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Review Article

Comparison between flavonoids and phenolic acids in photoaging: A systematic review in preclinical and clinical settings

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Abstract

Purpose: *To qualitatively compare the efficacy of epigallocatechin gallate, quercetin, ellagic acid, and ferulic acid as antioxidant and photoprotective agents across preclinical and clinical photoaging studies.*
Methods: *A systematic search was conducted in PubMed, ScienceDirect, and the Cochrane Library, following the PRISMA 2020 guidelines, using the Boolean operators "flavonoids" OR "phenolic acids" AND "photoaging". Risk of bias was assessed using Cochrane RoB 2.0, ROBINS-I, SYRCLE, and ToxRTool. Data were extracted and qualitatively synthesized. A total of 24 studies were included, consisting of 19 preclinical and 5 clinical investigations. Thirteen were in vitro, three combined in vitro and in vivo, four were ex vivo or human ex vivo, and four were clinical trials. Study models encompassed human dermal fibroblasts, keratinocytes, reconstructed skin, zebrafish, and healthy adult participants. Investigated compounds included EGCG, quercetin, ellagic acid, and ferulic acid, derived from botanical sources.*
Results: *Primary outcomes demonstrated antioxidant, anti-inflammatory, and extracellular matrix-preserving effects, with clinical trials confirming reductions in erythema, improved dermal elasticity, and enhanced photoprotection against ultraviolet-induced skin damage.*
Conclusion: *Flavonoids and phenolic acids show consistent antioxidant and photoprotective effects in photoaging models, but evidence remains heterogeneous and clinical translation is uncertain. Standardized clinical trials are needed to confirm efficacy, optimize dosing and formulations, and establish long-term safety.*

Keywords: *Antioxidants, Flavonoids, Phenolic acids, Photoaging, Ultraviolet*

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INTRODUCTION

Photoaging is a chronic form of cumulative, sun-induced skin damage triggered by repeated exposure to ultraviolet radiation, which activates oxidative stress, inflammation, and extracellular matrix degradation pathways [1-3]. Ultraviolet radiation that reaches human skin consists mainly of ultraviolet A (315 - 400 nm) and ultraviolet B (290 - 320 nm). Both wavelengths

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increase the formation of reactive oxygen species. Those wavelengths also upregulate collagen-degrading matrix metalloproteinases, contributing to post-irradiation erythema [4-7]. Clinical studies that use minimal erythema dose and melanin index as objective endpoints show that these photobiological effects are quantifiable in humans. These measures also support a direct association between ultraviolet radiation exposure and activation of the inflammatory, collagenolytic transcriptional program implicated in photoaging pathogenesis [8]. The clinical burden of photoaging is amplified in tropical regions due to high ultraviolet intensity and frequent, unavoidable exposure. Therefore, comprehensive photoprotection should integrate physical barriers with pharmacological interventions [4,6].

Photoaging prevention has primarily been achieved via a daily, multi-layered strategy consisting of broad-spectrum sunscreen use, physical protection, and lifestyle modification to minimize cumulative ultraviolet radiation exposure [4,6]. Concurrently, topical and oral antioxidants have been studied for reactive oxygen species scavenging and modulation of inflammatory-collagenolytic signaling, with increasing support from mechanistic studies and clinical investigations [1,3,7,9]. In natural products research, polyphenols such as flavonoids and phenolic acids have attracted considerable attention and have been reported to possess antioxidant, anti-inflammatory, and photoprotective activities [3,10-12].

Epigallocatechin gallate suppresses p38 mitogen-activated protein kinase phosphorylation after ultraviolet exposure in zebrafish and human skin fibroblast models. Additionally, epigallocatechin gallate also reduces activation of NF-kB and activator protein-1, which are associated with lower proinflammatory cytokine production [13]. Quercetin interacts with protein kinase C delta and Janus kinase 2 (JAK2), modulating mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription (STAT) signaling. In human skin models, it reduces cyclooxygenase-2 (COX-2) and metalloproteinase-1 (MMP-1) expression [14]. Ellagic acid has been demonstrated to improve skin penetration barriers through hyaluronate-modified liposome-based delivery, followed by restoration of type I collagen and elastin expressions and suppression of MMPs in fibroblasts and zebrafish models [15]. Ferulic acid has been tested in formulations designed to enhance cutaneous stability and retention. Volunteer trials report reduced ultraviolet B-induced erythema and improved skin elasticity [16,17]. However, a narrative summary assessing the strength of evidence, mechanistic consistency, heterogeneity in preclinical models, and clinical efficacy signals among these four compounds is not yet available in the current antioxidant and photoprotection literature. This systematic review is aimed at preclinical and clinical studies to qualitatively evaluate epigallocatechin gallate, quercetin, ellagic acid, and ferulic acid as antioxidant and photoprotective agents in photoaging.

METHODS

This systematic review was conducted based on the references identified in the PRISMA assessment. This study was prospectively registered in PROSPERO (ID: 1047531).

Article search and study selection

Systematic search was conducted through PubMed, ScienceDirect, and the Cochrane Library from inception to October 10th, 2025, in accordance with PRISMA 2020 guideline. Database-specific strategies were applied to identify preclinical and clinical studies evaluating flavonoid and phenolic acid compounds in photoaging models. The Boolean operator used was “flavonoids” OR “phenolic acids” AND “photoaging”. Duplicates were removed before the screening process. Title and abstract screening, followed by full-text review, were independently performed by two reviewers, with any discrepancies resolved through discussion and consensus.

Inclusion and exclusion criteria

Studies were included if they investigated the effects of flavonoid or phenolic acid compounds, either as pure isolates, plant extracts, or formulations, on photoaging outcomes in preclinical (*in vitro* or *in vivo*) or human clinical settings. The included studies reported at least one photoaging-related endpoint, such as oxidative stress markers, histological or morphological skin changes, or clinical parameters. Exclusion criteria comprised narrative reviews, meta-analyses, editorials, or conference abstracts lacking primary data, as well as studies focusing on non-photoaging contexts such as wound healing, pigmentation disorders, or carcinogenesis, and articles not available in full text or not published in English.

Study selection and quality assessment

Methodological quality and risk of bias were evaluated according to study design.

Randomized controlled trials were assessed using the Cochrane Risk of Bias 2.0 tool across the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Non-randomized controlled trials were appraised with the ROBINS-I tool, focusing on confounding, intervention classification, selection bias, and missing outcome data. *In vivo* studies were assessed with the SYRCLE Risk of Bias tool adapted from the Cochrane Collaboration, focusing on random sequence generation, blinding, allocation concealment, and selective reporting. *In vitro* studies were evaluated for methodological rigor using a modified ToxRTool checklist emphasizing reproducibility, exposure characterization, and data integrity. *Ex vivo* models were assessed for tissue viability, exposure control, and endpoint consistency. Two reviewers independently appraised each study, resolving disagreements by consensus or third-reviewer adjudication when needed.

Extraction and analysis of data

Two reviewers independently extracted data using a prespecified standardized extraction form. Extracted variables comprised bibliographic details (author, year), compound and class (flavonoid or phenolic acid), study design, experimental model or participant characteristics, ultraviolet exposure protocol, dosing regimen (dose, route, duration), comparator where applicable, and predefined photoaging outcomes. Preclinical data captured cell or animal characteristics, exposure conditions, formulations, and endpoints such as oxidative stress, inflammatory mediators, extracellular matrix integrity, and key signalling pathways. Clinical data captured population features, trial design, interventions, and outcomes, including erythema, collagen, and barrier function. Heterogeneity in study designs, models, and outcome measures precluded quantitative pooling. Therefore, structured qualitative synthesis was conducted by grouping findings based on compound class, experimental or clinical model, and mechanistic pathway. This approach enabled comparison of preclinical signals with human evidence and appraisal of overall photoprotective and reparative effects.

RESULTS

Search strategy

A total of 1,393 records were identified from three databases: PubMed (n = 111), ScienceDirect (n = 1,282), and Cochrane (n = 0). After removing 2 duplicate records and 1,233 records marked as ineligible by automation tools, 158 studies remained for title and abstract screening. One hundred twenty-three records were excluded for not meeting the inclusion criteria. No reports were excluded due to retrieval failure. Eleven studies were excluded due to irrelevant data, while none were excluded for incomplete information. Consequently, 24 studies met all eligibility criteria and were included in the qualitative synthesis, representing the final set of studies analyzed in this systematic review (Figure 1).

Characteristics and subjects of the study

Among the 24 included studies, EGCG was evaluated in 6 studies [13,18-22], quercetin in 10 studies [8,15,23-30], and ferulic acid in 6 studies [16,17,31-34]. Across the 24 included studies, 13 used *in vitro* designs [18,24,33,35], three combined *in vitro* and *in vivo* approaches [13,15,16], four incorporated human *ex vivo* skin components [14,22,30,32], and four were clinical trials (three randomized controlled trials and one split-face study) [8,20,21,31]. Experimental design included human dermal fibroblasts (for example, Hs68) [13,15,18,29], human keratinocytes (for example, HaCaT) [24,26,33,35], reconstructed human skin and *ex vivo* skin tissue [22,23,30,32], zebrafish or other small-animal models [13,15,16], and healthy or photoaged adult participants in clinical studies [8,20,21,31]. Regarding compound provenance, EGCG was derived from *Camellia sinensis* [13,18-22], quercetin from multiple botanical sources (for example, *Quercus acuta* and *Allium cepa*) [14,26,36], ellagic acid-rich extracts from *Punica granatum* [8,29,30,35], and ferulic acid was evaluated either as a single compound or within topical combination or encapsulation-based formulations (Table 1) [16,17,31-34]. Four studies evaluated epigallocatechin gallate/EGCG [13,18,19,22], quercetin was evaluated in 6 studies across multiple formulations [14,24-27,36], whereas 5 studies examined ellagic acid or ellagic acid-rich pomegranate (*Punica granatum*) extracts [15,29,30,35,37], and 4 assessed ferulic acid [16,17,33,38]. Most investigations were *in vitro* assays [17,18,24-27,29,33-37], while a smaller subset incorporated non-*in vitro* components. Specifically, two studies combined human cell systems with zebrafish larvae [13,15], one study integrated human skin cells with *ex vivo* tissue [14], one study used an *ex vivo* reconstructed human skin model [30], one combined a cell model with a small animal model [16], and another study utilized a skin microbiota model and reconstructed human skin [22].

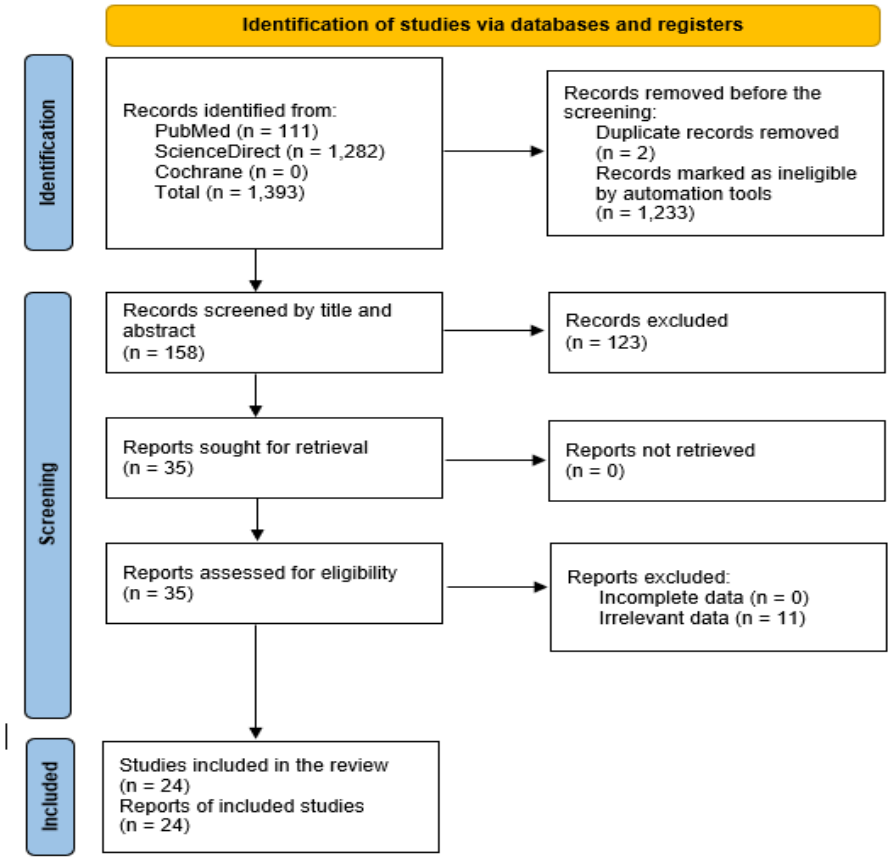


Figure 1: PRISMA flowchart

Two studies evaluated green tea catechin-based EGCG [20,21], one assessed ellagic acid through pomegranate consumption [8], and three assessed ferulic acid in topical preparations, often in combination with vitamins C and E [16,31,32]. Study designs included double-blind randomized trials in healthy adults with Fitzpatrick phototypes I–II (two RCTs for EGCG), a three-arm trial in healthy women (juice, extract, and placebo) for ellagic acid, and ferulic acid studies, including an investigator-blinded post-laser split-face trial, a clinical study with an *ex vivo* human skin component, and a healthy-volunteer study evaluating treated-site responses. The EGCG study used simulated ultraviolet radiation at 3×MED to quantify dermal matrix outcomes, ultraviolet B radiation patch testing before and after intervention (ellagic acid), a nonablative fractional laser post-recovery model (ferulic acid), an ultraviolet and diesel exposure paradigm (ferulic acid), and ultraviolet B-induced erythema on treated skin (ferulic acid; Table 1).

Primary outcomes varied by compound and endpoint. For EGCG, studies reported reduced extracellular matrix degradation, including preservation of fibulin-5, relative to placebo. However, cyclobutane pyrimidine dimer-positive cells did not decrease versus placebo at 24 hours, even at moderate doses. For ellagic acid, trials reported greater erythema resistance, reflected by an increased minimal erythema dose, alongside changes in skin microbiome profiles. For ferulic acid, outcomes included attenuation of the erythema time-course with improved hydration and treated-site healing. Additional studies reported protection against combined ultraviolet radiation and diesel exposure. Formulation-based work also showed a significant reduction in UVB-induced erythema and faster resolution, consistent with improved release and skin permeation (Table 1).

Risk of bias

In RoB 2.0 assessments, the randomization process was rated as low risk when sequence generation and allocation concealment were clearly described, with some concerns where reporting was insufficient. Charoenchon *et al* [20] conducted a double-blind randomized controlled trial evaluating a green tea catechin regimen. The study reported dermal matrix protection; therefore, the risk of bias for outcome measurement was judged as low. In contrast, the risk of reporting bias remained of “some concern” due to limited DNA endpoint coverage [20].

Farrar *et al* used a double-blind randomized controlled trial design with calibrated solar-simulated ultraviolet radiation. However, outcomes were limited to cyclobutane pyrimidine dimers without accompanying extracellular matrix endpoints, which restricted cross-domain interpretation. Accordingly, the risk of bias judgment remained “some concerns” [21]. In the topical ferulate combination intervention, assessor-blinded split-face trials reduced the risk of measurement bias and intervention bias. However, details of sequence generation on the face side were not always complete [31]. The pomegranate consumption RCT had good randomization and compliance, with low risk of bias in missing data, but some domains remained of “some concern” due to potential reporting bias in the complex microbiome (Figure 2 A) [8].

Across ROBINS-I-assessed studies, the most common concerns involved confounding and intervention classification, including in translational studies using *ex vivo* human tissue. Non-random allocation of topical application sites and differential environmental exposure between sites may introduce serious confounding. This concern applied to studies evaluating C/E/FA antioxidant mixtures and ferulate double-emulsion formulations in healthy volunteers [16,32]. Blinding of outcome assessors was generally reported only partially or unclearly, resulting in the measurement domain being rated as "some concern." Missing data were infrequent and appeared selective. However, selective reporting cannot be excluded because outcome endpoints varied substantially across studies (Figure 2 B).

In the animal study (SYRCLE), most randomization and concealment domains were inadequately reported. These items were judged as unclear. Blinding of intervention delivery and outcome assessment was frequently absent or not reported, leading to judgments of high risk of bias. Furthermore, data completeness and ultraviolet protocol consistency were generally adequate. Accordingly, the risk of bias due to missing outcome data was judged to be low. This pattern aligns with evidence from ferulate and ellagic acid liposomal formulations evaluated with accompanying *in vivo* components. (Figure 2 C) [15,16].

Within SciRAP-like appraisals of *in vitro*/*ex vivo* evidence, risk of bias was driven primarily by incomplete reporting. Some articles did not state the number of biological replicates, blinding strategies for image/protein analysis, or justification for effect sizes and dose ranges, resulting in the reporting and measurement selection domain being rated as “some concern.” Representative examples include studies of EGCG in HSF/zebrafish and UVA in HSF, which are mechanistically robust but limited in replication transparency and quantitative normalization [13,18]. Similar concerns were observed in quercetin studies based on engineered carriers such as NLCs, ZnO nanoparticles, and polymerization, which often provide detailed formulation characterization but do not consistently blind outcome assessment in cell-based assays [242,25,27]. In the ellagic acid-pomegranate and ferulate groups, studies reported improved matrix metalloproteinase/extracellular matrix modulation and enhanced stability or penetration with chitosan niosomes, O-HA liposomes, and other encapsulation systems. However, dosing levels and incubation conditions were not fully reported in some experiments, resulting in an “unclear” judgment for these parameters (Figure 2 D) [15,17,29,30,35,37].

DISCUSSION

Across preclinical and clinical models, evidence for four key compounds indicates consistent photoprotective effects on oxidative stress markers and extracellular matrix homeostasis. By contrast, protection against direct DNA damage is less consistent, particularly under high-intensity ultraviolet exposure. Formulation and delivery strategies, as well as antioxidant combinations, appear to influence the magnitude and reproducibility of observed effects. For epigallocatechin gallate, studies in human dermal fibroblasts and zebrafish show reduced reactive oxygen species and inflammatory mediators, with preservation of matrix integrity, including suppression of mitochondrial reactive oxygen species. In human studies, this translates into protection against post-ultraviolet dermal matrix degradation. However, protection against direct DNA damage is not consistently observed under high-energy solar-simulated ultraviolet exposure, and activity may be enhanced by alpha-glucosylation through interactions with the skin microbiota [13,19–22].

Quercetin has been reported to modulate pro-aging signalling, including JAK2 and PKCδ, as well as ERK/AP-1 and NF-kB pathways, with concomitant reductions in COX-2 and MMPs expression in *in vitro* and *ex vivo* models. Its apparent efficacy is also formulation-dependent.

Table 1a: Characteristics of the studies

Author	Setting	Compound and Sources	Sample (cells/animals)	Induction	Dose / Concentration	Primary Outcomes
Zhang *et al* [13]	Preclinical studies	EGCG; *Camellia sinensis* (green tea)	Human skin fibroblasts (HSF); zebrafish larvae (4dpf)	Cells: UVA 10 J/cm² + UVB 30 mJ/cm²; Zebrafish: UV exposure model	25-50 μM EGCG for 72h in cells	Reduced ROS/inflammatory mediators; zebrafish skin/fin photoprotection
Jia *et al* [18]		EGCG; *Camellia sinensis* (green tea)	Primary human skin fibroblasts	UVA 10, 20, 30 J/cm² (over 2 weeks)	EGCG 25 μg/mL (per protocol)	Attenuated UVA-induced senescence/oxidative markers; preserved collagen-related readouts
Boira *et al* [22]		EGCG (α-glucosylated); *Camellia sinensis* (green tea catechins)	Skin microbiota model; reconstructed human skin (*ex vivo*)	Pigmentation/lightening and microbiota modulation assays	Not reported	Potentiated skin-lightening; microbiota involvement
Park *et al* [19]		EGCG; *Camellia sinensis* (green tea)	Human skin cell model	Mitochondrial oxidative stress / UV-related	Not reported	Lowered mitochondrial ROS linked to skin aging
Shin *et al* [23]		Quercetin; Multiple botanical sources (not specified)	JB6 P+ cells; *ex vivo* human skin explants	Cells: solar UV 26 kJ/m² (~94.5 % UVA/5 % UVB) for 26 min; *Ex vivo*: daily UV for 10 days	Quercetin pretreatment (working μM NR; stock 20mM in DMSO reported)	Targeted JAK2/PKCδ; suppressed AP-1/NF-κB/COX-2; prevented UV-induced photoaging signatures
Nisar *et al* [24]		Quercetin@ZnO (nanoparticles); Multiple botanical sources (not specified)	Human HaCaT keratinocytes	UVA 150 kJ/m²; oxidative/inflammatory readouts	(NPs ratios described; UV-controlled quercetin release)	Restored viability post-UVA; antioxidant, anti-inflammatory, and iron-sequestration effects
Costa *et al* [25]		Quercetin (NLC hydrogel; with pomegranate oil); Quercetin (pomegranate oil carrier)	Human keratinocytes; fibroblasts (viability)	UVB-related photoprotection assays in keratinocytes	(NLC ~200-300 nm; ~55 % entrapment); hydrogel delivery system	Demonstrated photoprotective effect in keratinocytes; robust rheology; long-term colloidal stability

Table 1b: Characteristics of the study *continued*

Author	Setting	Compound and Sources	Sample (cells/animals)	Induction	Dose / Concentration	Primary Outcomes
Hong *et al* [26]		Quercetin (within extract); *Quercus acuta* (fruit extract; contains flavonoids incl. quercetin)	Human keratinocytes	UVB-induced ERK/AP-1 pathway activation	Not reported	ERK/AP-1 suppression; anti-photoaging effects
Sunoqrot *et al* [27]		Quercetin (polymerized nanoparticles)	Antioxidant/cellular test systems	Oxidative stress assays (non-UV specific)	Not reported	Improved stability/antioxidant capacity; skin-tone matching coloration (formulation insight)
Messias *et al* [36]		Quercetin-rich onion peel extract	*In vitro* SPF and cell viability systems	UV filter/SPF paradigms	Not reported	Natural UV-filter potential with acceptable safety
Abd-Elghany & Mohamad [37]		Ellagic acid (chitosan-coated niosomes); Multiple botanical sources (not specified)	Skin cell line	Cellular anti-aging/photoaging markers	Not reported	*In vitro* anti-aging activity
Yang *et al* [15]		Ellagic acid (O-HA liposomes)	Human dermal fibroblasts; zebrafish	UV-related assays in cells and zebrafish	Not reported (formulation-specific dosing across assays)	Enhanced skin permeability and anti-aging efficacy; MMP suppression/collagen I support
Chang *et al* [35]		Pomegranate peel extract (ellagic-rich)	Human HaCaT keratinocytes	UVB irradiation	Not reported	Protection against oxidative damage; improved anti-photoaging markers
Mariné-Casadó *et al* [29]		Ferulic Acid; Pomegranate extract (Pomanox®)	Hs68 human dermal fibroblasts	Normal vs UV-induced photoaging conditions	Not reported	Positive modulation of skin health-related parameters

Table 1c: Characteristics of the study *continued (2)*

Author	Setting	Compound and Sources	Sample (cells/animals)	Induction	Dose / Concentration	Primary Outcomes
Pannakal *et al* [30]		Ferulic Acid; Pomegranate pericarp extract	Reconstructed human skin model	UVA-induced damage	Not reported	Protection against UVA-induced damage
Mancuso *et al* [16]		Ferulic acid (multiple emulsions);	Cell models; small animals	UVB-erythema and photo-oxidative paradigms	0.2 % w/v ferulic acid (topical); timing vs UV evaluated	Enhanced antioxidant activity; in vitro and in vivo efficacy; better release/permeation
Pueknang & Saewan [17]		Ferulic acid (phosphorylated rice starch encapsulation)	*In vitro* stability and anti-aging assays	Accelerated stability/UV-relevant assays	Not reported	Improved FA stability and anti-aging indicators
Peng *et al* [33]		Ferulic acid + retinol	Human HaCaT keratinocytes	UVB-induced photoaging	Not reported	Synergistic reduction of oxidative injury vs UVB
Kim *et al* [34]		Ferulic acid (herbal formula context)	*In vitro* antioxidant/formulation assays	Oxidative stress assays (non-UV specific)	Not reported	Antioxidant activity; FA determination as active component
Charoenchon *et al* [20]	Clinical studies	EGCG (green tea catechins)	Healthy adults, Fitzpatrick I-II (randomized, double-blind RCT)	Solar-simulated UVR at 3 × MED to assess dermal matrix changes	Green tea catechins 540mg + vitamin C 50mg, orally, twice daily for 12 weeks	Attenuation of UVR-induced ECM degradation (e.g., fibulin-5) vs placebo
Farrar *et al* [21]		EGCG (green tea catechins)	Healthy white adults, Fitzpatrick I-II (double-blind RCT)	Solar-simulated UVR at 3× MED (5 % UVB/95 % UVA) on buttock skin; pilot arm 2× MED	1080mg GTC + 100mg vitamin C daily for 12 weeks	No reduction in CPD-positive cells vs placebo at 24h; no effect at moderate (2× MED) dose as well
Henning *et al* [8]		Ellagic acid (via pomegranate juice/extract)	Healthy women (three arms: juice, extract, placebo)	UVB patch testing to determine MED pre-/post-intervention	PomJ 240 mL/day (~100mg punicalagin A/B + ~23 mg ellagic acid) OR PomX 1000 mg/day for 12 weeks	Increased UVB-induced erythema resistance (higher MED) and skin microbiome modulation
Qin *et al* [31]		Ferulic acid (CE Ferulic serum with Vit C + E)	Adults with facial photoaging (split-face, investigator-blinded)	Nonablative fractional laser (Fraxel) recovery model	Topical CE Ferulic applied immediately post-laser on one side, then once daily for 7 days	Reduced erythema trajectory and improved hydration/healing vs the control side

Table 1d: Characteristics of the study *continued (3)*

Author	Setting	Compound and Sources	Sample (cells/animals)	Induction	Dose / Concentration	Primary Outcomes
Ivarsson *et al* [32]		Ferulic acid (topical mix with Vit C + E)	Human skin/*ex vivo*-supported	UV and diesel exposure paradigms	Topical antioxidant mixture containing vitamin C, E, and ferulic acid (exact % NR)	Protection against combined UV and diesel-related cutaneous damage
Mancuso *et al* [16]		Ferulic acid (multiple emulsions)	Healthy volunteers (treated sites) + *in vitro* assays	UVB-induced erythema on treated skin sites	Topical multiple emulsion with ferulic acid 0.2 % (w/v); pre- vs post-UV protocols evaluated	Reduced magnitude and faster resolution of UVB-induced erythema; improved release/permeation

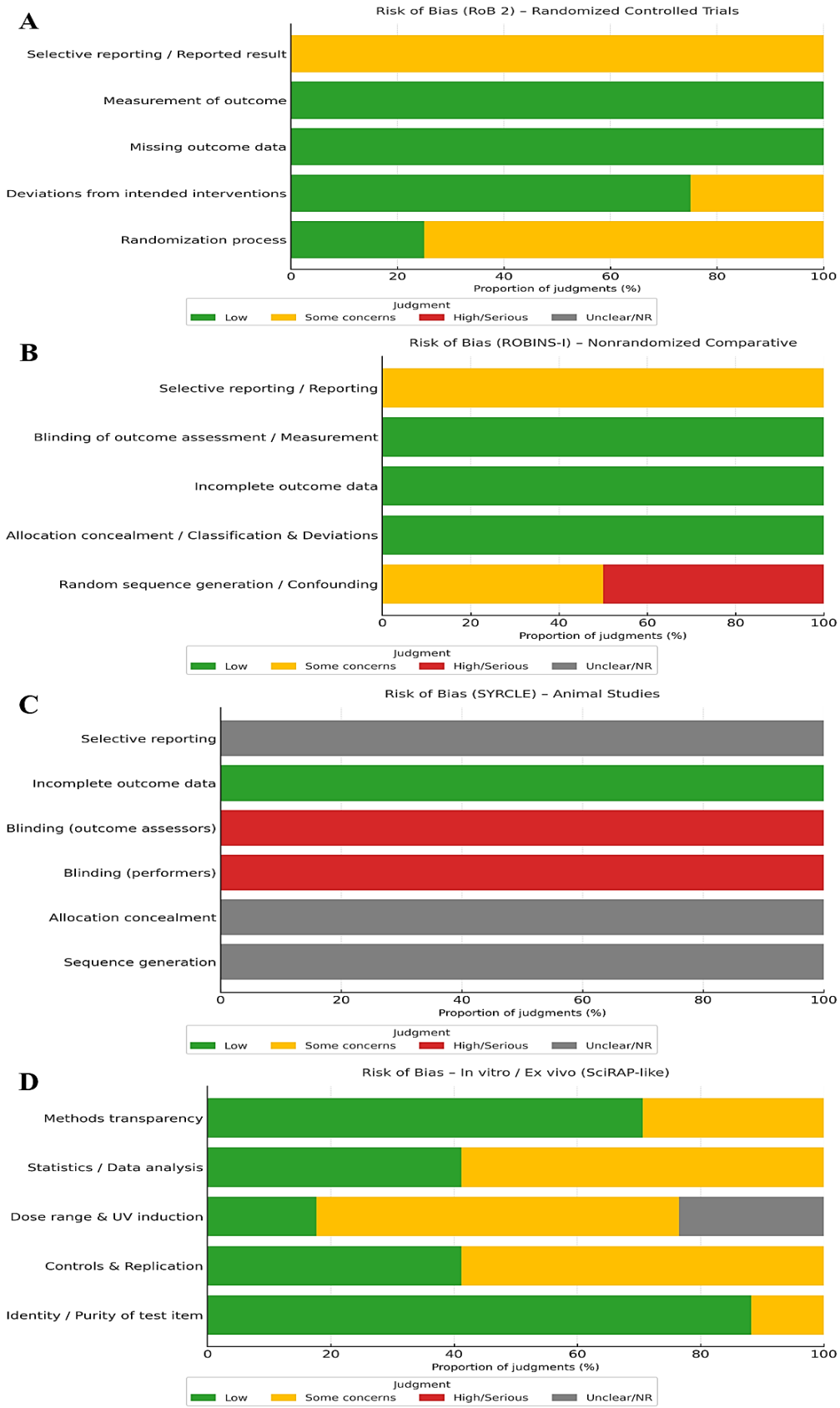


Figure 2: (A) Risk of Bias (RoB 2) for randomized controlled trials. (B) Risk of Bias (ROBINS-I) for nonrandomized comparative studies. (C) Risk of Bias (SYRCLE) for animal studies. (D) Risk of Bias (SciRAP-like) for *in vitro* and *ex vivo* studies

Nanostructured lipid carriers, zinc oxide complexes, and polymerized systems have been used to enhance stability, control release, and improve photoprotective performance [14,24–27,36]. Ellagic acid showed consistent anti-photoaging activity across multiple models and delivery platforms. As a pure compound, ellagic acid delivered via chitosan niosomes or oligomeric hyaluronic acid-modified liposomes enhanced skin permeation and suppressed MMPs expression. Similar effects were also reported for ellagic acid-rich pomegranate extracts, with benefits observed in keratinocytes, reconstructed skin models, and clinical skin health parameters.

In humans, minimal dose-dependent increases in erythema and modulation of the skin microbiome were reported after consumption of pomegranate juice or extract [8,15,29,30,35,37]. For ferulic acid, translational strength was found in its synergistic role in antioxidant mixtures with vitamins C and E or with retinol and in the clinical adjuvant context after laser procedures associated with reduced erythema and increased hydration. This pattern is in line with the literature that places polyphenols as photoprotectants that primarily work through the antioxidant and anti-inflammatory axis and control of matrix remodelling [3,11,16,17,31–33].

The specificity of each compound class was highlighted based on the consistency of findings and translational readiness. Epigallocatechin gallate was reported to consistently protect human skin fibroblasts and zebrafish models by decreasing mitochondrial reactive oxygen species, so that in clinical trials, protection against the dermal matrix was observed. In contrast, protection against direct DNA damage in high-dose solar-simulated ultraviolet exposure was not confirmed. Its activity was reported to be enhanced through alpha-glucosylation modification involving skin microbiota [13,18–22]. Furthermore, suppression of pro-aging signaling pathways such as JAK2 and PKCδ, as well as ERK and AP-1, has been found in studies evaluating quercetin compounds. However, bioactivity is strongly formulation-dependent, with improved stability and permeation reported for nanostructured lipid carriers, ZnO complexes, and polymerized systems [14,24–27,36].

Ellagic acid is limited by poor solubility and skin permeation, but these can be improved with delivery systems such as chitosan-coated niosomes and O-HA-modified liposomes, as well as nanostructured lipid carriers, double emulsions, and polymeric encapsulation. These platforms enhance penetration and retention, enabling local concentrations sufficient to suppress MMPs expression. These systems protect ellagic acid from degradation and provide targeted release to skin layers relevant to the collagenolytic pathway, resulting in a more measurable anti-photoaging profile. Meanwhile, ellagic acid-rich pomegranate extracts demonstrated broader benefits on keratinocytes, structured skin models, and clinical skin parameters. Even in small clinical trials, improvements in the minimum threshold erythema dose were reported, accompanied by modulation of the skin microbiome. However, signaling toward the ROS-MMPs pathway appeared stronger and more consistent with ellagic acid formulations using these advanced delivery technologies [8,15,29,30,35,37]. Ferulic acid showed strong translational potential driven by topical formulation and antioxidant pairing. A 0.2 % double emulsion accelerated UVB erythema resolution, phosphate starch encapsulation improved stability, and synergy was reported with vitamin C/vitamin E post-nonablative fractional laser and with retinol in vitro. Overall, phenolic acids appear most translatable when delivered through clinically optimized formulations and combination strategies [16,17,31–33]. Reduced MMP activity with preservation of collagen and elastin was supported for EGCG and ellagic acid by both preclinical data and clinical signals. Ellagic acid effects were most evident with chitosan niosomes or O-HA-modified liposomes and with ellagic acid-rich pomegranate extracts evaluated in keratinocytes, reconstructed skin models, and skin health parameters [15,29,30,35,37].

In humans, post-ultraviolet protection of dermal connective tissue by green tea catechins has been reported. At the same time, direct DNA damage prevention was not demonstrated at high doses of solar-simulated ultraviolet exposure, suggesting that the primary efficacy targets of the compound are more likely caused by the redox axis and matrix, rather than primary DNA repair [20,21]. Similarly, ferulic acid exhibits more pronounced antioxidant effects and MMP suppression is observed when the compound is combined with topical antioxidants or delivered via advanced formulations. Clinical signals include reduced erythema, improved hydration, and faster post-procedure recovery. These translational benefits appear to reflect redox-driven modulation of inflammation and ECM homeostasis rather than consistent protection against direct DNA damage [3,5,16,31–33].

Delivery technologies and combination strategies emerged as key determinants of translational efficacy, where increased stability, permeation,

and retention in the skin have been reported to enhance antioxidant and anti-inflammatory efficacy. O-HA-modified liposomes and chitosan-coated niosomes have been used to enhance tissue penetration and achieve more consistent MMP suppression. For quercetin, hydrogel-based nanostructured lipid carriers, ZnO nanocarriers, and polymerized systems that stabilize the flavonoid core have been associated with improved photoprotective performance under ultraviolet challenge [15,24,25,27,37]. In ferulic acid, double emulsion at a concentration of 0.2 % and encapsulation in phosphate starch have been reported to enhance controlled release and oxidative resistance, which are further maximized through topical combination with vitamin C and vitamin E or synergy with retinol [3,16,17,31–33].

Methodological heterogeneity should be emphasized because ultraviolet challenge protocols varied widely, ranging from isolated UVA or UVB exposure to solar-simulated ultraviolet radiation (95 % UVA/5 % UVB) and post-procedure nonablative fractional laser models. As a result, studies prioritized different endpoints, including DNA damage, matrix degradation, and erythema, which limits direct comparability. External validity is also constrained by substantial differences in experimental and clinical models, spanning HaCaT keratinocytes, human dermal fibroblasts, zebrafish larvae, human skin tissue or cells, healthy volunteers, and photoaged patient populations [13,18,20,31]. Variations in doses and regimens between micromolar concentrations, topical percentages, and oral supplementation with vitamin C, vitamin E, or retinol co-interventions emphasize the need for standardization of reporting of doses and topical contact times. A more balanced set of clinical endpoints is recommended to capture efficacy across domains. This should include MED and erythema for photoreactivity, hydration or barrier measures (for example, transepidermal water loss or occlusivity) for recovery and function, extracellular matrix biomarkers for dermal remodeling, and CPD markers for DNA photodamage [3,8,16,21].

This review has notable strengths, particularly its qualitative, pathway-oriented synthesis that links evidence from preclinical cell and animal models with early clinical and volunteer studies. This integration enables readers to identify which mechanisms, ROS scavenging, MMP suppression, and formulation-driven barrier delivery, show the clearest alignment with human endpoints. The review also compares two major polyphenol classes, flavonoids (EGCG and quercetin) and phenolic acids (ellagic acid and ferulic acid), and then evaluates evidence at the individual compound level. This design supports conclusions based on compound-to-compound contrasts across comparable experimental settings rather than relying on findings from a single molecule. However, this study has several limitations, including high heterogeneities in induction methods, dose, formulation, duration, and endpoints. The presence of unreported data in some studies requires author correspondence or additional searches, small sample sizes with potential selection and performance bias, the risk of publication bias in the preclinical setting, and limited generalizability of cellular or reconstructed skin models to clinical populations with diverse phototypes and ages.

CONCLUSION

EGCG and quercetin suppress ROS and signaling pathways, while ellagic and ferulic acids show translational potential through delivery technologies and antioxidant combinations. Across the available human studies, signals of benefit include preservation of ECM-related biomarkers, increased MED, and reduced erythema. Standardized clinical trials with clear UV induction, reporting of dose and topical contact time, composite endpoints, delivery optimization, evaluation of rational combinations, microbiome monitoring, long-term safety, and inclusion of diverse phototypes and age groups are recommended.

DECLARATIONS

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Ethical approval

None provided. All data generated or analyzed in this systematic review are included in this published article and its supplementary material.

Use of Artificial Intelligence/large language models

AI was used specifically for generating alternative reference suggestions and structuring the reference list based on author-provided topics; and conducting initial, non-exhaustive literature searching and thematic structuring to

map studies on flavonoids and phenolic acids in photoaging.

Use of research reporting tool

This study used the PRISMA guideline.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Komang Harry Supradnyan conceived and designed the study, developed the research question, supervised the protocol, and coordinated the overall manuscript preparation. Gusti Ayu Agung Praharsini conducted the literature search, performed data extraction, and contributed to drafting the sections on photoaging mechanisms and compound classification. Made Jawi contributed to the methodological framework, verified the extracted data, and performed critical revision of the biological and pharmacological interpretations. Made Ratna Saraswati contributed to data interpretation, refined the clinical translational perspective, and edited the manuscript for intellectual and structural clarity. All authors read and approved the final version of the manuscript for publication.

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