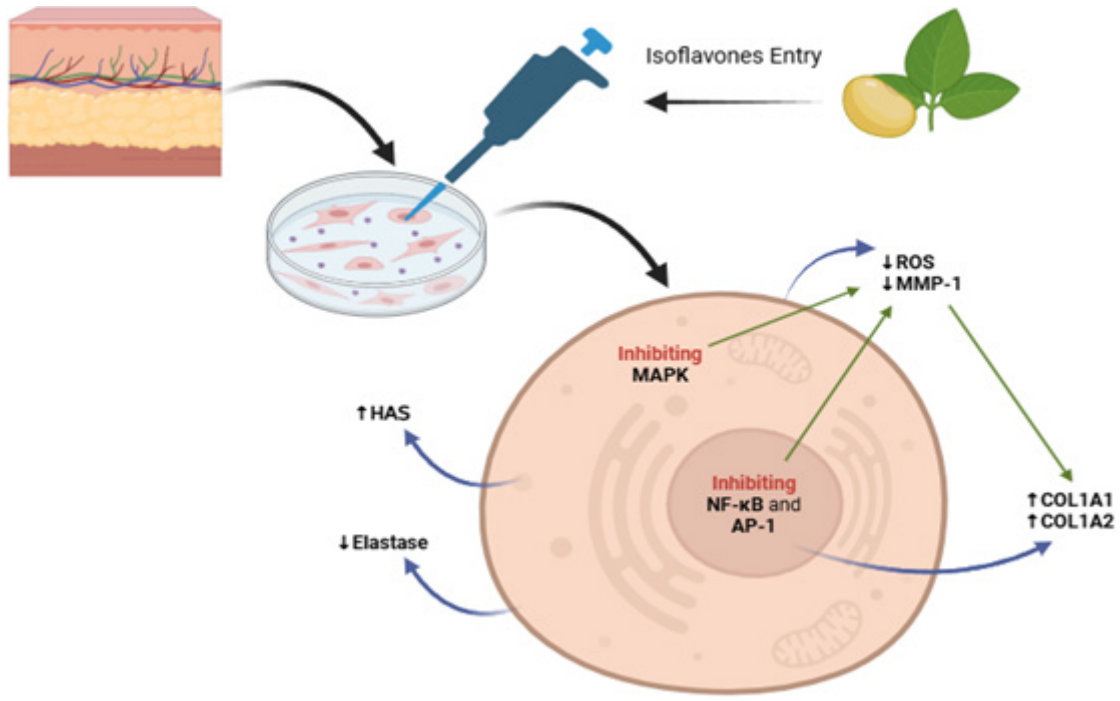


Figure 3. Molecular mechanism of isoflavones in photoaging: the *in vitro* (cellular) model.
The figure illustrates the protective pathway of soy isoflavones (e.g., Genistein/Daidzein) at the cellular level, typically observed in human fibroblasts or keratinocytes in culture. Upon entry into the cell, isoflavones intervene in the early damaging cascade by blocking the activation and translocation of key transcription factors, specifically NF-κB, MAPK, and AP-1, which are located in the cytoplasm and nucleus. This inhibition has two critical downstream effects: (1) Prevention of Degradation: The blockade leads to a significant decrease (↓) in the gene expression and secretion of destructive enzymes such as MMP-1 into the extracellular space. (2) Reduction of Stress and Promotion of Repair: Isoflavones decrease (↓) the production of ROS (Reactive Oxygen Species) in the mitochondria and cytoplasm, and simultaneously promote an increase (↑) in COL1A1 gene expression, stimulating new collagen production in the cytoplasm and extracellular space. Overall, based on the *in vitro* studies, isoflavones function as potent antioxidants and gene expression modulators that protect against oxidative stress-induced cell damage and positively impact dermis structure.

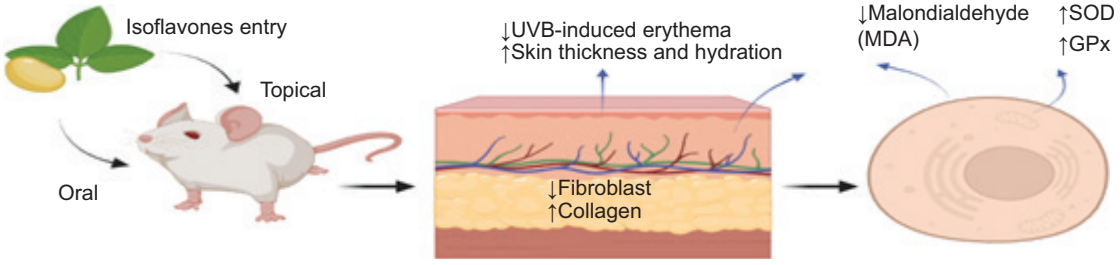


Figure 4. Physiological effects of isoflavones in photoaging: the *in vivo* (animal tissue) model.
This figure details the systemic and tissue-level effects of isoflavones within a living organism (e.g., UV-exposed animal models). Following oral or topical administration (Systemic Circulation → Skin Tissue), isoflavones are integrated into the epidermis and dermis. Their primary mechanism involves enhancing the body's defense system, causing an increase (↑) in the activity of endogenous antioxidant enzymes such as SOD and GPx in the cytoplasm and mitochondria of skin cells, respectively. This action leads to a measurable decrease (↓) in oxidative damage markers such as MDA (Malondialdehyde) in the cell membranes and dermis, resulting in the reduction in lipid oxidation and overall oxidative stress. Structurally, this biochemical protection translates to an increase (↑) in the number of dermal fibroblasts and collagen fibers located within the dermal layer. Clinically and phenotypically, this is observed as a reduction (↓) in UVB-induced erythema (redness) and an improvement (↑) in overall skin thickness and hydration in the epidermis. *In vivo* studies thus confirm the biological validity and physiological relevance of isoflavones' antiaging effects in the context of whole-tissue UV exposures.

mitochondria of skin cells, isoflavones enhance the capacity of the dermal tissue to scavenge ROS and mitigate subsequent cellular damage (Padmavathi et al., 2020).

The biochemical protection offered by isoflavones translates directly into structural and histological improvements within the skin. Duchnik et al. and other studies observed favorable histological changes, including a significant increase in the number of dermal fibroblasts (cells responsible for producing matrix proteins) and collagen fibers. These effects also led to an improvement in overall epidermal thickness and the general histological appearance of the skin (Duchnik et al., 2019). Furthermore, Padmavathi et al. provided compelling evidence regarding the clinical relevance of these structural changes. Their research on the topical application of soy isoflavonoids demonstrated high efficacy in both preventing and reversing UVB-induced erythema (skin redness). Notably, they reported that the photoprotective effects of the isoflavonoid extract were equivalent to, or even superior to, the standard retinoid drug tretinoin, but critically, without the common irritating side effects associated with retinoids (Padmavathi et al., 2020). Collectively, *in vivo* models lend significant strength to the biological validity and physiological relevance of isoflavones, reinforcing claims of antiaging effects in the context of real environmental exposures like UVB radiation.

7.3. *In Silico* models

Recent molecular docking studies have contributed valuable mechanistic insights into how isoflavones may exert their antiphotoaging activity through specific interactions with molecular targets (Table 2). Computational simulations, particularly docking analyses using platforms such as AutoDock, SwissDock, and CBDock, have shown that key isoflavones (genistein, daidzein, biochanin A, and formononetin) exhibit favorable binding affinities toward matrix metalloproteinases (MMP-1, MMP-3, and MMP-9), the principal enzymes involved in collagen degradation during photoaging (Forli et al., 2016; Nayak & Sundararajan, 2023; Zakłos-Szyda et al., 2020). For instance, docking studies by Yuseran et al. show that Genistein has strong binding affinity with MMP-9, with a binding energy (ΔG) of −8.3 kcal/mol. Key interactions involve Lys-177 and Asp-173 residues, suggesting direct inhibition of this collagen-degrading enzyme, thus protecting skin structure (Yuseran et al., 2019) (Figure 5).

Moreover, *in silico* investigations have also predicted interactions between isoflavones and inflammatory mediators. Daidzein and its metabolite equol have been shown to dock favorably with IL-6 receptors, with binding energies ranging from −8.4 to −9.2 kcal/mol, suggesting their capability to modulate IL-6 signaling, a key pathway in UV-induced inflammation (Márquez-Flores et al., 2024). While direct docking to the COL1A1 gene product is limited due to its fibrous nature, indirect mechanisms have been proposed. Molecular modeling of daidzein and apigenin binding to PP1c, a regulatory subunit of the TGF-β/Smad pathway, indicates a potential route by which isoflavones may upregulate Type I collagen synthesis, supporting observations from *in vitro* and *in vivo* studies.

Together, these computational findings strengthen the hypothesis that isoflavones can exert dual protective effects in photoaged skin: (1) by directly inhibiting collagen-degrading enzymes, and (2) by indirectly enhancing collagen biosynthesis and reducing inflammation. Though predictive, these docking insights align well with experimental data and help elucidate plausible molecular mechanisms for the observed biological activities of isoflavones in skin aging models.

Despite promising results, current *in silico* studies on isoflavones and skin aging are limited in several aspects. Most docking analyses are restricted to static binding models and do not incorporate molecular dynamics (MD) simulations, which are essential for assessing the stability of ligand–protein interactions over time and under physiological conditions. Additionally, docking studies on key photoaging targets such as estrogen receptor β (ER-β), a critical mediator of isoflavone activity in skin, remain scarce. Moreover, comprehensive

Table 2
Summary of molecular docking of key isoflavones to photoaging-related targets.

Isoflavone compound	Target protein	Binding energy (ΔG)	Key interacting residues	Docking tool/Reference
Genistein	MMP-9	−8.3 kcal/mol	Lys-177, Asp-173	AutoDock Vina, Qamar et al. (2024)
Formononetin	MMP-1	−3.986 kcal/mol / XP	Tyr240, Ala184; Zn275	CB-Dock, Shunmuga Priya et al. (2021)
Biochanin A	MMP-3	−10.1 kcal/mol	Glu202, His211, Zn^{2+} site	CBDock-based study, Liu et al. (2022)
Daidzein	IL-6 Receptor	−8.8 kcal/mol	Asp34, Tyr103, Ser107	DockThor, Ubaid et al. (2023)
Daidzen/Apigenin	PP1c (TGF-β/Smad regulator)	−8.9 kcal/mol	Arg96, Glu59, Asp64	Modeling study from Tang et al. (2022)
Equol (metabolite)	ER-β (Estrogen Receptor β)	−9.2 kcal/mol	Glu305, Arg346, His475	SwissDock, Lephart & Naftolin (2022)

ADMET profiling, quantitative structure–activity relationship (QSAR) analysis, and network pharmacology approaches are still underutilized in evaluating isoflavones' bioavailability, skin permeability, and off-target interactions.

7.4. Clinical models

Evidence from clinical studies confirms the essential translational relevance of laboratory findings into practical human applications, demonstrating the efficacy and safety of isoflavone use in mitigating photoaging signs. Natarelli et al. (2023), through a comprehensive systematic review of clinical trials, established that both topical and oral administration of soy supplementation consistently yielded beneficial dermatological outcomes (Figure 6). Specifically, these studies reported significant improvements across key parameters of skin health: increased skin hydration, enhanced elasticity, increased dermal density, and notable decreases in the appearance of wrinkles and pigmentation. This systemic evidence strongly validates the antidegradative and prosynthetic mechanisms observed in *in vitro* and *in vivo* models. Further

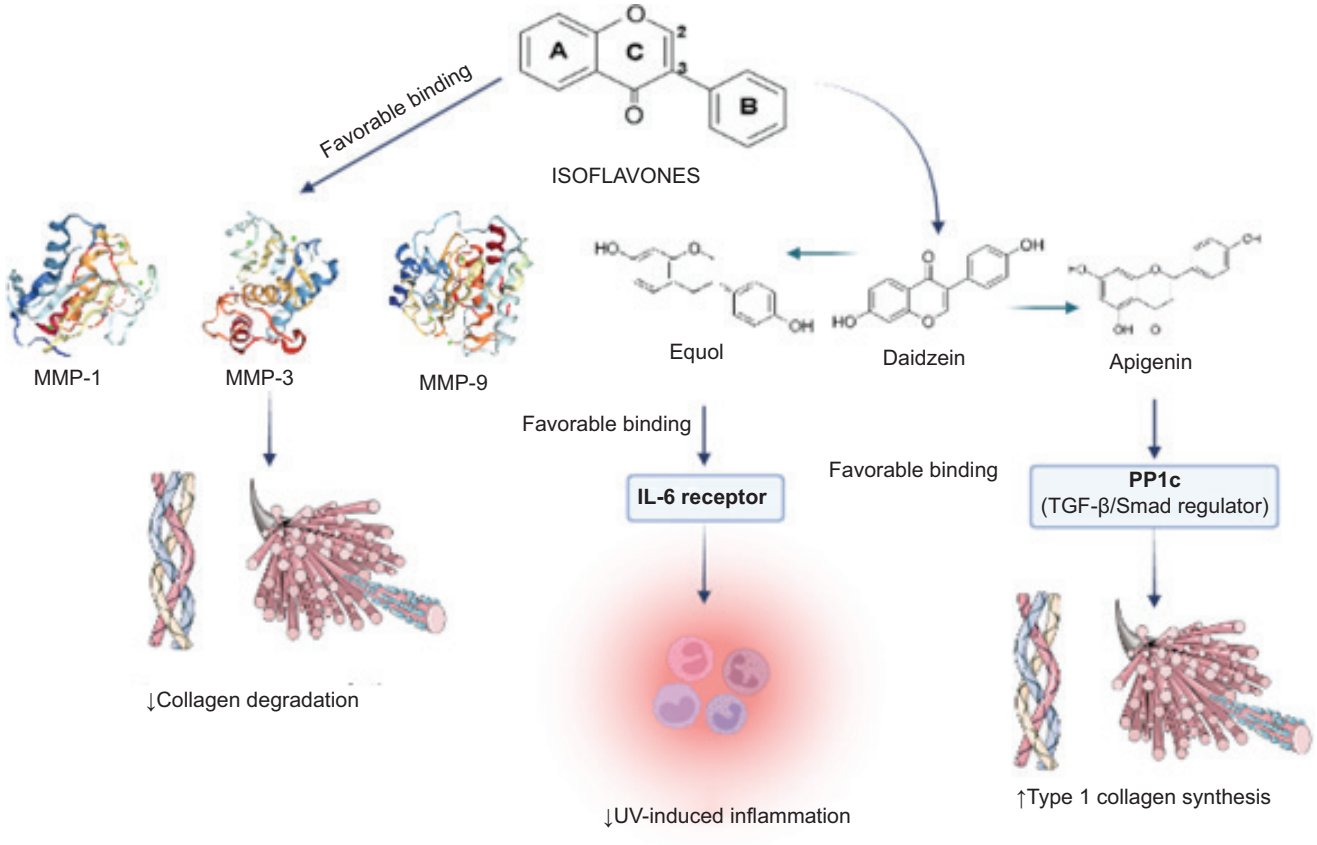


Figure 5. Predictive molecular modeling of isoflavone antiphotoaging activity: the *in silico* (computational) model.
This figure represents the predicted molecular interactions of isoflavones derived from computer simulation (molecular docking). These models explore three main activities within the virtual binding pocket (active site) of target proteins. (1) Direct Inhibition of Degradation: Isoflavones (e.g., Genistein, Formononetin) show a strong, favorable Binding Affinity (ΔG≈−8 to −10 kcal/mol) for the active sites of collagen-degrading enzymes MMP-1, MMP-3, and MMP-9, which are normally secreted into the Extracellular Matrix (ECM). This strong binding predicts a high potential for collagen degradation to decrease (↓). (2) Inflammation Modulation: Daidzein and its metabolite Equol are modeled to bind favorably to the IL-6 receptor on the surface of immune and skin cells, predicting a potential decrease (↓) in UV-induced inflammation. (3) Indirect Repair: Other isoflavones (e.g., Daidzein/Apigenin) are modeled to interact with regulators like PP1c (located in the cytoplasm/nucleus), suggesting a mechanism for the potential increase (↑) of Type I collagen synthesis. These computational findings strengthen the overall hypothesis by providing plausible molecular mechanisms for isoflavones' dual protective role: direct enzyme inhibition and indirect repair enhancement.

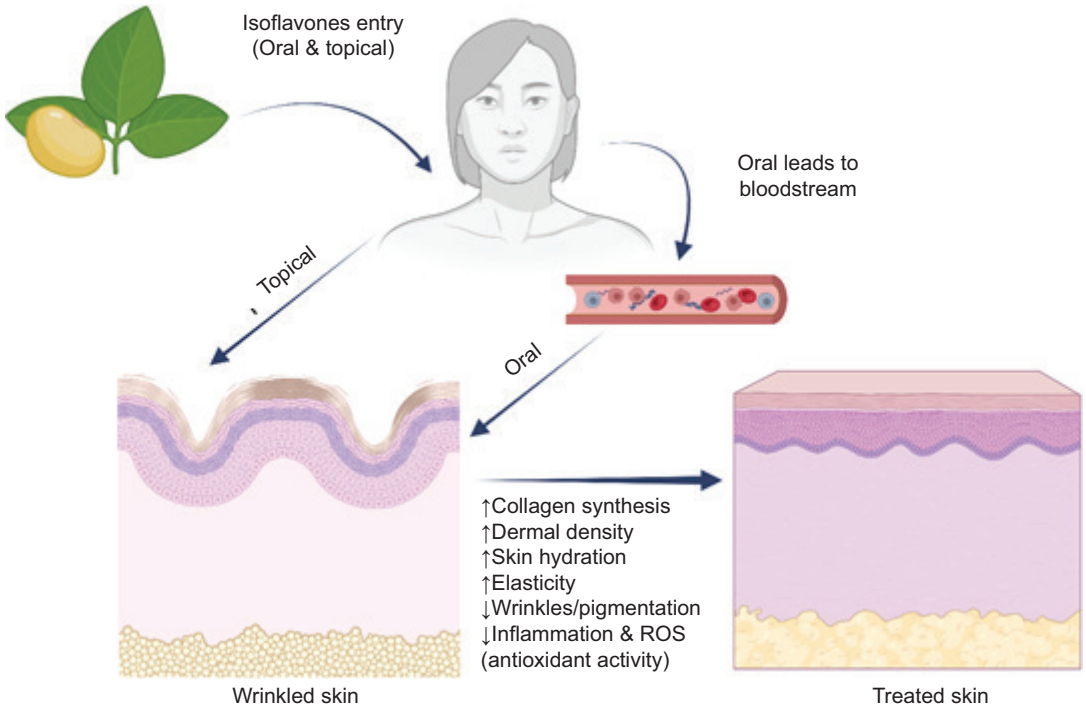


Figure 6. Translating isoflavone efficacy: the clinical (human outcome) model.
The figure illustrates the observable clinical outcomes and delivery pathways of isoflavones in human subjects. The action begins with oral administration (Isoflavones enter the systemic circulation and reach the skin via blood flow) or topical administration (Isoflavones penetrate locally into the epidermis and dermis). The combination of these delivery routes provides a synergistic effect on the target tissue. The underlying biological effects (including increased collagen synthesis, enhanced antioxidant activity, and reduced inflammation) translate into four measurable clinical outcomes in the facial skin and surrounding areas: (1) ↑ Skin Hydration, (2) ↑ Skin Elasticity, (3) ↑ Dermal Density, and (4) ↓ Wrinkles and Pigmentation. Clinical trials confirm that these effects are achieved safely and are particularly relevant in populations prone to accelerated photoaging, such as postmenopausal women. The conclusion from clinical evidence is that isoflavones are safe, well-tolerated, and effective for long-term intervention, providing the highest level of validation for their antiphotoaging properties.

reinforcing this clinical utility, Rizzo et al. (2023) conducted a prospective, randomized, double-blind controlled trial (RCT) focusing on a particularly relevant demographic postmenopausal women, whose natural decline in estrogen levels accelerated skin aging. Their findings demonstrated that a 24-week intervention of soy protein supplementation containing 160 mg of isoflavones significantly improved various facial signs of photoaging and boosted skin hydration. These rigorously controlled human trials underscore that isoflavones are not only safe and well-tolerated but also effective for long-term intervention in managing skin aging. The body of work suggests that the combination of oral (systemic) and topical (local) application results in a superior synergistic effect, optimizing both the internal biochemical defense and the external structural repair of the skin (Natarelli et al., 2023). Clinical research thus provides the highest level of evidence, concluding that isoflavones are a viable and effective strategy for improving the visible hallmarks of photoaging.

7.5. Models conclusion

Overall, the comprehensive findings derived from the multidisciplinary approach (spanning *in vitro*, *in vivo*, *in silico*, and clinical models) do not merely align but actively complement and corroborate one another, solidifying the case for the antiphotoaging efficacy of soy isoflavones, particularly genistein and daidzein (Table 3).

The mechanistic foundation is established by *in vitro* studies, which pinpoint the ability of isoflavones to function as potent antioxidants by directly suppressing ROS production and simultaneously acting as modulators of gene expression. This cellular protection is mediated through the inhibition of crucial stress and inflammation-signaling pathways, namely NF-κB, MAPK, and AP-1, thereby effectively turning off the transcription of destructive enzymes such as MMP-1.

This molecular hypothesis is rigorously supported by *in silico* models, which provide predictive evidence of a strong,

Table 3
Isoflavone study categories, effects, and biomarkers.

Study category	Main effects of isoflavones	Key pathways or biomarkers
In Vitro	↓ ROS,↓ MMP-1/3,↑ COL1A1,↓ IL-6	MMP-1, COL1A1, IL-6, ROS
In Vivo	↓ MMP-1/9,↑ skin thickness,↑ hydration,↑ COL1A1	MMP-1, COL1A1, TEWL, dermis thickness, MDA
In Silico	↓ROS, ↓IL-6, ↓ECM breakdown, ↑ COL1A1	Binding affinity, IL-6, MMP-1/9, COL1A1
Clinical	↓ wrinkles,↑ skin elasticity,↑ skin hydration	Clinical score, TEWL, Corneometer, elastometry

↓ = decrease in skin biomarkers/beneficial effects, ↑ = increase in skin-beneficial biomarkers/effects.
COL1A1: Major gene encoding type I collagen, TEWL: Transepidermal Water Loss, MMP-1/3/9: Matrix metalloproteinases that break down collagen, ROS & IL-6: Markers of oxidative stress and inflammation, Corneometer: Skin hydration measurement tool, Clinical score: Clinical assessment of skin condition (wrinkles, pigmentation, elasticity).

favorable binding affinity (ΔG) between isoflavones and various MMPs, validating their potential to physically inhibit collagen degradation.

The functional relevance of these mechanisms is unequivocally confirmed by *in vivo* models. In animal tissues, the systemic delivery of isoflavones translates the antioxidant effect into measurable physiological changes, demonstrating increased endogenous antioxidant enzyme activity (SOD/GPx) and decreased lipid oxidation markers (MDA). This biochemical defense subsequently leads to structural improvement in the dermal layer, marked by an increase in collagen fibers and fibroblasts.

Crucially, the final step in the translational pipeline the clinical models validates this entire sequence for human use. Human trials confirm that both oral and topical administration of isoflavones result in significant and consistent improvements in objective clinical parameters, including enhanced skin hydration, elasticity, and dermal density, besides a reduction in wrinkles and pigmentation. Therefore, the evidence consistently and robustly demonstrates that soy isoflavones exert a powerful multitarget protective action spanning antioxidant, anti-inflammatory, and collagen gene expression modulation that is effective across the cellular, animal tissue, and human levels.

8. PHOTOPROTECTIVE AND ANTIAGING MECHANISMS OF ISOFLAVONES

Photoaging is primarily driven by UV-induced mechanisms, including the generation of ROS, activation of the AP-1 and NF-κB pathways, and the subsequent upregulation of MMPs that degrade the ECM (Chen et al., 2021; Hussen et al., 2025; Tanveer et al., 2023). The findings of this integrative review confirm that soy isoflavones, particularly genistein and daidzein, are potent photoprotective agents that directly counteract these core processes. Isoflavones were shown to suppress the UV-induced expression of MMP-1, MMP-3, and MMP-9. This critical finding was consistently observed across in vitro studies by Shin et al. (2017) and Kim (2021), as well as in vivo studies by Padmavathi et al. (2020) and Duchnik et al. (2019). Beyond simply protecting existing collagen, isoflavones also actively promote new synthesis. This is shown by increased COL1A1 gene expression in fibroblasts and a greater density of dermal collagen fibers in animal models (Duchnik et al., 2019). This mechanism is closely linked to the activation of the pro-regenerative TGF-β/Smad pathway, which supports dermal structure repair (Wójciak et al., 2024b). Furthermore, the phytoestrogenic properties of isoflavones appear to translate these molecular benefits into clinical reality, especially in postmenopausal skin. Clinical trials by Rizzo et al. (2023) and Natarelli et al. (2023) have confirmed the ability of these compounds in improving skin elasticity and hydration and reducing pigmentation. These clinical outcomes are in line with the findings of Kim (2021) and Wójciak et al. (2024a), who described the role of isoflavones in stimulating collagen synthesis and inhibiting chronic inflammation due to UV exposure.

9. SAFETY AND TOLERABILITY

Soy isoflavones are generally considered safe for oral and topical use. Clinical studies by Natarelli et al. (2023) and Rizzo et al. (2023) reported no serious adverse effects over 4–24 weeks of use. Mild effects such as gastrointestinal disturbances are rare and usually transient. Genistein and daidzein also showed good safety profiles in *in vivo* tests and were non-irritating. In topical studies by Padmavathi et.al. (2020), however, long-term use and high doses still require further evaluation, especially regarding estrogenic effects in sensitive populations.

10. LIMITATIONS

Although the results of the studies show a consistent protective effect of isoflavones against skin aging, there are several limitations. The variations in dose, isoflavone type, and route of administration (topical or oral) make it difficult to set therapeutic standards. Most clinical trials are short-term, and thus, long-term effectiveness data are still limited. Also, the results from *in vitro* and *in vivo* studies cannot be fully generalized to humans due to physiological differences. In addition, the number of studies with high methodological quality is limited, and there have not been many direct comparisons between isoflavones and other standard therapies such as retinoids.

11. CONCLUSIONS AND CLINICAL IMPLICATIONS

Soy isoflavones, particularly genistein and daidzein, show strong potential as antiaging and photoprotective agents through mechanisms of decreased oxidative stress, inhibition of MMP expression, and increased collagen synthesis. These effects have been consistently confirmed in i*n vitro* and *in vivo* models and clinical studies, including improved hydration, skin elasticity, and decreased wrinkles in humans. From a clinical standpoint, isoflavones have the potential to be a safe and effective natural alternative in preventing and improving skin aging due to UV exposure. However, further research is needed to ensure long-term effectiveness and optimal dosage standards. The utilization of isoflavones in dermatology and functional cosmetics has broad prospects.

FURTHER RESEARCH RECOMMENDATIONS

Further research is recommended to explore the effects of soy isoflavones on biomarkers of oxidative stress (such as MDA) and collagen synthesis (such as COL1A1 gene expression) in an *in vitro* model using human skin fibroblast cells. This study is important for strengthening the understanding of the molecular mechanisms of isoflavones in the context of skin aging as well as providing a scientific basis for the development of more targeted topical or oral therapies. Studies on the testing of optimal dose and exposure time, and comparison with conventional antioxidants, are required to improve translational validity to clinical applications. Integrate *in silico* methods with *omics*-based data and systems biology approaches to map the multitarget actions and pathways of isoflavones. Incorporating 3D skin modeling, TGF-β/Smad pathway simulations, and virtual screening against broader skin aging–related targets will also enhance the translational value of computational findings in developing isoflavone-based cosmeceuticals.

ORCID

Yuri Amelia	0009-0001-8974-3737
Wahyu Widowati	0000-0002-5401-7794
Fen Tih	0000-0003-1280-9969
Rizky Pratama	0009-0006-0772-664X

ACKNOWLEDGMENTS

The authors would like to thank the supervisor and all those who have provided guidance and support in the process of preparing this review.

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AUTHOR CONTRIBUTIONS

Yuri Amelia took the lead in conceptualization, literature search, and drafting the manuscript. Wahyu Widowati and Fen Tih made valuable contributions to the critical review of the literature, refinement of the analysis, and improvement of the scientific clarity and accuracy of the manuscript. All authors contributed meaningfully to the development of this review, approved the final version, and agreed to take responsibility for all aspects of this work.

FUNDING

This integrative review was supported by a research grant from the Directorate General of Higher Education, Research and Technology (DIKTI), awarded to Yuri Amelia as part of a postgraduate research scheme. The grant number will be listed once available.

DATA AVAILABILITY

Not applicable.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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