Role of *Nigella sativa* L. seed (black cumin) in preventing photoaging (Review)

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Received February 3, 2025; Accepted April 30, 2025

DOI: 10.3892/br.2025.2009

Abstract. Photoaging is a group of clinical and pathological manifestations caused by ultraviolet (UV) radiation, characterized by deep wrinkles, rough skin textures, dyspigmentation and disturbance of skin elasticity. UV radiation can cause skin damage due to reactive oxygen species (ROS) accumulation, which activates matrix metalloproteinase and increases collagen damage. One natural ingredient that has antioxidant properties by reducing ROS production is black cumin or *Nigella sativa* (*N. sativa*) seeds; this effect is attributed to key components such as thymoquinone, flavonoids, essential fatty acids and essential minerals. The present review aimed to describe the potential ingredients of *N. sativa* and its mechanism against photoaging. PubMed, ScienceDirect, Springer and Google Scholar databases were searched between 2014 and March 2024. The keywords were *N. sativa*, black seed, thymoquinone and photoaging. The search was limited to articles in Indonesian and English. Based on the critical appraisal, the eligibility of the included articles was evaluated; nine eligible articles were selected. The authors indicated that *N. sativa* and its active ingredient, thymoquinone, may have a role in preventing photoaging through various potential mechanisms, including its antioxidant and anti-inflammatory properties. Some studies have compared the effects of various types (oral and topical) of *N. sativa* and thymoquinone with good outcomes. *N. sativa* and thymoquinone may prevent photoaging by neutralizing UV-induced ROS accumulation. More studies are required to determine the exact mechanism of *N. sativa* and thymoquinone as an alternative therapy for photoaging.

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Key words: antioxidant, black cumin, decelerating aging, natural compound, thymoquinone

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1. Introduction

Photoaging due to exposure to ultraviolet (UV) radiation results in the appearance of rough skin, wrinkles, xerosis, hyperpigmentation and epidermal thickening owing to the progressive loss of function and regenerative potential of the skin tissue (1). Collagen is the main supporting skin structure; its excessive degradation is directly related to wrinkle formation (2). Matrix metalloproteinase (MMP) is a matrix-degrading enzyme that degrades and modifies some components of the extracellular matrix (ECM). UV radiation can increase MMP-1 production, which in turn increases collagen degradation in human skin (3).

An increase in the ROS content caused by UV exposure can cause oxidative stress accumulation, which activates MMP and increases collagen damage (4). Antioxidants are chemical substances that neutralize or interfere with the action of free radicals (5); these agents are often used to prevent or slow down the oxidation of macromolecules that cause oxidative stress. One natural ingredient that has antioxidant properties by reducing ROS production is black cumin or *Nigella sativa* (*N. sativa*) seeds (6).

N. sativa is a small shrub, 20-90 cm in height, which belongs to the *Ranunculaceae* family; it is known for its antioxidant, antiviral, antifungal, antiparasitic and anti-inflammatory effects (7). The effects of these agents against free radicals are related to their activities of free radical scavenging and inhibiting 5-lipooxygenase during the inflammatory phase (8). This ability is attributed to several important components, such as thymoquinone (TQ), flavonoids, essential fatty acids and various mineral components, which have been widely studied (9). *N. sativa* has a therapeutic

effect by reducing cytotoxicity, oxidative stress, inflammatory response and cell death caused by mitochondrial dysfunction in keratinocyte cells irradiated with ultraviolet A (UVA) light (10). Another study found that *N. sativa* extract inhibits the formation of advanced glycation end products, collagen cross-linking, collagenase activity and elastase activity (2). An animal study with rats exposed to UVB light showed a significant increase in collagen levels after being given topical *N. sativa* extract (11).

2. Photoaging

Photoaging is a group of clinical and pathological manifestations caused by skin exposure to UV radiation (12). UVA and UVB both play a role in photoaging, although UVA rays have longer wavelengths because UVA-1 rays (340-400 nm) can be absorbed deeply into the human skin and exert effects directly through the dermal fibroblast level (13); however, UVC is fully reflected by the ozone layer (14). Photoaging involves all skin layers, with primary effects on the dermis and paracrine effects on other skin layers. This condition comprises acute and chronic cellular processes characterized by rough wrinkling, decreased skin elasticity, pigmentation, xerosis, keratosis and telangiectasis (15).

The clinical manifestations of normal aging and photoaging often appear simultaneously; however, there are several differences (12). Normal aging is characterized by sagging skin and an excessive expression of frown lines. Aging skin has decreased hydration and elasticity, permeability and susceptibility to irritation owing to skin barrier damage (16). The manifestations of photoaging include deep wrinkles, rough skin texture, dyspigmentation and skin elasticity disturbance (17). The distribution of photoaging is mostly limited to the face, neck and hands and rarely to the arms and lower legs. Of photoaging cases ~80% are caused by chronic low-level UV exposure, although exposure to high levels of acute UV light can also cause skin burning, darkening and skin structure disorders (18). Microscopic examination showed an increase in the epidermal thickness, dystrophic elastin accumulation and irregular collagen in the dermal layer. Skin susceptibility to UV damage depends on the melanin content and Fitzpatrick skin types I, II and III are more susceptible to photoaging than skin types IV, V and VI (19).

There are three main causes of photoaging: i) Dysfunction of keratinocytes in the basal layer, which inhibits their ability to regenerate and repair the skin; ii) loss of the ability of fibroblasts to synthesize and produce collagen; iii) changes in intracellular homeostasis through certain paracrine mechanisms (20). These changes are related to UV exposure on the skin, which causes oxidative stress (21).

Photoaging and UV exposure. Large amounts of UVB can reach the skin due to direct sunlight exposure during the day (22). UVA is rarely absorbed when passing through the atmosphere (23). High UVA radiation throughout the day causes greater UVA exposure on the skin than UVB exposure under normal conditions (24). UVB exposure can cause erythema, burning, skin damage and skin cancer, whereas intense UVA exposure can cause erythema and blood vessel damage (25). To produce this effect, UVA requires an amount 1,000 times greater than UVB. However, UVA can penetrate deeper than UVB, causing damage to collagen and elastic fibers in the dermal layer (24,26).

UV radiation as photons needs to be absorbed by chromophores, followed by various photochemical events to produce photoaging skin manifestations (19); this process involves fibroblasts, keratinocytes and neutrophils (27). Therefore, the skin is a notable part of the immune system and consists of numerous molecular mechanisms that protect the skin from UV radiation (28). The epidermal layer provides the first line of defense against hazardous external agents consisting of keratinocytes, antigen-presenting cells, Langerhans cells, T lymphocytes and melanocytes (29).

Keratinocytes have an immune function against UV by producing cytokines, hormones, chemokines, neuropeptides and antimicrobial peptides (30). Melanin is produced by melanocytes; it works by inhibiting and absorbing UV rays that enter the epidermis layer. As UV exposure increases, the melanin formation rate increases, causing the skin to appear darker and providing additional protection against further radiation injury (22). Furthermore, DNA damage caused by UV rays can be repaired by nucleotide repair and base excision mechanisms, apoptosis and cell cycle checkpoint system activation (31).

Photoaging and oxidative stress. Humans are constantly exposed to oxidants daily; oxidative stress occurs because of a disturbance in the oxidant-antioxidant balance (32,33). Excessive UV radiation can induce ROS production while downregulating peroxidase and glutathione reductase production, which depends on the amount of UV radiation absorbed (34). UV rays can not only directly damage the skin by destroying lipids, proteins and DNA cells but also indirectly through the increased oxidation of various substances, especially lipids and DNA (24).

The effects of UVB radiation in human keratinocyte cells are characterized by enhanced ROS production, release of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, cyclooxygenase (COX) and nuclear factor-κB (NF-κB) (24). The aging process of fibroblasts during photoaging owing to UVB exposure is associated with ROS accumulation, which escalates proteasomes inhabitation and autophagy initiation (35). Autophagy suppression is required to switch the cell pathway from senescence to the apoptotic process (36). Inactivation of the proteasome system in fibroblast cells is related to the generation of singlet oxygen, protein oxidation and transcriptional agents that regulate MMP-1 expression activation (31).

Molecular impact of ROS on photoaging. Human bodies produce ROS consisting of superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radicals (OH), singlet oxygen ($^1O_2$), lipid peroxide and nitrogen oxide (37). O_2 molecules gain a single unpaired electron to establish O_2^- and thus become the early stage of ROS in cells (38). O_2^- molecules will form H_2O_2 through antioxidant enzyme catalysis (39). O_2^- can release iron ions under stress conditions from the iron-sulfur of proteins, participating in the Fenton reaction and converting H_2O_2 to OH (40). Hydroxyl radicals are easily reacted with other molecules with a half-life of 10^{-9} sec (41).

Normal skin aging and photoaging both involve similar signaling pathways, although they are induced differently (42,43). In photoaging, ROS can increase MMP synthesis by stimulating mitogen-activated protein kinase (MAPK) and protein-1 (AP-1) heterodimers (44). MMP-1 is capable of breaking down the integrated fibrillar collagen, whereas MMP-2, MMP-3 and MMP-9 break down the fragments and degraded forms (44-46). ROS and activated MAPK signaling pathways stimulate NF-κB and induce the expression of several proinflammatory cytokines (46,47). NF-κB organizes the expression of hemeoxygenase-1 and increases free iron levels in cells, thereby encouraging ROS execution through the Fenton reaction (48,49). NF-κB also excites MMP-8 to accelerate collagen breakdown; at the same time, AP-1 downregulates the expression of transforming growth factor-β (TGF-β) receptor type II, which disrupts the downstream Smad/TGF-β signal pathway, thereby reducing the transcription of the COL1A1 and COL3A1 genes encoding type I and type III collagen (41,50-52). Photoaging is caused not only by increased degradation of collagen by various MMPs, serine and other proteases but also by decreased collagen production by fibroblasts (1).

Photoaging and MMP activities. The main function of MMPs is to degrade the ECM, glycoproteins, cytokines, receptors and growth factors (52). Impaired regulation of MMP activity causes various pathologies and is divided into the following: i) Tissue damage; ii) fibrosis; and iii) matrix weakness (53). UV exposure can increase MMPs levels, which are responsible for ECM damage, including collagen, elastin, fibronectin and proteoglycans (54). This exaggerated degradation can cause clinical signs of photoaging, resulting in deep wrinkles and sagging skin through photodestruction, phototransformation and photo-oxidation of collagen and elastin fiber processes (31).

DNA damage following UVB exposure induces MMP-1 production by increasing MMP-1 gene expression in keratinocytes (31,54,55). Protein expression changes have a substantial role in photoaging, including the transformation of TGF-β, MMP-1, MMP-3 and MMP-9 (56). ROS stimulates the MAPK signal pathway, which is responsible for AP-1 formation (57). AP-1 plays a crucial role in the transcription regulation of MMP-1, MMP-3 and MMP-9, which progressively damage collagen (58). In addition, AP-1 can inhibit TGF-β, which regulates type I procollagen production and subsequently results in decreased collagen synthesis (59). Another notable transcription factor involved in the UV response is NF-κB (60). It can regulate the production of MMPs, such as MMP-1 and MMP-3, by fibroblasts (31).

Photoaging and collagen levels. Collagen is a structural protein responsible for maintaining skin elasticity (61). Collagen produced by fibroblasts varies according to the amino acid primer sequence of the polypeptide chain (62). Type I collagen is found in 90% of the human body (63); it is notably discovered in bones, tendons, ligaments, corneas and various interstitial connective tissues (64).

Type I collagen production is regulated by two genes, COL1A1 and COL1A2, which structurally consist of α-1 chain and α-2 chain (62). The COL1A1 gene is located in chromosome 17q21.33 (65); its synthesis and maturation are arranged at various levels: Epigenetic and transcriptional, posttranscriptional and posttranslational (66). In photoaged skin, COL1A1 mRNA expression levels are reduced, whereas MMP-1 mRNA expression levels are increased in association with collagen metabolism (67).

Collagen fibers are thicker and coarser in the inner dermal layer than in the outer layer, with thinner and more tenuous collagen fibers (68). Collagen fibers in younger skin are intact, dehydrated, elastic and damage-resistant (69). Collagen levels in aging skin begin to decrease, fade, stretch and lose their elasticity (70). The destruction of collagen and damage of other structural components, including elastic and reticular fibers, underlie the characteristic changes in aging skin and photoaging (64). Significant reductions in the amount and collagen structure can weaken the flexibility of the dermal layer, causing wrinkles and xerosis (71).

UV radiation exposure indirectly initiates MMP activation without upregulating collagen production, causing decreased collagen levels and ECM fragmentation (72). MMP activation is influenced by photochemical reactions that change the UV energy absorbed by cellular macromolecules into ROS (73). Over time, ROS levels exceed antioxidant defense, which promotes increased collagen-degrading MMP production. ROS inhibits the activation of protein tyrosine phosphatase, causing receptor tyrosine kinase phosphorylation and activating the MAPK signaling pathway that forms AP-1 (74). AP-1 is important for upregulating the transcription of MMP-1, MMP-3 and MMP-9, where excessive MMP expression can cause increased dermal ECM fragmentation (56,58).

Apart from collagen degradation owing to excessive MMP expression, ROS also triggers a decrease in collagen production by inhibiting the TGF-β signal pathway (75). ROS-induced AP-1 prevents the TGF-β/Smad signal pathway in fibroblasts that control collagen synthesis to prevent a decrease in collagen production (76). TGF-β interacts with cell surface receptors and triggers the Smad2/3 transcription factor. The phosphorylated Smad2/3 then associates with, and moves to, Smad4, thereby triggering the transcription of TGF-responsive genes (71); this leads to decreased phosphorylation and production of the Smad 2/3 transcription factor required for type I procollagen transcription (75).

3. *N. sativa* seed (black cumin)

N. sativa is a member of the *Ranunculaceae* family and is known as Black Seed or Black Cumin (77). *N. sativa* seeds originate from Africa and Southwest Asia (78). High-quality seeds come from Egypt, where a suitable environment exists for this plant (77). *N. sativa* is an annual herbal plant, 20-30 cm tall, with linear leaves, 5-10 pale bluish-white flower petals and tiny black seeds similar to cumin; therefore, it is called black cumin (79). This plant has green branching stems and green leaves that turn red as they grow (80); it starts flowering between April and August and its fruit consists of 3-6 carpels, each of which contains seeds (81). The seeds are oval and 2-3.5 mm in size, composed of three to four fine-grained corners; the color turns black after being cooked and exposed to air (77,79).

The nutritional value of *N. sativa* seeds includes protein, fat, fiber and total carbohydrates (82). *N. sativa* seeds also contain significant amounts of iron, copper and zinc (83). *N. sativa*

has phytoconstituents such as alkaloids, sterols, saponins and essential oils (84). Their seeds comprise primary fatty acids, linoleic acid, palmitic acid and phenolics and quinones (TQ, thymol, dithymoquinone and thymohydroquinone) (85,86). TQ ($C_{10}H_{12}O_2$) has a basic quinone structure with methyl and isopropyl side chain groups added at 2 and 5 positions (87). TQ has COX and 5-lipooxygenase activities, which can inhibit eicosanoid formation during inflammatory phases and lipid membrane peroxidation (88).

Quercetin and kaempferol are the main flavonoid glycosides in *N. sativa* (86). *N. sativa* also contains phenolic and triterpene compounds such as saponins (89). Saponin is a group of glycosides comprising one or more hydrophilic groups combined with lipophilic triterpenes or steroid derivatives. Triterpene saponins are typical compounds found in *N. sativa* seeds (85).

N. sativa extract has been accepted and recognized as safe by the Food and Drug Association in the United States (90). *N. sativa* is available in dietary supplements, oils, topical creams and powders (91). The acceptable and effective dose is equivalent to 1-3 g of *N. sativa* extract powder once daily, 40 mg/Kgbw of *N. sativa* extract once daily, or 1 ml of *N. sativa* extract cream three times daily, based on clinical trial data on humans (92). However, there is considerable variability in doses and extract preparation, including oil-based formulations, methanol extracts and advanced nanoformulations, which might affect bioavailability and clinical efficacy.

The *in vivo* TQ pharmacokinetic dose study showed a maximum concentration (Tmax) of 3.96±0.19 h reaching 4811.33±55.52 ng/ml as the maximum blood concentration (Cmax), while the elimination half-life (T1/2) was 4.4933±0.015 h. This indicates the suitability of TQ for extravascular administration through nanoparticle formulation, which has been shown to increase bioavailability (93). The seed extract and its constituents appear to have low levels of toxicity (94). The lethal dose 50 (LD50) of TQ is 2.4 g/kg bw in Swiss albino mice (95). Giving 6.4 g/kg bw of *N. sativa* extract orally every day for 6 weeks to mice caused the death of one mouse following 2 weeks of therapy, while the second and third mice died in the third and fifth weeks after being given 21 and 60 g/kg bw of *N. sativa* extract, respectively (83). Toxicity in mice after using fixed oil content from *N. sativa* extract administered intraperitoneally and intraorally showed that the LD50 was found to be 89.7-119. 7 mg/Kgbw and 647.1-1,094.8 mg/Kgbw, respectively (96). Additional studies are needed to confirm the refined dosage recommendations and evaluate *N. sativa*'s long-term safety in other animals and also in clinical studies.

In recent decades, a number of extraction methods, such as cold pressing, supercritical fluid extraction, Soxhlet extraction, hydro distillation method, microwave-assisted extraction, ultrasonic-assisted extraction, steam distillation and accelerated solvent extraction, have been used to extract oil from black seeds under optimal conditions (97). The cold pressing method using hexane as a solvent does not involve heating or chemical treatment during oil extraction but gives low yields, whereas the Soxhlet extraction method using methanol as a solvent has low costs; however, solvent residues remain in the extracted oil. Thymoquinone in black cumin oil is encapsulated to enhance its oxidative stability. Microencapsulation was achieved through emulsification, spray drying and nanoprecipitation. These processes are more time consuming and involve hot gas flow; therefore, they are not suitable for heat-sensitive bioactives. For sensitive compounds, alternative techniques are required to overcome the drawbacks of conventional encapsulation methods. A recently developed encapsulation technology is electrospray; this process is cost-effective and simple for producing a wide range of nanoparticles. No heat is required during drying and the formation of smaller encapsulations of 1-5 μm is increasingly important for the encapsulation of temperature-sensitive bioactives (97). Continued investigation is required to assess the formulation-dependent differences in bioavailability to ensure consistent therapeutic outcomes, optimal absorption and effective systemic distribution.

No severe side effects have been reported after using the *N. sativa* extract, either orally or topically. Three women were reported to have acute allergic contact dermatitis after using the topical pure oil of *N. sativa* extract (90). Other studies have reported the side effects of gastrointestinal disorders, gastric irritation and stomach cramps (98). Gastrointestinal disturbances occurred in 9 of 49 children who orally consumed *N. sativa* extract at a dose of 80 mg/kg twice daily on an empty stomach (99). Further clinical research under controlled conditions is necessary to comprehensively examine the safety profile of *N. sativa* in dermatological applications.

4. *N. sativa* seed (black cumin) mechanism against photoaging

N. sativa mechanism is mainly because of its active ingredients, especially TQ (91,100). TQ has a quinone molecular structure for redox activity and the infinite capability to cover all physiological barriers so that it has easy access to subcellular compartments, which affects radical scavenging (101). TQ is known to have anti-inflammatory and antioxidant effects that can protect cells from free radicals. In addition, TQ stimulates the proliferation and migration of cells involved in tissue repair, encouraging the formation of new tissue (102). TQ reduces NF-κB transcription factor activity so that MMP-1 expression can be suppressed (103). Decreased expression of MMP-1 can further reduce collagen degradation. TQ also acts directly on type I collagen synthesis by preserving the physiological state of the interstitial system (104). Currently, there is no recommended dose of TQ for its role in preventing photoaging. Research by Ghorbanibirgani *et al* (105) using a topical extract of *N. sativa* twice a day for 6 months in vitiligo cases found significant improvement in patient scores. Unfortunately, this study did not clearly state the manufacture of the topical cream and its concentration. Research by Yousefi *et al* (106) using a topical extract of *N. sativa* at a dose of 2% twice a day for 4 weeks in hand eczema cases showed equally effective results as the use of topical betamethasone. The two studies mentioned the anti-inflammatory and antioxidant effects of *N. sativa* and TQ as their working mechanisms.

Flavonoids, especially quercetin and kaempferol, play a role as strong antioxidants by interrupting free radical chain reactions and protecting against UV radiation (107). Several studies have reported that quercetin has a photoaging defense mechanism by inhibiting MMP-1 in a dose-dependent manner (108-111). Quercetin shows strong antioxidant activity through *in vitro* chemical tests, showing an increase in quercetin

Table I. *Nigella sativa* contents and their possible mechanism against photoaging.

Ingredients	Role against photoaging	Mechanism	(Refs.)
Thymoquinone	Prevents oxidative injury and prevent membrane lipid peroxidation	• Inhibits the activation of NF-κB • Works directly on the fibrillogenesis of type I collagen	(97-99)
Flavonoids (quercetin and kaempferol)	Interrupts free radical chain reactions and protect against UV radiation	• Inhibits MMP-1 mRNA levels • Inhibits ERK and p38 MAPK activation • Reduction in NF-κB	(101-105)
Saponins	Modulates inflammatory response, protects against ECM degradation, enhances collagen production and improves wrinkle appearance	• Inhibits MAPK signaling, AP-1, and NF-κB activation	(35,104)
Linoleic and oleic acids	Maintains water permeability barrier and epidermal integrity of the skin	• Suppresses UV-induced changes in TEWL, skin hydration, and erythema	(105,108,111)
Minerals (Cu, Zn and Fe)	Decreases oxidative stress biomarkers and inflammatory cytokines	• Cofactor for many enzymes against oxidants	(96,112,114)

NF-κB, nuclear factor-kappa B; UV, ultraviolet; MMP-1, matrix metalloproteinase-1; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; ECM, extracellular matrix; AP-1, activator protein-1; TEWL, transepidermal waterloss; Cu, cuprum; Zn, zinc; Fe, iron.

activity following efficient formulation at the cellular level, as quercetin shows cell-protective action on keratinocytes and *in vivo* on animal skin. This antioxidant effect is also supported by the ability of quercetin to exert anti-inflammatory actions, such as the inhibition of NF-κB and IL-6 induction by UV irradiation. The combination of antioxidant and anti-inflammatory actions and their cross-linking mechanism highlight quercetin as a novel sunscreen. Furthermore, as quercetin has antioxidant and anti-inflammatory activities, it could be beneficial for wound healing; here, fibroblasts are the main target in contrast to keratinocytes in sunscreens. Furthermore, quercetin has a promising rejuvenating effect on keratinocytes with a supportive whitening effect (112). Kaempferol protects against UVB-induced photoaging by preventing p38 MAPK and c-Jun N-terminal kinase activation (113). These agents prevent the action and amount of MMP-1 and increase collagen levels in the dermal layer. Flavonoids can also stimulate macrophage activity, trigger the epithelialization process and escalate ECM production, growth factors, cytokines and angiogenesis by releasing keratinocyte growth factor (10).

Saponin is a type of glycoside from pentacyclic triterpenoids that has pharmaceutical, nutritional and cosmetic potentials with anti-inflammatory and antioxidant properties. Thus, it has the potential to protect against the detrimental effects of photoaging (114). Saponin modulates the inflammatory response, protects against ECM degradation, enhances collagen production and improves wrinkle appearance by preventing UVB-induced MAPK signaling, AP-1 and NF-κB activation (111,115).

Linoleic acid comprises >50% of the total fatty acids and can preserve water permeability and skin integrity (116,117). Linoleic acid, which is known for its percutaneous absorption, can increase drug absorption, whereas the oil emulsion of the substance can reduce skin irritation and improve the skin's moisturizing function (118). Topical application rich in linoleic and oleic acids can suppress transepidermal water loss changes, increase skin hydration, reduce skin erythema and protect against histological changes caused by UVR exposure (119).

N. sativa seeds contain various elements, such as Cu, Zn and Fe (100). Cu is a common cofactor for a number of enzymes and in the skin acts by provoking fibroblast proliferation, increasing collagen (types I, II and V) synthesis and acting as a cofactor for superoxide dismutase (SOD) to interfere with cellular oxidative effects (100,120). Zn also inhibits the accumulation of oxidative stress markers and proinflammatory cytokines. Zn ties up to the sulfhydryl groups of oxidation-protecting biomolecules and increases the activation of glutathione (GSH), catalase and SOD and decreases the activity of enzymes that increase oxidant levels, such as inducible nitric acid synthase (iNOS) and NADPH oxidase and slows the formation of peroxidation products, lipids (121). Iron plays a role in oxygen transport and oxidation-reduction reactions as well as in various oxygenases, including procollagen-proline dioxygenase, which is associated with the skin (122). Table I lists the active ingredients of *N. sativa* seeds and their mechanism against photoaging.

Sunlight contains UVA and UVB, which reach the skin surface, triggering oxidative reactions that result in ROS (13). Excessive ROS accumulation in the skin activates the MAPK signaling pathway and the NF-κB pathway (123). The activated MAPK pathway triggers AP-1 production. ROS-induced AP-1 inhibits the TGF-β/Smad signaling pathway in dermal fibroblasts, which controls collagen synthesis to prevent a decrease in collagen production. TGF-β interacts with cell surface receptors and triggers the transcription factor Smad2/3. The phosphorylated Smad2/3 then connects and moves to Smad4, thereby triggering the transcription of genes responsive to TGF-ß. This causes a decrease in the phosphorylation and

activation of the transcription factor Smad 2/3, which is required for the transcription of type I procollagen, a precursor of type I collagen, namely the COL3A1 and COL1A1 genes (1,55,57).

ROS and activated MAPK signaling pathways can also activate NF-κB; this activation can increase the expression of proinflammatory cytokines such as IL-1β, IL-6, TNF-α and COX-2 to regulate the inflammatory response and unbalance the MMPs/tissue inhibitors of metalloproteinases (TIMPs) ratio by activating MMPs and reducing TIMPs expression, thereby decompressing the ECM (6,31,41). NF-κB also increases the formation of the MMP1 enzyme to accelerate collagen degradation, especially type 1 collagen (31).

N. sativa contains an active ingredient, TQ, which is a potent antioxidant (6,9,10). The active substance TQ has a therapeutic effect by reducing oxidative stress and inflammatory responses, thereby preventing the activation of the MAPK and NF-κB pathways. Kaymak *et al* (124) reported that intraperitoneal administration of TQ 10 mg/kg bw in rats for 10 days showed a significant decrease in various inflammatory mediator levels, such as P38 MAPK and NF-kb, in the testes of rats induced by methotrexate. Activating NF-κB is directly associated with an increase in MMP-1 (125). Chen *et al* (103) investigated the effect of TQ on MMP expression in an animal model of osteoarthritis. Accordingly, the downregulation of MMP-1, MMP-3 and MMP-13 expressions and the upregulation of TIMP-1 expression were reported due to the use of TQ in chondrocytes and cartilage in the animal model. The authors also showed that TQ could inhibit the NF-κB p65 protein level. MMP-1 can degrade fibrillar collagen in its three-helical domain, which causes the molecules to be thermally unstable so that they break down to form gelatin, which can then be degraded by other members of the MMP family (126).

Several photoaging therapies are often used with different working mechanisms. Topical retinoids during photoaging are mediated by their interaction with specific cellular and nucleic acid receptors. They improve photoaging by modifying cellular differentiation programs by increasing epidermal proliferation and thickening, compacting the stratum corneum and improving the deposition of glycosaminoglycans in the stratum corneum and intercellular spaces of the epidermis (127). Vitamin C is a naturally occurring antioxidant that has been shown to be effective for preventing and treating sun-damaged skin; it not only has an antioxidant, anti-inflammatory and photoprotective effect against UVA and UVB but also enhances collagen synthesis (128). The major adverse effects of topical retinoids and topical vitamin C are local skin irritation, including erythema, peeling, dryness, burning and itching, which depend on the concentration and formulation of the product (129,130). In addition, the use of retinoid agents is not recommended in pregnant women and topical vitamin C preparations are occasionally unstable, limiting their clinical use.

The summarized mechanism of *N. sativa* seed extract therapy in combating photoaging is shown in Fig. 1. *N. sativa* plays a protective role in inhibiting photoaging manifestations by modulating oxidative stress and inflammatory pathways. UV exposure induces the production of ROS, which subsequently activate the NF-κB and MAPK signaling pathways, leading to increased transcription of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6 and COX-2) and MMP-1, both of which contribute to inflammation and collagen degradation. However, *N. sativa* inhibits ROS generation, thereby downregulating NF-κB and AP-1 activity. These result in reduced inflammatory cytokine expression and decreased MMP-1 levels, preserving collagen density. Additionally, *N. sativa* enhances TIMPs and TGF-β receptor Smad signaling, which promotes the expression of collagen-related genes (COL1A1 and COL3A1). Collectively, these actions reduce inflammation, prevent collagen breakdown and promote skin integrity, ultimately inhibiting the visible manifestations of photoaging.

While multiple studies highlight the anti-photoaging effects of *N. sativa*, inconsistencies exist in its reported efficacy. Some studies emphasize strong antioxidant and anti-inflammatory benefits, while others suggest limited or unclear results (2,10,131-134). The concentration of TQ in different extracts varies widely, which may contribute to the heterogeneity in study outcomes. Furthermore, variations in study design, including animal models compared with human clinical trials, need further standardization to ensure comparability.

Despite promising preliminary findings, several research gaps remain. The optimal dosage of TQ for anti-photoaging effects has not been established and most studies lack standardized extraction methods. Future research should focus on well-controlled, long-term clinical trials to assess both efficacy and safety. Additionally, the interaction of *N. sativa* with other dermatological treatments (such as retinoids, vitamin C, or chemical peels) warrants further investigation to determine possible synergistic or antagonistic effects. A number of studies on *N. sativa* and photoaging have been conducted with small sample sizes, often in preclinical settings, making it difficult to generalize findings. Additionally, industry-funded research may introduce bias in reporting only positive results and there is a lack of large-scale, double-blind, placebo-controlled clinical trials. This raises concerns about publication bias, which may interfere the perceived efficacy of *N. sativa* in photoaging treatment.

5. *N. sativa* seed (black cumin) potential role against photoaging

The use of *N. sativa*, both orally and topically, has been widely studied and its use has been shown to have a potential role against photoaging. The potential antioxidant and anti-inflammatory effects are possibly caused by the active composition of *N. sativa*, TQ (6). There are two *in vitro* studies regarding antiaging and photoaging effects of TQ. Li *et al* (2) analyzed Thymocid®, a standardized TQ extract, which can inhibit the formation of advanced glycation end products, collagen cross-linking, collagenase and elastase activities *in vitro*. Thymocid® has potential as an antiaging property by maintaining its protein structure against glycation (135). In addition, Thymocid® can also protect the type I collagen structure from glycation-induced cross-linking; there is a possibility that its antiglycation effect may be because of the antioxidant effect of Thymocid® (136). Unfortunately, this study states that other phytochemical compounds besides TQ in Thymocid® are present, such as alipathic compounds, so there could be a bias that the effect is caused purely by the TQ compound, not the other compounds. In addition, further research on the effects

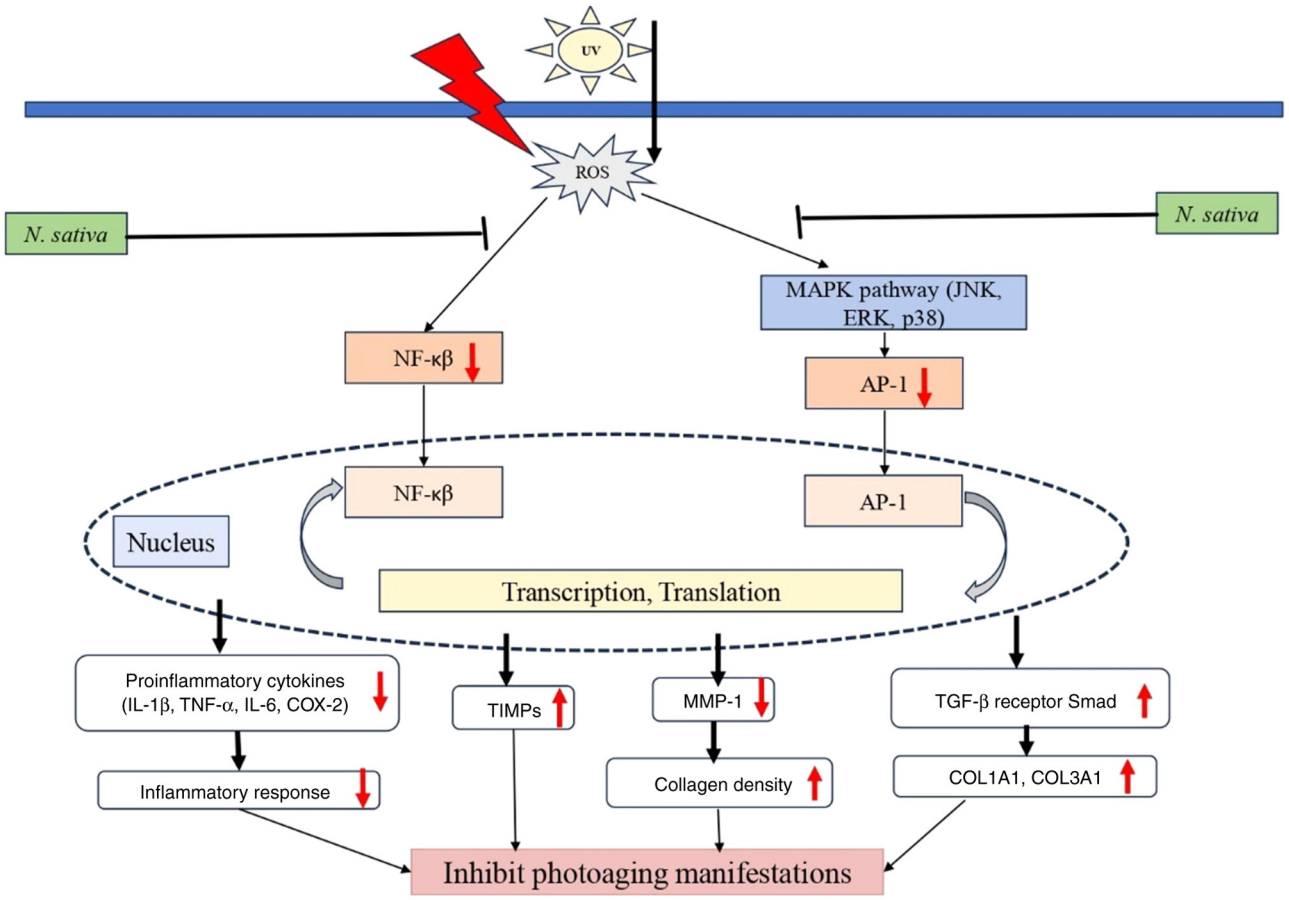

Figure 1. Possible mechanism of *N. sativa* and thymoquinone against photoaging. UV, ultraviolet; ROS, reactive oxygen species; NF-κB, nuclear factor-kappa B; MAPK, mitogen activated protein kinase; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; AP-1, activator protein-1; TIMP, tissue inhibitor of metallopreoteinase; MMP-1, matrix metalloproteinase-1; IL-1ß, interleukin 1ß; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; COX-2, cyclooxygenase-2; TGF-ß, tumor growth factor-ß.

of Thymocid® on elastase in human dermal fibroblast cells is needed to confirm its antiwrinkle effects.

Liang *et al* (10) then conducted research on TQ for its photoprotective action on human skin keratinocytes irradiated with UVA, finding that the use of pure TQ extract at doses of 6 and 12 μM could improve inflammation, oxidative stress, cytotoxicity and mitochondrial dysregulation caused by UVA radiation. From this research, it was concluded that TQ mechanism for skin damage caused by UVA radiation inhibits COX-2 expression by activating the NrF2/ARE pathway (10). The NrF2/ARE pathway is an important signaling pathway that reduces skin damage caused by UVB radiation (137). In addition, COX-2 is the main trigger of oxidative and inflammatory responses that are often detected in photoaging and other stress/inflammatory disorders (138). Nevertheless, this study suggested that high doses of TQ (>16 μM) may exhibit cytotoxicity to keratinocytes and the most effective protective concentration of TQ should be explored in further studies.

Pandey *et al* (131) investigated the methanol extract of *N. sativa* given orally at a dose of 200 mg/100 g bw/day in mice to determine its protective effect against radiation exposure. Oxidative stress caused by free radicals following ionizing radiation can damage normal cells; therefore, protecting normal tissue against radiation injury is important (139). This study showed that *N. sativa* can prevent radiation-induced increases in lipid peroxide levels in intestinal tissue homogenates. In addition, histological examination showed the prevention of villous loss, shortening of villous height and collagen deposition owing to radiation exposure (131). In this study, it was found that the use of *N. sativa* extract markedly increased the antioxidant properties of the irradiated rats compared with the control group. This study also stated that repeated oral administration of *N. sativa* extract for 14 days resulted in a survival rate of 100% up to 200 mg/100 g bw, so that this dose was considered the optimum dose. The antiaging effect of the oral administration of *N. sativa* extract was also supported by Khalaf and Mostafa (140), who administered *N. sativa* at a dose of 10 ml/kg bw/day to adult male rats exposed to cigarette smoke. Photoaging and tobacco smoke-induced aging are similar and include the adverse effects of oxidative stress (141). This study also found that *N. sativa* oil can prevent smoking-induced skin changes because of its antioxidant effects (140). In both studies, the antioxidant effect of *N. sativa* on organs other than the skin was due to free radicals originating from ionizing radiation and smoking. Furthermore, oral administration is not uniform, so further research is needed to assess the optimal dose of *N. sativa* extract.

Several studies have investigated the topical use of *N. sativa* extract and TQ as antiaging agents. Çanakci *et al* (132) used cold-pressed *N. sativa* oil extract at 100% concentration topically on the nasal mucosa of mice following exposure

Table II. Studies that support the potential role of *Nigella sativa* against photoaging.

First author, year	Subjects	Methods	Results	(Refs.)
Li *et al*, 2020	*In vitro*	Analysis of molecular process within glycation, collagen cross-linking, collagenase and elastase activities in murine melanoma B16F10 cells measured with collagenase activity assay kit.	Thymocid® (50, 100 and 300 μg/ml) interfered with the production of advanced glycation end-products, collagen cross-linking, collagenase activity, and elastase activities (type I and III)	(2)
Liang *et al*, 2021	*In vitro*	Analysis of oxidative stress and mitochondrial function on HaCaT cells irradiated by UVA using colorimetry, spectrophotometry, bioluminescence and dual-luciferase reporter assay. Cell viability was also evaluated using MTT and ELISA assay.	TQ pure extract (6 and 12 μM) not only significantly improved the UVA-induced cytotoxicity, oxidative stress and inflammation but also promoted mitochondrial dysregulation in HaCaT cells.	(10)
Pandey *et al*, 2015	*In vivo*, in rats	Radio-protective effect of oral *Nigella sativa* methanolic extract (200 mg/100 g bw/day) in albino rats 2 h before Total Body Irradiation at 4, 6, 10 Gy and continued until 7 consecutive days. They evaluated for histology and antioxidant parameters	Oral *Nigella sativa* methanolic extract (200 mg/100 g bw/day) significantly increased superoxide dismutase and catalase enzymes and inhibited lipid peroxidation activities.	(131)
Khalaf and Mostafa, 2014	*In vivo*, in rats	Twenty adult male rats were exposed to side and main stream smoke for 10 min twice daily for 4 weeks and treated orally with *Nigella sativa* oil 10 ml/Kgbw. Histological examination was performed.	Oral *Nigella sativa* extract 10 ml/kg bw/day had a protective role against tobacco smoking with collagen fiber content almost the same as the nonsmoking group (negative control).	(140)
Canakci *et al*, 2017	*In vivo*, in rats	Radio-protective effect of topical cold pressed *Nigella sativa* oil (0.05 ml at 100% concentration) given on days 1 to 3 to each nostril of female rats (n=18) after radiotherapy with a single dose of 40 Gy. Histopathological evaluation was measured.	Decrease of inflammatory cell infiltration, vascular dilatation, superficial erosion, and exudates in *Nigella sativa* group compared with the control.	(132)
Turhan *et al*, 2019	*In vivo*, in rats	Collagen density and wound closure were measured with histological morphometric analysis on skin defects in 20 albino rats. The wounds were treated with 2 ml cold-pressed *Nigella sativa* extracts twice daily for 15 days.	Higher collagen density was achieved in *Nigella sativa* group compared with the nano silver solution and control group. In addition, the combination of *Nigella sativa* and nano silver solution (1:1) had the highest collagen density among the groups.	(133)
Han *et al*, 2017	*In vivo*, in rats	A total of 42 female albino Wistar rats with skin defects were randomly treated with 50% *Nigella sativa* oil cream,	A significant decrease in the MDA, GSH and skin CAT levels and an increase in GPx and SOD levels were found	(142)

Table II. Continued.

First author, year	Subjects	Methods	Results	(Refs.)
		50% *Hypericum perforatum* oil cream, and placebo cream twice daily for 14 days. Histological and biochemical evaluations were performed.	in the *Nigella sativa* group when compared with the other two groups on the 14th day of treatment.	
Algahtani *et al*, 2021	*In vivo*, in rats	Collagen fiber was measured with histopathological analysis on 16 Wistar rats with skin defects treated with 0.5% TQ nanoemulsion-based hydrogel twice a day for 20 consecutive days.	Nanoemulsion-based hydrogel of TQ 0.5% (w/w) group had significantly more extensive and organized collagen fiber than the 1% silver sulfadiazine group.	(134)

HaCat, human adult low calcium temperature; UVA, ultraviolet A; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; ELISA, enzyme linked immunosorbent assay; TQ, thymoquinone; Gpx, glutathione peroxidase; SOD, superoxide dismutase; MDA, malondialdehyde; GSH, glutathione; CAT, catalase.

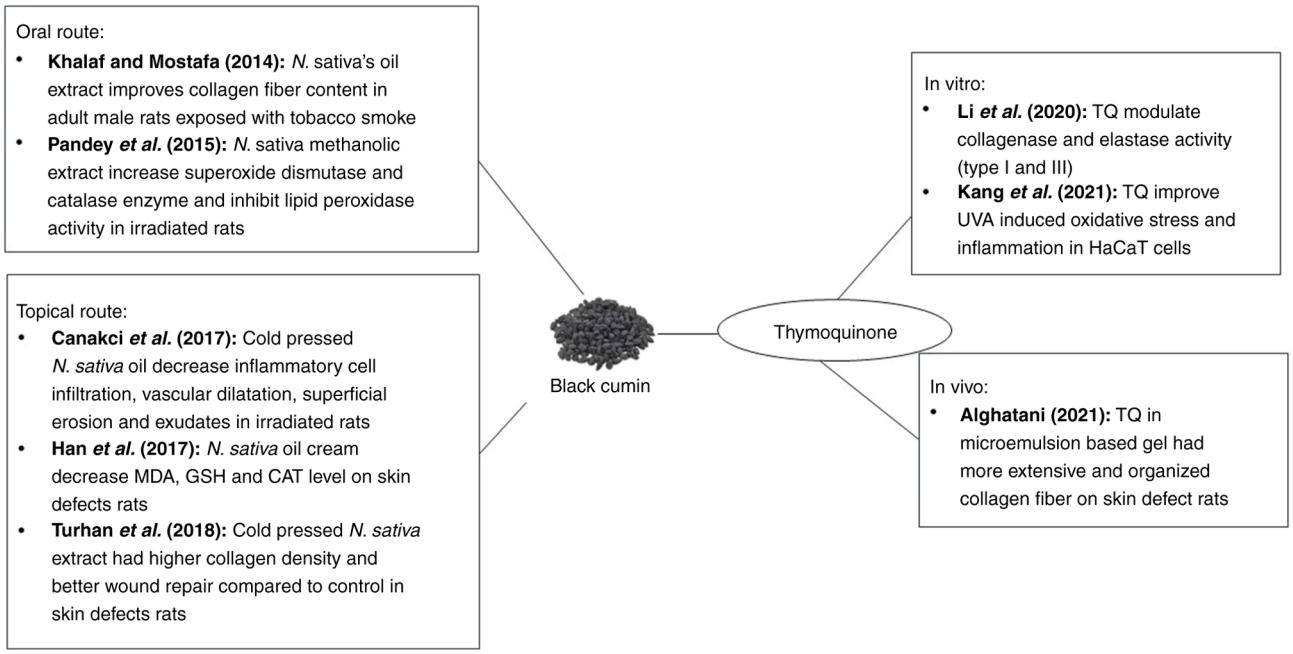

Figure 2. Summary of potential role of *N. sativa* against photoaging. MDA, malondialdehyde; GSH, glutathione; CAT, catalase; TQ, thymoquinone; UVA, ultraviolet A; HaCat, human adult cutaneous tumor cell line.

to radiotherapy radiation and found that its use could lower inflammatory cell infiltration, superficial erosion, vascular dilatation and exudates compared with the control. This study demonstrated the antioxidant and anti-inflammatory effects of *N. sativa* extract, even with topical use. In fact, in this study, histological images showed the protective role of *N. sativa* through its antioxidant, cytoprotective, anti-inflammatory and antineoplastic activities. Although this study did not review further the immunohistochemical and biochemical features, it is sufficient to confirm the role of *N. sativa* in preventing the detrimental effects of radiation.

Increased collagen density and accelerated wound repair in mice following topical application of *N. sativa* extract was studied by Turhan *et al* (133) who compared the use of *N. sativa* extract, nano-silver solution gold as the standard agent and a combination of the two agents applied twice daily for 15 days on 20 albino rats. The use of *N. sativa* extract alone resulted in improved collagen density and wound repair than that of the control group, although combined use had the best effect (133). In conclusion, *N. sativa* can play a synergistic role with other topical agents for wound healing. This research also suggests that *N. sativa* extract can be used as an agent that protects

against sunburn and wounds caused by exposure to sunlight. In addition, the small sample size is a limitation of this study.

This wound healing enhancer effect was also supported by Han *et al* (142) regarding the topical use of 50% *N. sativa* oil cream twice daily for 14 days on the skin of mice with skin defects. The use of *N. sativa* extract reduced oxidant parameters, such as malondialdehyde (MDA), glutathione (GSH) and skin catalase (CAT) and increased antioxidant-supporting enzyme parameters, such as glutathione peroxidase (GPx) and SOD levels, markedly compared with controls. It can be concluded that *N. sativa* extract exerts wound healing effects through its antioxidant properties. Topical application of *N. sativa* in the form of oil cream at a concentration of 50% enhances the healing of open wounds in a reliable manner.

Algahtani *et al* (134) proved the effect of nanoemulsion-based hydrogel of TQ 0.5% (w/w) on collagen fibers in mice with skin defects. Nanoemulsion-based hydrogel systems provide more efficient drug delivery to increase the biopharmaceutical attributes of drugs that are difficult to dissolve. TQ, which is difficult to dissolve in water, can be encapsulated into the lipophilic environment of nano-dimensional oil droplets and stabilized to be more optimal (143). In this study, it was found that the use of nanoemulsion-based hydrogel systems provided higher and more regular collagen density compared with the use of the standard gel form TQ and the gold standard therapy, 1% silver sulfadiazine. All research summaries supporting the potential of *N. sativa* in fighting photoaging are summarized in Table II.

Various studies, both *in vitro* and *in vivo*, have shown that the use of *N. sativa* extract and its active substance, TQ, has a potential role against photoaging because of their antioxidant and anti-inflammatory effects (10,135,139,141). The antioxidant effect was demonstrated by improvements in parameters such as MDA, CAT and GSH levels and increased levels of the SOD enzyme (135,141). In several studies, the anti-inflammatory effect improved inflammatory parameters and histopathological features in irradiated mice (2,10,139). These two effects are thought to modulate collagenase and elastase activity, which in turn improves collagen density and skin hydration, especially in skin exposed to sunlight (2,137,140,142). A summary of the protective effects of *N. sativa* against photoaging is presented in Fig. 2.

These studies have several limitations that require evaluation. First, the use of *N. sativa* extract has not been standardized in terms of ingredients, extraction methods, ingredient content, oral and topical preparation and concentration of active ingredients contained therein; second, research on the effects of *N. sativa* against UV rays and photoaging is limited; third, the outcome assessment criteria are not yet standardized; and fourth, a number of studies use relatively small sample sizes, animal studies and have a high potential for bias. Further studies are needed, especially using human samples with large sample sizes and randomized control trial methods, to clarify the role of *N. sativa* as a photoaging protective agent. Nevertheless, from all available sources, it can be summarized that *N. sativa* extract and its active components may have some potential to counteract the detrimental effects of UV radiation.

6. Conclusion

N. sativa seeds contain a number of active ingredients and play a potential role in photoaging therapy. The mechanism underlying the accumulation of free radicals caused by UV rays is unclear. Essential active ingredients, including TQ, flavonoids, saponins, fatty acids and minerals, can participate in this effect. Their mechanism possibly not only inhibits the MAPK signaling and NF-κB pathways but also decreases the expression of proinflammatory cytokines in the inflammatory state. Blocking this pathway will reduce MMP1 production and collagen degradation. Several studies have shown that *N. sativa* seed extract and TQ have potential as antiaging agents. However, further research is needed to demonstrate its protective ability against photoaging. The use of *N. sativa* extract is still limited because of its preventive effects on photoaging, so further research is needed, especially in clinical trials, to determine the optimal dose or its use as a combination therapy.

Acknowledgements

Not applicable.

Funding

The present study was supported by Maranatha Christian University, Bandung, Indonesia.

Availability of data and materials

Not applicable.

Authors' contributions

AE collected articles and wrote the first draft of manuscript, JWG initiated the study and revised the manuscript and TLW finalized the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Mohiuddin AK: Skin aging & modern age anti-aging strategies. Glob J Med Res 7: 15-60, 2019.
2. Li H, DaSilva NA, Liu W, Xu J, Dombi GW, Dain JA, Li D, Chamcheu JC, Seeram NP and Ma H: Thymocid®, a standardized black cumin (*Nigella sativa*) seed extract, modulates collagen cross-linking, collagenase and elastase activities, and melanogenesis in murine B16F10 melanoma cells. Nutrients 12: 2146, 2020.
3. Hwang E, Lee TH, Park SY, Yi TH and Kim SY: Enzyme-modified Panax ginseng inhibits UVB-induced skin aging through the regulation of procollagen type I and MMP-1 expression. Food Funct 5: 265-274, 2014.
4. Tu Y and Quan T: Oxidative stress and human skin connective tissue aging. Cosmetics 3: 28, 2016.

5. Ahmed OM and Mohammed MT: Oxidative stress: The role of reactive oxygen species (ROS) and antioxidants in human diseases. Plant Arch 20: 4089-4095, 2020.
6. Ardiana M, Pikir BS, Santoso A, Hermawan HO and Al-Farabi MJ: Effect of *Nigella sativa* supplementation on oxidative stress and antioxidant parameters: A meta-analysis of randomized controlled trials. ScientificWorldJournal 2020: 2390706, 2020.
7. Sudhir SP, Deshmukh VO and Verma HN: *Nigella sativa* seed, a novel beauty care ingredient: A review. Int J Pharm Sci Res 7: 3185-3196, 2016.
8. Adam GO and Shuaib YA: Antioxidant and anti-tyrosinase potentials of extracts of *Nigella sativa* and Senna alexandrina from sudan. J Appl Vet Sci 7: 41-45, 2022.
9. Shahroudi MJ, Mehri S and Hosseinzadeh H: Anti-aging effect of *Nigella sativa* fixed oil on D-galactose-induced aging in mice. J Pharmacopuncture 20: 29-35, 2017.
10. Liang J, Lian L, Wang X and Li L: Thymoquinone, extract from *Nigella sativa* seeds, protects human skin keratinocytes against UVA-irradiated oxidative stress, inflammation and mitochondrial dysfunction. Mol Immunol 135: 21-27, 2021.
11. Rizaoglu T: Effects of ozonated oils (sesame oil, *Nigella sativa* oil, and hypericium perforatum oil) on wound healing process in rats. Gov Polit Contemp Middle East Contin Chang, pp77-116, 2018.
12. Huang AH and Chien AL: Photoaging: A review of current literature. Curr Dermatol Rep 9: 22-29, 2020.
13. Krutmann J, Schikowski T, Morita A and Berneburg M: Environmentally-induced (extrinsic) skin aging: Exposomal factors and underlying mechanisms. J Invest Dermatol 141: 1096-1103, 2021.
14. Lee LY and Liu SX: Pathogenesis of photoaging in human dermal fibroblasts. Int J Dermatol Venereol 3: 37-42, 2022.
15. Venkatesh S, Maymone MBC and Vashi NA: Aging in skin of color. Clin Dermatol 37: 351-357, 2019.
16. Karim PL, Aryani IA and Nopriyati: Anatomy and histologic of intrinsic aging skin. Biosci Med J Biomed Transl Res 5: 1065-1077, 2021.
17. Tobin DJ: Introduction to skin aging. J Tissue Viability 26: 37-46, 2017.
18. Sachs DL, Varani J, Chubb H, Fligiel SEG, Cui Y, Calderone K, Helfrich Y, Fisher GJ and Voorhees JJ: Atrophic and hypertrophic photoaging: Clinical, histologic, and molecular features of 2 distinct phenotypes of photoaged skin. J Am Acad Dermatol 81: 480-488, 2019.
19. Tanveer MA, Rashid H and Tasduq SA: Molecular basis of skin photoaging and therapeutic interventions by plant-derived natural product ingredients: A comprehensive review. Heliyon 9: e13580, 2023.
20. Cao C, Xiao Z, Wu Y and Ge C: Diet and skin aging-from the perspective of food nutrition. Nutrients 12: 870, 2020.
21. Cho S: Pathogenesis and prevention of skin aging. J Korean Med Assoc 64: 438-446, 2021.
22. Mohania D, Chandel S, Kumar P, Verma V, Digvijay K, Tripathi D, Choudhury K, Mitten SK and Shah D: Ultraviolet radiations: Skin defense-damage mechanism. Adv Exp Med Biol 996: 71-87, 2017.
23. Roy C and Gies P: Ultraviolet light and short-term hazards to the skin and eyes. Wiley Online Libr 3: 47-66, 2017.
24. Chen X, Yang C and Jiang G: Research progress on skin photoaging and oxidative stress. Postepy Dermatol Alergol 38: 931-936, 2021.
25. Teng Y, Yu Y, Li S, Huang Y, Xu D, Tao X and Fan Y: Ultraviolet radiation and basal cell carcinoma: An environmental perspective. Front Public Health 9: 666528, 2021.
26. Furukawa JY, Martinez RM, Morocho-Jácome AL, Castillo-Gómez TS, Pereda-Contreras VJ, Rosado C, Velasco MVR and Baby AR: Skin impacts from exposure to ultraviolet, visible, infrared, and artificial lights-a review. J Cosmet Laser Ther 23: 1-7, 2021.
27. Pittayapruek P, Meephansan J, Prapapan O, Komine M and Ohtsuki M: Role of matrix metalloproteinases in photoaging and photocarcinogenesis. Int J Mol Sci 17: 868, 2016.
28. Bernard JJ, Gallo RL and Krutmann J: Photoimmunology: How ultraviolet radiation affects the immune system. Nat Rev Immunol 19: 688-701, 2019.
29. Chambers ES and Vukmanovic-Stejic M: Skin barrier immunity and ageing. Immunology 160: 116-125, 2020.
30. Hart PH, Norval M, Byrne SN and Rhodes LE: Exposure to ultraviolet radiation in the modulation of human diseases. Annu Rev Pathol 14: 55-81, 2019.
31. Gromkowska-Kępka KJ, Puścion-Jakubik A, Markiewicz-Żukowska R and Socha K: The impact of ultraviolet radiation on skin photoaging-review of in vitro studies. J Cosmet Dermatol 20: 3427-3431, 2021.
32. Mirończuk-Chodakowska I, Witkowska AM and Zujko ME: Endogenous non-enzymatic antioxidants in the human body. Adv Med Sci 63: 68-78, 2018.
33. Costantini D: Understanding diversity in oxidative status and oxidative stress: The opportunities and challenges ahead. J Exp Biol 222: jeb194688, 2019.
34. De Jager TL, Cockrell AE and Du Plessis SS: Ultraviolet light induced generation of reactive oxygen species. Adv Exp Med Biol 996: 15-23, 2017.
35. Cavinato M and Jansen-Dürr P: Molecular mechanisms of UVB-induced senescence of dermal fibroblasts and its relevance for photoaging of the human skin. Exp Gerontol 94: 78-82, 2017.
36. Rajendran P, Alzahrani AM, Hanieh HN, Kumar SA, Ben Ammar R, Rengarajan T and Alhoot MA: Autophagy and senescence: A new insight in selected human diseases. J Cell Physiol 234: 21485-21492, 2019.
37. Evas O: The role of reactive oxygen species and antioxidants in oxidative stress. Int J Res Pharm Biosci 56: 433-437, 2016.
38. Madkour LH: Function of reactive oxygen species (ROS) inside the living organisms and sources of oxidants. Pharm Sci Anal Res J 2: 180023, 2019.
39. Ighodaro OM and Akinloye OA: First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. Alexandria J Med 54: 287-293, 2018.
40. Galaris D, Barbouti A and Pantopoulos K: Iron homeostasis and oxidative stress: An intimate relationship. Biochim Biophys Acta Mol Cell Res 1866: 118535, 2019.
41. Gu Y, Han J, Jiang C and Zhang Y: Biomarkers, oxidative stress and autophagy in skin aging. Ageing Res Rev 59: 101036, 2020.
42. Davinelli S, Bertoglio JC, Polimeni A and Scapagnini G: Cytoprotective polyphenols against chronological skin aging and cutaneous photodamage. Curr Pharm Des 24: 99-105, 2018.
43. Cho BA, Yoo SK and Seo JS: Signatures of photo-aging and intrinsic aging in skin were revealed by transcriptome network analysis. Aging (Albany NY) 10: 1609-1626, 2018.
44. Shukla A and Mossman BT: Chapter 9 cell signaling by oxidants: Pathways leading to activation of mitogen-activated protein kinases (MAPK) and activator protein-1 (AP-1). Curr Top Membr 61: 191-209, 2008.
45. Singh D, Rai V and K Agrawal DK: Regulation of collagen I and collagen III in tissue injury and regeneration. Cardiol Cardiovasc Med 7: 5-16, 2023.
46. Taniguchi K and Karin M: NF-κB, inflammation, immunity and cancer: Coming of age. Nat Rev Immunol 18: 309-324, 2018.
47. Wang Y, Wang L, Wen X, Hao D, Zhang N, He G and Jiang X: NF-κB signaling in skin aging. Mech Ageing Dev 184: 111160, 2019.
48. Pourzand C, Albieri-Borges A and Raczek NN: Shedding a new light on skin aging, iron-and redox-homeostasis and emerging natural antioxidants. Antioxidants (Basel) 11: 471, 2022.
49. Gendrisch F, Esser PR, Schempp CM and Wölfle U: Luteolin as a modulator of skin aging and inflammation. Biofactors 47: 170-180, 2021.
50. Ke Y and Wang XJ: TGFβ signaling in photoaging and UV-induced skin cancer. J Invest Dermatol 141: 1104-1110, 2021.
51. Ansary TM, Hossain MR, Kamiya K, Komine M and Ohtsuki M: Inflammatory molecules associated with ultraviolet radiation-mediated skin aging. Int J Mol Sci 22: 3974, 2021.
52. Cui N, Hu M and Khalil RA: Biochemical and biological attributes of matrix metalloproteinases. 1st edition. Elsevier Inc., 2017.
53. Laronha H and Caldeira J: Structure and function of human matrix metalloproteinases. Cells 9: 1076, 2020.
54. Zorina A, Zorin V, Kudlay D and Kopnin P: Molecular mechanisms of changes in homeostasis of the dermal extracellular matrix: Both involutional and mediated by ultraviolet radiation. Int J Mol Sci 23: 6655, 2022.
55. Riihilä P, Nissinen L and Kähäri VM: Matrix metalloproteinases in keratinocyte carcinomas. Exp Dermatol 30: 50-61, 2021.
56. Shin JW, Kwon SH, Choi JY, Na JI, Huh CH, Choi HR and Park KC: Molecular mechanisms of dermal aging and antiaging approaches. Int J Mol Sci 20: 2126, 2019.
57. Yue J and López JM: Understanding MAPK signaling pathways in apoptosis. Int J Mol Sci 21: 2346, 2020.

58. Cole MA, Quan T, Voorhees JJ and Fisher GJ: Extracellular matrix regulation of fibroblast function: Redefining our perspective on skin aging. J Cell Commun Signal 12: 35-43, 2018.
59. Rogowski-Tylman M, Narbutt J, Woźniacka A and Lesiak A: Molecular aspects of skin aging. Literature review. Przegl Dermatol 103: 139-142, 2016.
60. Kanigur Sultuybek G, Soydas T and Yenmis G: NF-κB as the mediator of metformin's effect on ageing and ageing-related diseases. Clin Exp Pharmacol Physiol 46: 413-422, 2019.
61. Cheng W, Yan-Hua R, Fang-Gang N and Guo-An Z: The content and ratio of type I and III collagen in skin differ with age and injury. Afr J Biotechnol 10: 2524-2529, 2011.
62. Hwang SJ, Kim SH, Seo WY, Jeong Y, Shin MC, Ryu D, Lee SB, Choi YJ and Kim KJ: Effects of human collagen α-1 type I-derived proteins on collagen synthesis and elastin production in human dermal fibroblasts. BMB Rep 54: 329-334, 2021.
63. Naomi R, Ridzuan PM and Bahari H: Current insights into collagen type I. Polymers (Basel) 13: 2642, 2021.
64. Fligiel SEG, Varani J, Datta SC, Kang S, Fisher GJ and Voorhees JJ: Collagen degradation in aged/photodamaged skin in vivo and after exposure to matrix metalloproteinase-1 in vitro. J Invest Dermatol 120: 842-848, 2003.
65. Yilmaz ÖÖ, Polat T, Tacal Aslan B and Ulucan K: Can skin aging be reversible by anti-aging treatments with genetic analysis? İstanbul Gelişim Üniversitesi Sağlık Bilim Derg 21: 1242-1250, 2023.
66. Devos H, Zoidakis J, Roubelakis MG, Latosinska A and Vlahou A: Reviewing the regulators of COL1A1. Int J Mol Sci 24: 10004, 2023.
67. Yamaba H, Haba M, Kunita M, Sakaida T, Tanaka H, Yashiro Y and Nakata S: Morphological change of skin fibroblasts induced by UV Irradiation is involved in photoaging. Exp Dermatol 25 (Suppl 3): S45-S51, 2016.
68. Balasubramanian P, Prabhakaran MP, Sireesha M and Ramakrishna S: Collagen in human tissues: Structure, function, and biomedical implications from a tissue engineering perspective. Adv Polym Sci 251: 173, 2013.
69. Derby B and Akhtar R: Mechanical properties of aging soft tissues. Eng Mater Process 10: 237-263, 2015.
70. Biskanaki F, Kefala V, Lazaris AC and Rallis E: Aging and the impact of solar ultraviolet radiation on the expression of type I and type VI collagen. Cosmetics 10: 48, 2023.
71. Liu H, Dong J, Du R, Gao Y and Zhao P: Collagen study advances for photoaging skin. Photodermatol Photoimmunol Photomed 40: e12931, 2024.
72. Watson RE, Gibbs NK, Griffiths CE and Sherratt MJ: Damage to skin extracellular matrix induced by UV exposure. Antioxid Redox Signal 21: 1063-1077, 2014.
73. Svobodova A, Walterova D and Vostalova J: Ultraviolet light induced alteration to the skin. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 150: 25-38, 2006.
74. Kamata H, Honda SI, Maeda S, Chang L, Hirata H and Karin M: Reactive oxygen species promote TNFalpha-induced death and sustained JNK activation by inhibiting MAP kinase phosphatases. Cell 120: 649-661, 2005.
75. Calvo MJ, Navarro C, Durán P, Galan-Freyle NJ, Parra Hernández LA, Pacheco-Londoño LC, Castelanich D, Bermúdez V and Chacin M: Antioxidants in photoaging: From molecular insights to clinical applications. Int J Mol Sci 25: 2403, 2024.
76. Liu Z, Li Y, Song H, He J, Li G, Zheng Y and Li B: Collagen peptides promote photoaging skin cell repair by activating the TGF-β/Smad pathway and depressing collagen degradation. Food Funct 10: 6121-6134, 2019.
77. Ahmad MF, Ahmad FA, Ashraf SA, Saad HH, Wahab S, Khan MI, Ali M, Mohan S, Hakeem KR and Athar MT: An updated knowledge of black seed (*Nigella sativa* Linn.): Review of phytochemical constituents and pharmacological properties. Elsevier GmbH, 2021.
78. Ahmad M, Khan A, Marwat K, Zafar M, Khan MA, Hassan U and Sultana S: Useful medicinal flora enlisted in holy quran and ahadith. Am J Agric Environ Sci 5: 126-140, 2009.
79. Hannan MA, Rahman MA, Sohag AAM, Uddin MJ, Dash R, Sikder MH, Rahman MS, Timalsina B, Munni YA, Sarker PP, *et al*: Black cumin (*Nigella sativa* L.): A comprehensive review on phytochemistry, health benefits, molecular pharmacology, and safety. Nutrients 13: 1784, 2021.
80. Dalli M, Bekkouch O, Azizi SE, Azghar A, Gseyra N and Kim B: *Nigella sativa* l. phytochemistry and pharmacological activities: A review (2019-2021). Biomolecules 12: 20, 2022.
81. Eisenman SW, Zaurov DE and Struwe L: Medicinal plants of central asia: Uzbekistan and kyrgyzstan. Springer New York, pp1-340, 2013.
82. Ramadan MF: Black cumin (*Nigella sativa*) oils. Elsevier Inc., 2015.
83. Yimer E, Tuem KB, Karim A, Rehan N, Mariod AA, Saeed Mirghani ME and Hussein I: *Nigella sativa* L. (black cumin): A promising natural remedy for wide range of illnesses. Hindawi Publ Corp 2019: 73-80, 2017.
84. Javed S, Shahid AA, Haider MS, Umeera A, Ahmad R and Mushtaq S: Nutritional, phytochemical potential and pharmacological evaluation of *Nigella sativa* (kalonji) and trachyspermum ammi (Ajwain). J Med Plants Res 6: 768-775, 2012.
85. Majeed A, Muhammad Z, Ahmad H, Rehmanullah, Hayat SSS, Inayat N and Siyyar S: *Nigella sativa* L.: Uses in traditional and contemporary medicines-an overview. Acta Ecol Sin 41: 253-258, 2021.
86. Hossain MS, Sharfaraz A, Dutta A, Ahsan A, Masud MA, Ahmed IA, Goh BH, Urbi Z, Sarker MMR and Ming LC: A review of ethnobotany, phytochemistry, antimicrobial pharmacology and toxicology of *Nigella sativa* L. Biomed Pharmacother 143: 112182, 2021.
87. Fatima Shad K, Soubra W and Cordato DJ: The role of thymoquinone, a major constituent of *Nigella sativa*, in the treatment of inflammatory and infectious diseases. Clin Exp Pharmacol Physiol 48: 1445-1453, 2021.
88. Rajabian A and Hosseinzadeh H: Dermatological effects of *Nigella sativa* and its constituent, thymoquinone: A review. Elsevier Inc., 2020.
89. Benazzouz-Smail L, Achat S, Brahmi F, Bachir-Bey M, Arab R, Lorenzo JM, Benbouriche A, Boudiab K, Hauchard D, Boulekbache L and Madani K: Biological properties, phenolic profile, and botanical aspect of *Nigella sativa* L. and Nigella damascena L. seeds: A comparative study. Molecules 28: 571, 2023.
90. Hwang JR, Cartron AM and Khachemoune A: A review of *Nigella sativa* plant-based therapy in dermatology. Int J Dermatol 60: e493-e499, 2021.
91. Eid AM, Elmarzugi NA, Abu Ayyash LM, Sawafta MN and Daana HI: A review on the cosmeceutical and external applications of *Nigella sativa*. J Trop Med 2017: 7092514, 2017.
92. Santoso ARB, Huwae TECJ, Kristianto Y and Putera MA: Effect of thymoquinone: the extract of *Nigella sativa* in accelerating soft callus formation in fracture. Int J Res Med Sci 7: 4068-4072, 2019.
93. Nyemb JN, Shaheen H, Wasef L, Nyamota R, Segueni N and El-Saber Batiha G: Black Cumin: A review of its pharmacological effects and its main active constituent. Pharmacogn Rev 16: 107-125, 2022.
94. Ali BH and Blunden G: Pharmacological and toxicological properties of *Nigella sativa*. Phyther Res 14: 299-305, 2003.
95. Mashayekhi-Sardoo H, Rezaee R and Karimi G: An overview of in vivo toxicological profile of thymoquinone. Toxin Rev 39: 115-122, 2020.
96. Thakur S, Kaurav H and Chaudhary G: *Nigella sativa* (kalonji): A black seed of miracle. Int J Res Rev 8: 342-357, 2021.
97. Rahim MA, Shoukat A, Khalid W, Ejaz A, Itrat N, Majeed I, Koraqi H, Imran M, Nisa MU, Nazir A, *et al*: A narrative review on various oil extraction methods, encapsulation processes, fatty acid profiles, oxidative stability, and medicinal properties of black seed (*Nigella sativa*). Foods 11: 2826, 2022.
98. Nasiri N, Ilaghi Nezhad M, Sharififar F, Khazaneha M, Najafzadeh MJ and Mohamadi N: The therapeutic effects of *Nigella sativa* on skin disease: A systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med 2022: 7993579, 2022.
99. Kalus U, Pruss A, Bystron J, Jurecka M, Smekalova A, Lichius JJ and Kiesewetter H: Effect of *Nigella sativa* (black seed) on subjective feeling in patients with allergic diseases. Phyther Res 17: 1209-1214, 2003.
100. Srinivasan K: Cumin (cuminum cyminum) and black cumin (*Nigella sativa*) seeds: Traditional uses, chemical constituents, and nutraceutical effects. Food Qual Saf 2: 1-16, 2018.
101. Darakhshan S, Bidmeshki Pour A, Hosseinzadeh Colagar A and Sisakhtnezhad S: Thymoquinone and its therapeutic potentials. Pharmacol Res 95-96: 138-158, 2015.
102. Modarresi Chahardehi A, Ojaghi HR, Motedayyen H and Arefnezhad R: Nano-based formulations of thymoquinone are new approaches for psoriasis treatment: A literature review. Front Immunol 15: 1416842, 2024.

103. Chen WP, Tang JL, Bao JP and Wu LD: Thymoquinone inhibits matrix metalloproteinase expression in rabbit chondrocytes and cartilage in experimental osteoarthritis. Exp Biol Med (Maywood) 235: 1425-1431, 2010.
104. Rasheeda K, Samyuktha D and Fathima NN: Self-association of type I collagen directed by thymoquinone through alteration of molecular forces. Int J Biol Macromol 140: 614-620, 2019.
105. Ghorbanibirgani A, Khalili A and Rokhafrooz D: Comparing *Nigella sativa* oil and fish oil in treatment of vitiligo. Iran Red Crescent Med J 16: e4515, 2014.
106. Yousefi M, Barikbin B, Kamalinejad M, Abolhasani E, Ebadi A, Younespour S, Manouchehrian M and Hejazi S: Comparison of therapeutic effect of topical Nigella with Betamethasone and Eucerin in hand eczema. J Eur Acad Dermatol Venereol 27: 1498-1504, 2013.
107. Michalak M: Plant-derived antioxidants: Significance in skin health and the ageing process. Int J Mol Sci 23: 585, 2022.
108. Rivera-Yañez CR, Ruiz-Hurtado PA, Mendoza-Ramos MI, Reyes-Reali J, García-Romo GS, Pozo-Molina G, Reséndiz-Albor AA, Nieto-Yañez O, René Méndez-Cruz A, Méndez-Catalá CF and Rivera-Yañez N: Flavonoids present in propolis in the battle against photoaging and psoriasis. Antioxidants (Basel) 10: 2014, 2021.
109. Singh Joshan D and Singh SK: Investigational study of juglans regia extract and quercetin against photoaging. Biomed Aging Pathol 3: 193-200, 2013.
110. Sim GS, Lee BC, Cho HS, Lee JW, Kim JH, Lee DH, Kim JH, Pyo HB, Moon DC, Oh KW, *et al*: Structure activity relationship of antioxidative property of flavonoids and inhibitory effect on matrix metalloproteinase activity in UVA-irradiated human dermal fibroblast. Arch Pharm Res 30: 290-298, 2007.
111. He X, Wan F, Su W and Xie W: Research progress on skin aging and active ingredients. Molecules 28: 5556, 2023.
112. Hatahet T, Morille M, Hommoss A, Devoisselle JM, Müller RH and Bégu S: Quercetin topical application, from conventional dosage forms to nanodosage forms. Eur J Pharm Biopharm 108: 41-53, 2016.
113. Choi HJ, Alam MB, Baek ME, Kwon YG, Lim JY and Lee SH: Protection against UVB-induced photoaging by Nypa fruticans via inhibition of MAPK/AP-1/MMP-1 signaling. Oxid Med Cell Longev 2020: 2905362, 2020.
114. Maghsoudloo M, Aliakbari RBS and Velisdeh ZJ: Pharmaceutical, nutritional, and cosmetic potentials of saponins and their derivatives. Nano Micro Biosyst 2: 1-6, 2023.
115. Cavinato M, Waltenberger B, Baraldo G, Grade CVC, Stuppner H and Jansen-Dürr P: Plant extracts and natural compounds used against UVB-induced photoaging. Biogerontology 18: 499-516, 2017.
116. Keskin Çavdar H: Active compounds, health effects, and extraction of unconventional plant seed oils. In: Plant and Human Health. Ozturk M and Hakeem K (eds). Vol 2. Springer, Cham, pp245-285, 2019.
117. Sarkhail P, Esmaily H, Baghaei A, Shafiee A, Abdollahi M, Khademi Y, Madandar M and Sarkheil P: Burn healing potential of *Nigella sativa* seed oil in rats. Int J Pharm Sci Res 2: 34-40, 2011.
118. Pavlou P, Siamidi A, Varvaresou A and Vlachou M: Skin care formulations and lipid carriers as skin moisturizing agents. Cosmetics 8: 89, 2021.
119. Choi HJ, Song BR, Kim JE, Bae SJ, Choi YJ, Lee SJ, Gong JE, Lee HS, Lee CY, Kim BH and Hwang DY: Therapeutic effects of cold-pressed perilla oil mainly consisting of linolenic acid, oleic acid and linoleic acid on UV-induced photoaging in NHDF cells and SKH-1 hairless mice. Molecules 25: 989, 2020.
120. Borkow G: Using copper to improve the well-being of the skin. Curr Chem Biol 8: 89-102, 2014.
121. Prasad AS: Zinc is an antioxidant and anti-inflammatory agent: Its role in human health. Front Nutr 1: 14, 2014.
122. Polefka TG, Bianchini RJ and Shapiro S: Interaction of mineral salts with the skin: A literature survey. Int J Cosmet Sci 34: 416-423, 2012.
123. Azab AE, Adwas A, Elsayed ASI, Adwas AA, Elsayed ASI, Azab AE and Quwaydir FA: Oxidative stress and antioxidant mechanisms in human body. J Appl Biotechnol Bioeng 6: 43-47, 2019.
124. Kaymak E, Ceylan T, Akın T, Kuloğlu N, Sayan M, Değer N, Önal E, Yildirim AB and Karabulut D: Effect of thymoquinone on NRF2/NF-kB/MAPK pathway in methotrexate-induced rat testis injury. Iran J Basic Med Sci 27: 1410-1416, 2024.
125. Nguyen CH, Senfter D, Basilio J, Holzner S, Stadler S, Krieger S, Huttary N, Milovanovic D, Viola K, Simonitsch-Klupp I, *et al*: NF-κB contributes to MMP1 expression in breast cancer spheroids causing paracrine PAR1 activation and disintegrations in the lymph endothelial barrier in vitro. Oncotarget 6: 39262-39275, 2015.
126. Pardo A and Selman M: MMP-1: The elder of the family. Int J Biochem Cell Biol 37: 283-288, 2005.
127. Stratigos AJ and Katsambas AD: The role of topical retinoids in the treatment of photoaging. Drugs 65: 1061-1072, 2005.
128. Farris PK: Topical vitamin C: A useful agent for treating photoaging and other dermatologic conditions. Dermatol Surg 31: 814-818, 2005.
129. Correia G and Magina S: Efficacy of topical vitamin C in melasma and photoaging: A systematic review. J Cosmet Dermatol 22: 1938-1945, 2023.
130. Thielitz A and Gollnick H: Topical retinoids in acne vulgaris: Update on efficacy and safety. Am J Clin Dermatol 9: 369-381, 2008.
131. Pandey N, Kumar M, Pradhan S, Mandal A and Tripathi YB: Effect of methanolic fraction of the seeds of *Nigella sativa* linn on radiation induced Gi damage in rats. Sciforschen 10: 1-5, 2015.
132. Çanakci H, Yilmaz AAŞ, Canpolat MS, Şeneldir H, Kir G, Eriş AH, Mayadagli A and Oysu Ç: Evaluation of the effect of topical application of *Nigella sativa* on acute radiation-induced nasal mucositis. J Craniofac Surg 29: e279-e282, 2018.
133. Turhan Y, Arican M, Karaduman ZO, Turhal O, Gamsizkan M, Aydin D and Ozkan K: Comparison of the effects of *Nigella sativa* oil and nano-silver on wound healing in an experimental rat model. Iran Red Cresent Med J 21: e84650, 2019.
134. Algahtani MS, Ahmad MZ, Shaikh IA, Abdel-Wahab BA, Nourein IH and Ahmad J: Thymoquinone loaded topical nanoemulgel for wound healing: Formulation design and in-vivo evaluation. Molecules 26: 3863, 2021.
135. Khatoon M, Kushwaha P, Usmani S and Madan K: Dermaceutical utilization of *Nigella sativa* seeds: Applications and opportunities. Drug Res (Stuttg) 74: 5-17, 2024.
136. Balyan P, Khan J and Ali A: Therapeutic potential of *Nigella sativa* in the prevention of aggregation and glycation of proteins. In: Black Seeds (*Nigella sativa*). Khan A and Rehman M (eds). Elsevier, pp313-336, 2022.
137. Sun Z, Park SY, Hwang E, Zhang M, Seo SA, Lin P and Yi TH: Thymus vulgaris alleviates UVB irradiation induced skin damage via inhibition of MAPK/AP-1 and activation of Nrf2-ARE antioxidant system. J Cell Mol Med 21: 336-348, 2017.
138. Yadav DK, Kumar S, Saloni, Misra S, Yadav L, Teli M, Sharma P, Chaudhary S, Kumar N, Choi EH, *et al*: Molecular insights into the interaction of RONS and thieno[3,2-C]pyran analogs with SIRT6/COX-2: A molecular dynamics study. Sci Rep 8: 4777, 2018.
139. Shabeeb D, Musa AE, Ali HSA and Najafi M: Curcumin protects against radiotherapy-induced oxidative injury to the skin. Drug Des Devel Ther 14: 3159-3163, 2020.
140. Khalaf G and Mostafa HKK: Histological and immunohistochemical study on the effect of passive smoking on the skin of adult male albino rats and the possible protective role of *Nigella sativa* oil. Egypt J Histol 35: 87-94, 2012.
141. Lee H, Hong Y and Kim M: Structural and functional changes and possible molecular mechanisms in aged skin. Int J Mol Sci 22: 12489, 2021.
142. Han MC, Durmuş AS, Sağliyan A, Günay C, Özkaraca M, Kandemir FM, Çomakli S and Firat Öztopalan D: Effects of *Nigella sativa* and hypericum perforatum on wound healing. Turkish J Vet Anim Sci 41: 99-105, 2017.
143. Khatoon K, Ali A, Ahmad FJ, Hafeez Z, Rizvi MMA, Akhter S and Beg S: Novel nanoemulsion gel containing triple natural bio-actives combination of curcumin, thymoquinone, and resveratrol improves psoriasis therapy: In vitro and in vivo studies. Drug Deliv Transl Res 11: 1245-1260, 2021.