J Herbmed Pharmacol. 2024; 13(1): 28-42.

http://www.herbmedpharmacol.com doi: 10.34172/jhp.2024.48163

Journal of Herbmed Pharmacology

Dermatological effects of *Pistacia* species: A systematic review

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ARTICLE INFO

Article Type:
Review

Article History:
Received: 26 July 2023
Accepted: 1 October 2023

Keywords:
Herbal medicine
Natural products
Pistacia
Skin disorders
Traditional Persian medicine
Wound

ABSTRACT

Different parts of *Pistacia* species are traditionally used to treat various skin problems. Traditional experiences can be a good basis for research on the therapeutic effects of medicinal plants. The active compounds of plants can be identified and used in different disorders in an innovative way. There are several studies that have evaluated the *Pistacia* species for dermatological disorders. However, despite the valuable effects of the *Pistacia* species on skin disease, there is no comprehensive review of the dermal effects of these plants. So, in this study, current evidence regarding the dermatological effect of the *Pistacia* species has been reviewed. Electronic databases including PubMed, Scopus, and Google Scholar were searched for in vivo, in vitro, and clinical studies that examined dermatological effects of *Pistacia* species. According to the review, most of the evidence of dermatological effects in the *Pistacia* genus comes from preliminary studies on wound healing, cutaneous leishmaniasis, inflammation caused by UV rays and photo-protection, hyperpigmentation disorders, and atopic dermatitis. The *Pistacia* genus was implicated in 3 clinical studies and 30 in vivo/in vitro studies showing several mechanisms that go beyond its dermatological effects. The traditional medicinal effects of these herbs are supported by some scientific evidence. The potential protective/therapeutic effects of these herbs need to be studied further so that they can be considered as possible future candidates for use in skin care products.

Implication for health policy/practice/research/medical education:
This review demonstrated that the *Pistacia* genus had potential applications in different dermatological conditions like wounds, hyperpigmentation, leishmaniasis, and dermatitis. These data might be used for further research and preparation of new drugs.
Please cite this paper as: Bozorgi M, Iranzadasl M, Memariani Z. Dermatological effects of *Pistacia* species: A systematic review. J Herbmed Pharmacol. 2024;13(1):28-42. doi: 10.34172/jhp.2024.48163.

Introduction

Skin medicines and cosmetics can benefit from herbal medicines. Several herbal medicinal and cosmetic products have been developed in recent years for preventing and treating different skin problems (1,2). It has been shown that complementary and alternative medicine, including traditional medicines, can reduce healthcare costs and prevent the unnecessary use of drugs (3). Many studies are being conducted on plants that are traditionally used as skin care agents (4-6). *Pistacia* species are among the oldest plants that have been used for these conditions.

These species are resin-bearing shrubs and trees that belong to the Anacardiaceae family. According to economic and food industry factors, pistachio (*Pistacia vera* L.) is the most important plant in this genus. Mastic (*Pistacia lentiscus* L.) is another commercially important species used as a food additive. *P. terebinthus* L., *P. atlantica* Desf., and *P. integerrima* J. L. Stewart ex Brandis are other main species of the *Pistacia* family distributed from the Mediterranean basin to central Asia. The resin, leaves, seeds, and fruits of *Pistacia* species have been used for a variety of therapeutic purposes throughout the world for centuries (7). In particular, there is evidence from different systems of traditional and complementary medicine for using the oleo-resin of *P. lentiscus* and *P. atlantica* to prevent and treat skin diseases (8). A number

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of pharmacological effects of *Pistacia* species have been documented, including neurologic, gastrointestinal, anticancer, antidiabetic, antihyperlipidemic, anti-inflammation, antinociceptive, antioxidant, antimicrobial, and antiviral effects (9,10). Numerous phytochemicals have been detected in *Pistacia* species. Monoterpenes like α-pinene, limonene, α-terpinolene, and ocimene are the main constituents of essential oil (EO) of these plants. In addition, masticadienonic acid, masticadienolic acid, and morolic acid have been reported in resin of *Pistacia* species. Seeds of *Pistacia* species contain fatty acids and sterols like linolenic, palmitic, palmitoleic, stearic, and myristic acids (7,11). In various studies, these active ingredients have been shown to be effective in treating skin diseases (12)

A considerable number of studies have studied *Pistacia* species for dermatological conditions such as wound healing, cutaneous leishmaniasis, UV-induced inflammation, and atopic dermatitis (AD) (13-16). This makes the *Pistacia* species a valuable potential source for developing new drugs for the treatment of various skin diseases. In spite of this, there is a lack of comprehensive review about their dermal effects. In this study, we reviewed in vivo and in vitro studies on the dermatological effects of *Pistacia* species as a possible source of innovative dermatological products.

Search strategy

Electronic databases, including PubMed, and Scopus, were searched using the following search formula in the title/abstract/keywords: (pistacia OR pistachio OR mastic) AND (derm OR skin OR topical OR wound OR burn OR melanoma OR melasma OR leishmaniasis OR hyperpigmentation OR cosmetic OR urticaria OR eczema OR acne OR vitiligo OR psoriasis OR scar). For additional articles, Google Scholar was searched based on the title with pistachio or pistachio OR Pistacia OR mastic keywords with the name of each disease or disorder separately.

Articles were collected from inception to December 2022. Only papers with English full-texts were included in this review. All types of in vitro, in vivo, and clinical studies related to topical application or systemic administration of *Pistacia* species for the management of a skin disorder were considered. Congress abstracts with no full texts and research papers in non-English languages were excluded from our review (Figure 1). The final included articles were screened to extract the type of disease, part of Pistacia species, animal model for *in vivo* and type of cell line for in vitro studies, route of preparation of extract or topical formulation, concentration/dosage, duration of treatment and outcomes. The main outcomes of this review, represented as follow and effects of *Pistacia* species in different dermatological problems, are shown in Table 1. The risk of bias of each preclinical study was checked by two reviewers. The Systematic Review Center for Laboratory animal Experimentation (SYRCLE) was used for analyzing the methodological quality (Table 2) (17).

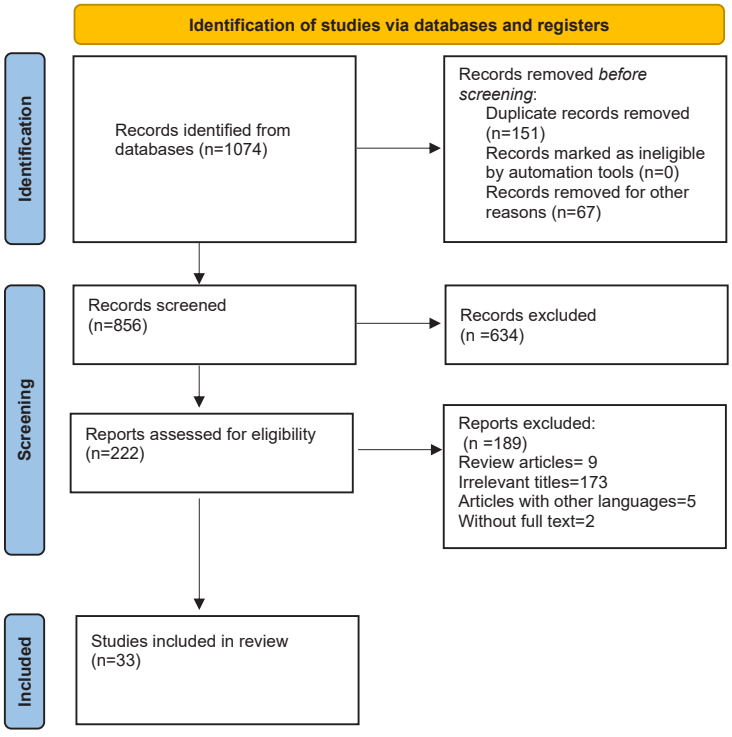

Figure 1. Flowchart of the selection process.

Table 1. Effect of *Pistacia* species on different dermatological problems (in vitro and in vivo studies)

Pistacia species	Plant part	Type of preparation	Type of skin problem	Type of study	Duration of study	Positive control	Result	Suggested responsible constituents	Ref.
Wounds									
P. vera	Nut	5% and 10% ointment (adding oil to ointment base)	Second-degree burn wound	Animal model in rats	22 days	Dexpanthenol	After 12 days: Significant burn wound repair in ointment (10%) group. After 22 days: No scar in ointment (10%) group. Denser collagen deposition in the reticular layer and repaired epithelium in ointment group.	-	(18)
	Oleoresin	Ointment 5% (adding EO to petroleum jelly)	Wound	Animal model in rabbits	16 days	Cicatryl-Bio	Strong wound healing effect	α-Pinene	(19)
	Oleoresin	Ointment 5% w/w (adding oleoresins to Vaseline	Wound	Animal model in rabbits	16 days	Cicatryl	Remarkable wound contraction from day 8 to day 16	α-Pinene, β-pinene, *trans*-pinocarveol	(20)
	Hull	Methanol 80% extract	Wound	Scratch assay on NIH/3T3 murine fibroblast cells	-	-	3-Epimasticadienolic acid determined as effective substance and at dose of 200 (µg/mL) significantly enhanced the fibroblast proliferation and migration and caused 45% reduction of the scratch area.	-	(21)
P. atlantica	Resin oil	Ointment (5, 10, and 20%)	Burn wound	Animal model in rats	14 days		↑Concentration of the platelet-derived growth factor, the bFGF and angiogenesis	α-Pinene, β -pinene, trans-verbenol, sabinene and trans-pinocarveol	(22)
	Resin oil	Oil with concentration of 300 µL/kg/d	Burn wound	Animal model in rats	14 days	Sulfadiazine	↓wound size, ↑VEGF and hydroxyproline, ↓ MDA	α-Pinene	(23)
	Fruit oil	Oil (5% and 10%) was added to gel base	Cutaneous wound	Animal model in rats	21 days		↑Antioxidant parameters (SOD, CAT, plasma glutathione peroxidase), ↓Plasma MDA	α -Tocopherol	(24)
	Fruit oil	Oil (5% and 10%) was added to gel base	Cutaneous wound	Animal model in rats	21 days		↑Tensile strength, ultimate stress, yield strength and stiffness. More organized pattern of collagen fibers and better tissue alignment	Tocopherols and tocotrienols	(25)
	Gum	Oral suspensions from hydroethanolic extract (30 and 60%) and topical creams from adding oil to Eucerin (30 and 60%)	Wound	Animal model in rabbits	21 days		The best wound healing effect was achieved with 60% cream treatment	Flavonoids, triterpenes and other phenolic compounds	(26)
	Hull	Ointment (1/5, 3 and 5%) hydroethanolic extract was added to Eucerin and Vaseline	Wound	Animal model in rats	21 days		↑Wound contraction ratio, ↑ Fibroblast distribution, ↓ Immune cells infiltration, ↑Mast cells up-regulation and neovascularization, ↓ Inflammation phase by stimulating the fibroblast proliferation	Phenols and flavonoids	(27)
	Hull	Ointment (2%) hydroethanolic extract was added to Eucerin and Vaseline with combination of flaxseed (2%)	Wound	Animal model in rabbits	21 days	Nitrofurazone ointment (0.2%, w/w)	↑Wound healing, ↓ Inflammation phase, ↑Cellularity, ↑Collagen synthesis High amount of α-pinene may be responsible for *P. atlantica* wound healing effect	α-Pinene	(28)
	Fruit	Fruit oil (20%) in combination with *Sesamum indicum* oil (60%), Cannabis sativa (12%) oil and *Juglans regia* oil (8%)	Burn wound	Animal model in mice	21 days	Silver sulfadiazine	↑Wound contraction, ↓Epithelialization time -Significant granulation tissue formation, scattered inflammatory cells infiltration, and collagenization in the dermis and skin appendages.	Oleic acid, linoleic acid, phenolic compounds and pheophytin	(29)

Table 1. Continued

Pistacia species	Plant part	Type of preparation	Type of skin problem	Type of study	Duration of study	Positive control	Result	Suggested responsible constituents	Ref.
P. khinjuk	Unripe fruit	Fruit methanolic extract ointment (4% and 8%)	Wound	Animal model in rats	20 days	Zinc oxide	-After the sixth day of treatment: faster epithelization in *P. khinjuk* group compared with zinc oxide. - No significant therapeutic difference with the control group	Phenolic compounds	(30)
*P. lentiscus*8	Fruits	Virgin fatty oil	Burn wounds	Animal model in rabbits	28 days	Madecassol®	↑Wound contraction and reduce epithelialization time	Unsaturated fatty acids, like oleic acid and linoleic acid	(31)
	Fruits	Fatty oil, saponifiable, unsaponifiable oily fractions was added to paraffin oil (10%, v/v)	Cutaneous wound	Animal model in rats	26 days	Madecassol®	↑Wound contraction compared with untreated group	-	(32)
	Fruits	Fruit oil (0.56 µL/mm^2), vehicle was Saline solution	CO2 laser fractional burn	Animal model in rats	8 days	CYTOL BASIC®	-Improvement of wound contraction and closure with more collagen turnover -Shorter epithelialization time than other groups	Linoleic acid, β-sitosterol	(33)
	Fruits	Ointment 30% (v/v) prepared by adding fruit oil to soft white Vaseline	Wound	Animal model in guinea pigs	21 days	Cicaderma®	↑Wound contraction effect,↑Epithelialization activity	Oleic acid, linoleic acid, tocopherols and carotenoids	(34)
	Fruit	Mixture of *P. lentiscus* berries fatty oil honey	Burn wound	Animal model in rabbits	21 days	Cicatryl ®	Mixture showed better effect than Cicatryl® and honey but pure *P. lentiscus* oil had the best wound contraction effect	-	(35)
	Leaves	Ointment (10% and 30%): Hydroethanolic extracts was added to petroleum jelly	Full-thickness wounds	Animal model in rats	15 days	Cicatryl-bio®	↑healing process, ↑wound contraction and ↓ epithelialization time	Phenolic compounds like gallic acid and paracoumaric acid	(36)
	Leaves	Distilled leaves by-product 5 and 20 mg/mL; and two isolated glycosylated flavonoids MM and QM with concentration of 1 mg/mL	Wound	Animal model in rats	14 days	Centasia cream	Distilled leaves by-product (20 mg/mL), MM and QM molecules exhibited faster wound contractions than the negative control and the Distilled leaves by-product (5 mg/mL) groups. Higher collagen biosynthesis, lower level of the CRP, low expression level of the TNF-α and the CD-31 were detected in Distilled leaves by-product (20 mg/mL), MM and QM treated groups. MM, and QM at 100 µg/mL performed the highest elastase inhibitory effect	Glycosylated flavonoids, MM and QM	(37)
		Oil was compared with Wireless network or WIFI signal (2.45 GHz) exposure	Sutured wounds	Animal model in rabbits	16 days		↑ Collagen deposition - Ameliorate the general aspect of wounds. - Extended inflammatory phase of wound healing was in the group of rabbits that received both WIFI and *P .lentiscus* oil	Linoleic acid and α-tocopherol	(38)

Table 1. Continued

Pistacia species	Plant part	Type of preparation	Type of skin problem	Type of study	Duration of study	Positive control	Result	Suggested responsible constituents	Ref.
Diabetic Wound									
P. atlantica	Resin	Resin oil (250 µL/day)	Wound	Streptozotocin-induced diabetic rats	14 days		- Wound healing ↑ Angiogenesis and collagen turnover	-	(39)
	Hulls	Hydroethanolic extracts of *P. atlantica* hulls and *Quercus infectoria* galls, alone or together. Qointment preparation: 5% of each extract was added to soft yellow paraffin	Wound	Streptozotocin-induced diabetic mice	14 days		- Full-thickness skin wound healing ↓ Inflammation phases, edema, immune cell migration and proliferation stage, ↑ New vessels formation, fibroblast infiltration and collagen synthesis, ↑ GLUT-1	-	(40)
Skin allergy (Atopic dermatitis)									
P. lentiscus	Resin	Ointments (1, 3, 5 and 30%) were prepared by dissolving highly purified mastic in caprylic/capric triglycerides	ACD and AD	Animal model in mice	6 weeks	Glycyrrhizic acid dipotassium salt (gk2, 0.1%) in caprylic/capric triglycerides	-In ACD: ↓ Inflammation, total IgE levels, lymphocyte proliferation in LNs and cytokine production. -In AD: Improvement of symptoms, itch behavior and cutaneous barrier function. -↓ Trans- epidermal water loss -In vitro: ↓ Production of IL-33, TSLP, and TARC levels	-	(14)
Cutaneous leishmaniasis									
P. atlantica var. *kurdica*	Gum		Cutaneous leishmaniasis *(Leishmania major)*	Animal model in mice	8 weeks	Meglumine antimoniate (Glucantime®)	Reduction in skin lesion size and decrease in parasite survival	α-Pinene, limonene, α-phellandrene, β-pinene, β-myrcene, 3-carene, aldehyde citral, epoxypinene, limonene oxide, oleanonic acid, moronic acid, 24Z-masticadienonic acid, 24Z-isomasticadienonic acid, 24Z-masticadienolic acid, and 24Z-isomasticadienolic acid	(16)

Table 1. Continued

Pistacia species	Plant part	Type of preparation	Type of skin problem	Type of study	Duration of study	Positive control	Result	Suggested responsible constituents	Ref.
P. khinjuk	Fruits	70% aqueous ethanol extract In vitro: 0–100 μg/mL In vivo: Lotion (20 and 30%)	*Cutaneous leishmaniasis*	In vitro (*L. tropica* (MRHO/IR/75/ER strain) and in vivo in mice	30 d	Meglumine antimoniate (Glucantime)	↓ Growth rate of promastigote (IC50: 58.6 ± 3.2 μg/mL) and intramacrophage amastigotes (37.3 ± 2.5 μg/mL) of *L. tropica* In vivo:↓ the number of parasites (30% extract)	Terpenoids, phenols, flavonoids, fatty acids	(41)
P. vera	Branch	EO, (0.1 mL in 0.97 mL of normal saline) in vitro: 3.125 to 100 µg/mL in vivo: (10, 20, and 30 mg/mL)	*Cutaneous leishmaniasis*	In vitro (*L. tropica* (MRHO/IR/75/ER strain) and in vivo in mice	30 d	Meglumine antimoniate (Glucantime)	↓ Growth rate of amastigote forms (IC50 of 21.3 ± 2.1 µg/mL) - In vivo: 87.5% recovery and ↓ mean diameter of the lesions (30 mg/mL)	Limonene, α-pinene and α-thujene	(42)
Hyperpigmentation disorders									
P. vera	Hull	80% aqueous methanol extract	Melanoma	Human melanoma SKMEL-3 cell		Tyrosinase inhibitor (kojic acid)	-Weak anti-tyrosinase effect compared with kojic acid - Strong antimelanogenic effect (~57%)	Phenolic and flavonoid compounds like gallic acid and quercetin	(43)
P. atlantica	Fruit	Different fractions (methanol, n-hexane, dichloromethane, butanol, ethyl acetate, water)	Melanoma	B16F10 murine melanoma cells		Tyrosinase inhibitor (kojic acid)	-Mushroom tyrosinase inhibition -Melanin synthesis inhibition -Strong intracellular tyrosinase inhibitory from methanol and ethyl acetate extracts	Polyphenols and flavonoids	(44)
P. lentiscus	Leaves	Ethyl acetate extract, purified QM and MM	Melanoma	B16 melanoma cells		Tyrosinase inhibitor (kojic acid)	-Mushroom tyrosinase inhibition activity -Reduced significantly tyrosinase activity on B16 cells	Flavonol glycoside, QM, MM, kaempferol-3-*O*-rhamnoside	(13)

MM, myricetin-3-O-rhamnoside; QM, quercetin-3-O-rhamnoside; ACD, Allergic contact dermatitis; AD, Atopic dermatitis; bFGF, basic fibroblast growth factor; VEGF, Vascular endothelial growth factor; MDA, Malondialdehyde; SOD, superoxide dismutase; CAt, catalase; CD-31, Cluster of Differentiation 31; CRP, C-reactive protein; TNF-α: tumor necrosis factor alpha; GLUT-1, Glucose transporter 1; IgE, immunoglobulin E; LN, lymph node; IL, Interleukin; TSLP, thymic stromal lymphopoietin; TARC, thymus- and activation-regulated chemokine.

Table 2. Risk of bias for *in vivo* studies (SYRCLE's RoB tool)

Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Random outcome assessment	Blinding	Incomplete outcome data	Others	Reference
?	Y	?	Y	?	?	Y	Y	14
?	Y	?	Y	?	?	N	Y	16
?	Y	?	Y	?	?	y	Y	18
?	Y	?	Y	?	?	y	Y	19
?	Y	?	Y	?	?	y	Y	20
?	Y	?	Y	?	?	y	Y	21
?	Y	?	Y	?	?	y	Y	22
?	Y	?	Y	?	?	y	Y	23
?	Y	?	Y	?	?	y	Y	24
?	Y	?	Y	?	?	y	Y	25
?	Y	?	Y	?	?	y	Y	26
?	Y	?	Y	?	?	y	Y	27
?	Y	?	Y	?	?	y	Y	28
?	Y	?	Y	?	?	y	Y	29
?	Y	?	Y	?	?	y	Y	30
?	Y	?	Y	?	?	y	Y	31
?	Y	?	Y	?	?	y	Y	32
?	Y	?	Y	?	?	y	Y	33
?	Y	?	Y	?	?	y	Y	34
?	Y	?	Y	?	?	y	Y	35
?	Y	?	Y	?	?	y	Y	36
?	Y	?	Y	?	?	N	Y	37
?	Y	?	Y	?	?	y	Y	38
?	Y	?	Y	?	?	y	Y	39
?	Y	?	Y	?	?	y	Y	40
?	Y	?	Y	?	?	y	Y	41
?	Y	?	Y	?	?	y	Y	42

"Y": low risk of bias, "N": high risk of bias, and "?": not sufficient information reported.
Note: Scale was adapted according to the use of different *in vivo* experimental models.

Results

Wounds

According to the following, several studies have investigated the effects of certain *Pistacia* herbs on wound healing in several molecular pathways (Figure 2).

Pistacia vera

Using a second-degree burn wound model in rats, Taghipour et al evaluated the effect of a topical ointment prepared from the extract of *Pistacia vera* (Pistachio) nut oil (5% and 10%). In 28 anesthetized animals, second-degree burn wounds were inflicted using a hot plate. The animals were treated with Pistachio creams, base creams, or dexpanthenol for 22 days. Pistachio ointment significantly improved burn wound healing after 12 days (10%). After 22 days, no scars were observed in animals treated with Pistachio ointment (10%). Pistachio ointment (10%) resulted in denser collagen deposition within the reticular layer and repaired epithelium (18).

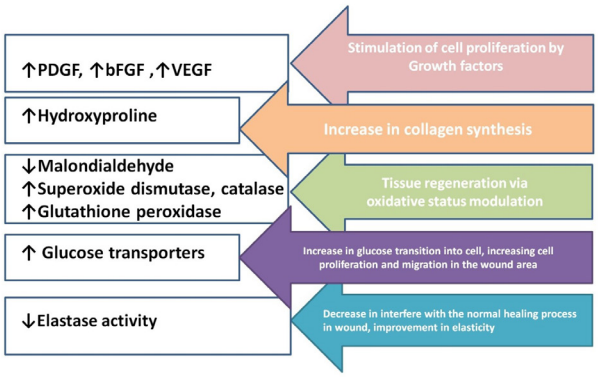

Figure 2. Molecular mechanisms of *Pistacia* genus in wound healing based on reviewed studies.

A study was conducted to investigate the wound healing properties of Algerian and Italian *P. vera* oleoresins. The EOs of oleoresins were obtained by hydrodistillation method. According to gas chromatography – mass spectrometry (GC-MS) analysis, α-pinene was the main composition of both EOs. For ointment preparation, EOs (5%) were separately mixed with petroleum jelly. An excision wound model was used in rabbits for 16 days and Cicatryl-Bio was used as a positive control. Algerian and Italian EOs both showed strong wound healing effects comparable to the control groups (19). A circular wound excision model was also used to investigate the efficacy of Algerian and Italian *P. vera* resins. Fraction analysis showed that oleoresins contained high levels of terpenoids.

Topical ointments were prepared by adding oleoresins to Vaseline (5% w/w). Wound excision induced on the dorsum of rabbits. Both ointments showed remarkable wound contraction from day 8 to day 16 as compared to the negative control and no statistically difference was observed with positive control (Cicatryl). Additionally, neither of these ointments caused any skin irritation (20). The phytochemical content of the studied resins was analyzed and the major compounds were reported as α-pinene and some oxygenated monoterpenes (Table 1).

In a study the methanol 80% extract of *P. vera* L. hulls was fractioned and investigated for wound healing activity by scratch assay on NIH/3T3 murine fibroblast cells. Higher wound healing effect was observed from chloroform fraction and 3-epimasticadienolic acid, which was determined as main effective compound using chromatographic methods. 3-Epimasticadienolic acid (200 μg/mL) significantly enhanced the fibroblast proliferation and migration and caused 45% reduction of the scratch area. Considerable inhibitory effect on gene expression of interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α), and a stimulation effect on NF-κB gene expression at the same dose was also reported from this compound (21).

Pistacia atlantica

The efficacy of *P. atlantica* resin extracts for the treatment of burn wounds has been studied in thirty-two Wistar rats. Resin oil was obtained using the hydro-distillation method. A topical ointment was prepared from resin oil with concentrations of 5%, 10%, and 20%. A higher resin oil concentration had a better impact on burn wound treatment after 14 days. The concentrations of platelet-derived growth factor and basic fibroblast growth factor increased with increasing resin oil levels. Further, higher concentrations of the ointment enhanced angiogenesis. The chemical composition of the studied extract was analyzed and the main compounds were reported as α-Pinene (46.57%) and the other monoterpenes (Table 1) (22).

Pistacia atlantica resin oil was tested on thirty rats with burn wounds. Topical use of *P. atlantica* resin oil for 14 days resulted in a significant reduction in wound size compared to sulfadiazine as a positive control. The mechanisms involved were vascular endothelial growth factor (VEGF), hydroxyproline elevation, and malondialdehyde (MDA) reduction. The α-pinene content of the studied resin oil enhanced wound healing (23).

In an experiment, Hamidi et al evaluated the antioxidant activity of *P. atlantica* fruit oil. Fruit powder was extracted with n-hexane, and obtained oil (5% and 10%) was added to a gel base. After cutaneous wound creation, animals received *P. atlantica* fruit oil gels or base gel for 21 days. *P. atlantica* gels (especially gel 10%) could reduce oxidative stress during wound closure by improving blood enzyme antioxidants (superoxide dismutase, catalase and glutathione peroxidase) as well as lipid peroxidation (plasma MDA) (24). In another study, Hamidi et al investigated the potential mechanisms underlying cutaneous wound healing by *P. atlantica* oil gels (5 and 10%). Treatment with *P. atlantica* fruit oil gel (10%) improved re-epithelialization with continuous stratum basalis, mature granulation tissue, and adnexa (hair follicles, sweat glands). Compared to the negative control, *P. atlantica* fruit oil gel (10%) enhanced the tensile strength, ultimate stress, yield strength, and stiffness, considerably. Both *P. atlantica* fruit oil gels resulted in more organized collagen fibers and better tissue alignment (25). The tocopherol and tocotrienol contents of the studied oil was suggested to enhance wound healing via modulating the oxidative stress (25).

Pistacia atlantica gum was investigated for its wound healing activity and its effect on blood serum biochemical parameters in 40 rabbits. Hydroethanolic extracts (30% and 60%) were added to distilled water to prepare oral suspensions. In order to prepare topical ointment (30% and 60%), EOs were added to Eucerin. A better wound healing progression was observed in the topically treated group after 21 days, especially in those who used ointment 60%. The enhancement of catalase, glutathione peroxidase, and superoxide dismutase in serum samples confirmed the antioxidant effects of *P. atlantica* ointment (26). The wound healing properties of *P. atlantica* hull ointment (1%, 3%, and 5%) were evaluated in white Wistar male rats. To prepare the ointment, hydroethanolic extract of *P. atlantica* hull was added to the base formulation (Eucerin and Vaseline in 1:3 proportions). Compared with a negative control, all doses of ointment accelerated wound healing, facilitated wound contraction, and enhanced neovascularization after 21 days. *P. atlantica* hull also increased collagen deposition by up-regulating mast cells and distributing fibroblasts. Additionally, no skin irritation was observed in any of the treated groups in the acute toxicity test. The high amounts of phenols and flavonoids found in *P. atlantica* hull extract may contribute to its wound healing properties (27).

A combination of *P. atlantica* hull ointment (2%) with flaxseed (2%) was used to evaluate wound healing in rabbits. Nitrofurazone ointment (0.2 %, w/w) was used as a positive control. Compared to the control group, flaxseed and pistachio oil ointment accelerated wound healing by shortening the inflammation phase, elevating cellularity, and promoting collagen synthesis. Antibacterial and anti-inflammatory properties of *P. atlantica* may contribute to its wound healing abilities. *P. atlantica* contains a high concentration of α-pinene (46.57%) and powerful antioxidant compounds that are known to accelerate wound healing (28).

The burn wound healing effect of *P. atlantica* fruit oil (20%) combined with *Sesamum indicum* oil (60%),

Cannabis sativa oil (12%) and *Juglans regia* oil (8%) was evaluated in 24 mice for 21 days. As a positive control, silver sulfa-diazine was used. When compared to the control, this combination significantly reduced epithelialization time and stimulated wound contraction. In addition, this combination resulted in a significant granulation tissue formation, scattered inflammatory cell infiltration, and collagenization in the dermis. Oil from *P. atlantica* fruit contains oleic, linoleic acids, phenolic compounds, and pheophytin, which may be responsible for its antioxidant, anti-inflammatory, and wound healing properties (29).

Topical use of *P. atlantica* resin oil (250 µL/day) was also evaluated for burn wound healing activity in thirty Streptozotocin-induced diabetic rats. After 14 days, a significant wound healing effect was observed in the *P. atlantica* oil-treated group compared with the negative control group. Improvement in antioxidant status was reported as one of the involved mechanisms. In addition, VEGF and hydroxyproline contents were elevated in the wound area indicating the effect of *P. atlantica* resin oil on angiogenesis and collagen turnover (39)

Hydroethanolic extracts of *P. atlantica* hulls and *Quercus infectoria* galls, alone or together, were administered topically for wound treatment in streptozotocin-induced diabetic mice. For ointment preparation 5% of each extract was added to soft yellow paraffin. After 14 days, a full-thickness skin wound healing effect was observed in all groups compared with the negative control group. The involved mechanisms included: reduction in inflammation phases, edema, immune cell migration, and proliferation stage, with an increase in new vessel formation, fibroblast infiltration, and collagen synthesis. In addition, *P. atlantica* hulls and *Q. infectoria* galls significantly increased glucose transporters (GLUT-1) and glypican-3 (GPC3) expression (Enhancement of GPC3 expression causes an increase in fibroblasts and fibrocytes) (40).

Pistacia khinjuk

The wound healing activity of methanolic extract of *P. khinjuk* unripe fruit was investigated in Wistar albino male rats. *P. khinjuk* fruit extract ointment was applied for 20 days to the animals, whereas zinc oxide ointment was used as a positive control. On the sixth day of treatment, faster epithelization was observed in the *P. khinjuk* ointment group compared with the control group. Reactive oxygen species (ROS) can prolong wound healing. The phenolic compounds of *P. khinjuk* due to their antioxidant activities can prevent ROS destructive effects (30).

Pistacia lentiscus

Virgin fatty oil from *P. lentiscus* fruits was obtained by the traditional cold-press method and applied topically to rabbit burn wounds. A comparison was made between the oil-treated group, the non-treated group, Vaseline gel, and Madecassol® (cream 1% that contains *Centella asiatica* as a main component). Compared to nontreated and Vaseline-treated groups, Madecassol® and fruit oil significantly increased wound contraction and reduced epithelialization time after 28 days. Oil from *P. lentiscus* fruit contains unsaturated fatty acids like oleic and linoleic acids. Compounds like these can help reduce trans epidermal water loss and promote wound healing by providing essential lipids (31).

Boulebda et al studied *P. lentiscus* fruits fatty oil and its saponifiable and unsaponifiable oily fractions on cutaneous wound in rats. Oil and fractions added to paraffin oil (10 %, v/v) as vehicle. Madecassol® was administered as positive control. After 26 days, *P. lentiscus* fruits fatty oil and its unsaponifiable fraction significantly promoted wound contraction compared with untreated group (32).

In a rat model, *P. lentiscus* fruit oil (0.56 L/mm^2) was applied for 8 days to carbon dioxide (CO2) laser fractional burns. The negative control was the saline solution (vehicle) while the reference cream was CYTOL BASIC® (restoring and soothing skin cream based on grape seed extract). Compared with other groups, *P. lentiscus* fruit oil significantly improved wound contraction and closure by increasing collagen turnover and reducing epithelialization time. It is possible that linoleic acid promotes wound healing by promoting epidermis differentiation. As the main compound of *P. lentiscus* fruit oil, sitosterol is capable of improving wound healing and angiogenesis (33).

Pistacia lentiscus fruit oil was also investigated for its wound healing effect in guinea pigs. Fruit oil was obtained using the cold press method. An oil-based ointment of 30% (v/v) was prepared by adding fruit oil to soft white Vaseline. Cicaderma® was used as a reference ointment. On the 15th of treatment (duration was 21 days), *P. lentiscus* oil-based ointment showed a significant wound contraction effect compared with reference ointment. A more significant epithelialization effect resulted from both *P. lentiscus* and Cicaderma® compared with the negative control and vehicle groups. The wound healing effects may be caused by linoleic acid, oleic acid, tocopherols, and carotenoids (34).

A mixture of *P. lentiscus* berries oil (*P. lentiscus* fatty oil) and honey was evaluated for the cicatrizing effect on burn wounds in rabbits. The duration of treatment was 22 days and Cicatryl® was used as a standard drug. In addition, the effect of the mixture of *P. lentiscus* oil and honey (0.5 g) was compared with the use of either honey (0.5 g) or *P. lentiscus* oil (0.5 mL) alone. All three groups significantly improved wound contraction compared to Cicatryl®. During the inflammatory and proliferative phases, the effect of pure *P. lentiscus* oil was better than honey or mixture. The mixture's wound contraction effect was significantly better than honey on the 14th day of treatment. So, researchers suggested that *P. lentiscus*

berries oil could modify the wound healing effect of honey during the inflammatory phase of the cicatrizing process (35).

Hydroethanolic extracts of *P. lentiscus* leaves (10% and 30%) were added to petroleum jelly and applied to full-thickness wounds (4 cm^2) in rats. Cicatryl-Bio® was used as a positive control and the duration of treatment was 15 days. *P. lentiscus* leaf ointments showed an accelerated healing process compared to control via promoting wound contraction and reducing epithelialization time. The antioxidant properties of *P. lentiscus* leaves phenolic compounds, such as gallic acid and paracoumaric acid, can aid in wound healing (36).

The wound healing properties of the by-product of *P. lentiscus* leaves after steam distillation (5 and 20 mg/mL), myricetin-3-O-rhamnoside (MM), and quercetin-3-O-rhamnoside (QM) at the concentration of 1 mg/mL were tested in rat models. Centasia cream and physiological serum were used respectively as positive and negative controls. After 14 days, distilled leaves by-product (20 mg/mL), MM and QM molecules exhibited faster wound contractions than the negative control and the distilled leaves by-product (5 mg/mL). Higher collagen biosynthesis, lower level of the C-reactive protein (CRP), lower expression level of the pro-inflammatory factor TNF-α, and the angiogenesis marker (Cluster of differentiation; CD-31) were detected in distilled leaves by-product (20 mg/mL), MM, and QM treated groups. In addition, MM, and QM at 100 μg//mL performed the highest elastase inhibitory effect (37).

A study conducted by Latrach et al, investigated the effects of topical *P. lentiscus* oil and wireless network (WIFI) signal exposure on rabbit sutured wounds. Results showed that separate use of *P. lentiscus* oil or WIFI could accelerate collagen deposition and improve the general aspect of wounds over 16 days. In contrast, the rabbits receiving both WIFI and *P. lentiscus* oil had a prolonged inflammatory phase of wound healing. Therefore, researchers suggested that *P. lentiscus* oil and WIFI signals should not be used together to treat wounds. Linoleic acid and α-tocopherol were suggested as the main responsible components for wound healing activity (38).

Skin allergy (Atopic dermatitis)

Using a murine model of allergic contact dermatitis (ACD) and atopic dermatitis (AD), *P. lentiscus* resin was studied in two steps. Highly purified mastic was dissolved in caprylic/capric triglycerides to prepare *P. lentiscus* ointments (1%, 3%, 5%, and 30%). Glycyrrhizic acid dipotassium salt (gk2, 0.1%) in caprylic/capric triglycerides was used as a positive control substance. The initial test was performed on the ACD mouse model. The anti-inflammatory effect of *P. lentiscus* ointments (3%) was confirmed by suppression of ear swelling, histological findings of inflammation, total immunoglobulin E (IgE) levels, lymphocyte proliferation in lymph nodes (LNs), and cytokine production. Anti-itch properties were also observed in the 30% mastic-treated group. In the second step, mastic ointments (3% and 5%) were evaluated in an AD murine model, and both products showed remarkable improvement in AD symptoms, itch behavior, and cutaneous barrier function. Moreover, these effects were confirmed by a reduction in trans-epidermal water loss. Mastic significantly reduced the production of interleukin-33, thymic stromal lymphopoietin (TSLP), thymus- and activation-regulated chemokine (TARC) levels (14).

Photoprotective effect

Twelve healthy volunteers (aged 25-35) were studied for a photoprotective effect of the extracts from the seeds and skin of *P. vera* L. Pistachio skin was extracted with methanol/water and pistachio decorticated seed was extracted in two steps with hexane and methanol/water. Each extract was prepared as an oil/water (O/W) emulsion (2% concentration) and tocopheryl acetate was administered as the reference ingredient at the same dose for an in vivo use. Both extracts, especially the Pistachio skin extract, reduced UV-B-induced skin erythema with comparable effects to a positive control. Pistachio skin extracts showed the highest phenolic level, with cyanidin-3-O-galactoside identifying as the main compound. Pistachio skin extract also had the highest antioxidant activity, which might contribute to its photoprotective properties (15).

Cutaneous leishmaniasis

Pistacia atlantica var Kurdica gum was investigated for its effects on the treatment of cutaneous leishmaniasis in mice. Glucantime® or *P. atlantica* gum was topically applied to mice infected with Leishmania major subcutaneously. *P. atlantica* gum and Glucantime® reduced skin lesion size and parasite survival after 8 weeks when compared with a negative control group (16). Monoterpenes and triterpenes in the studied gum were suggested as potential active compounds (16).

Pistacia khinjuk dry fruits were extracted with 70% aqueous ethanol and evaluated for antileishmanial activity in vitro and in vivo. The extracts (0–100 g/mL) were used for in vitro studies against promastigote and intracellular amastigote forms of *L. tropica* (MRHO/IR/75/ER). The lotion (20% and 30%) from *P. khinjuk* was applied topically every day for 30 days to mice suffering from cutaneous leishmaniasis caused by Leishmania major. Meglumine antimoniate (MA, Glucantime) was used as a positive control. In vitro assays showed significant inhibition of the growth rate of promastigote (IC50 58.6 ± 3.2 μg/mL) and intramacrophage amastigotes (37.3 ± 2.5 μg/mL) of *L. tropica* with a dose-dependent manner. Compared to MA, *P. khinjuk* extract (30%) caused a significant reduction in parasite numbers and a 75% recovery in infected mice.

Terpenoids, phenols, flavonoids, fatty acids, and sterols were suggested to be responsible for antileishmanial effects (41).

Pistacia vera branch EO was obtained by hydrodistillation method and evaluated *in vitro* (3.125 to 100 µg/mL) against intracellular amastigote forms of *L. tropica* (MHOM/IR/2002/Mash2) and in vivo (10, 20, and 30 mg/mL) against cutaneous leishmaniasis (*L. major*) in mice. MA (Glucantime®) was used as a positive control. The main EO components were limonene (26.21%), α-pinene (18.07%), and α-thujene (9.31%). In vitro studies showed significant inhibition of amastigote growth (IC50 of 21.3 ± 2.1 µg/mL) in a dose-dependent response compared with the control drug. In the in vivo assay, 87.5% recovery and a significant reduction in the mean diameter of the lesions resulted from a concentration of 30 mg/mL of the EO (42).

Skin toxicity resulted from cetuximab

Traditionally made soap from *P. terebinthus* fruit oil was evaluated for the treatment of grade 2 and 3 skin toxicity induced by cetuximab in metastatic colorectal cancer patients. Fifteen patients who received cetuximab in combination with chemotherapy and were suffering from skin toxicity used *P. terebinthus* soap twice daily for one week. The complete response rate was 100% in patients with grade 2 skin lesions. A complete response was observed in 33% of patients with grade 2 lesions, and grade 1 lesions were observed in the rest. Skin lesions reappeared in all patients after stopping using soap (45).

Nipple fissure

An ointment of *P. atlantica* (Saqez) was prepared with 7 g of Saqez, 7 g of beeswax, and 10 g of ghee, and topically administered to 100 volunteer mothers suffering from nipple fissures. The ointment was applied three times a day for one week in the intervention group. The control group was advised to apply two to three drops of breast milk to their nipple fissure. *P. atlantica* ointment caused an 83% reduction in fissure severity and an 85 % reduction in pain severity compared to the control. *P. atlantica's* anti-inflammatory effect was related to α-pinene, monoterpenoids, and triterpenoids. Moreover, α-pinene could be responsible for antibacterial activity (46).

Skin hyperpigmentation disorders

Skin hyperpigmentation disorders refer to conditions where patches of skin become darker than the surrounding skin due to an excess of melanin (47). A common form of hyperpigmentation is melasma, which typically affects women during pregnancy or while taking hormonal contraceptives (47,48). Pharmacotherapy options for hyperpigmentation disorders may involve topical preparations containing ingredients like hydroquinone, retinoids, or kojic acid (49). Herbal products for improving hyperpigmentation have gained interest recently (50). There are herbs such as the Pistacia genus which have potential to be used in skin lightening formulations with clinical efficacy.

In a study, *P. vera* pink and creamy white hulls were extracted in 80% aqueous/methanol. Assays of mushroom tyrosinase activity showed weak anti-tyrosinase activity of *P. vera* extract compared with tyrosinase inhibitor (kojic acid). The *P. vera* extract at a high dose (0.5 mg/mL) demonstrated significant cytotoxic activity (~63%) and strong anti-melanogenic effect (~57%) on human melanoma SKMEL-3 cells after 72 h of incubation. *P. vera* extract showed considerable DPPH radical scavenging activity attributed to its anti-melanogenic properties. Phenolics and flavonoids like gallic acid and quercetin were suggested as the main effective antioxidant compounds (43).

Various fractions (methanol, n-hexane, dichloromethane, butanol, ethyl acetate, water) and EO of *P. atlantica* subsp. Mutica unripe fruit were investigated for anti-melanogenesis and anti-tyrosinase activities. Mushroom tyrosinase was significantly inhibited by all extracts in comparison with Kojic acid (positive control). Different samples showed a significant inhibitory effect on melanin synthesis in B16F10 murine melanoma cells. However, this effect was not observed in EO and butanol extracts. Methanol and ethyl acetate extracts had strong cellular tyrosinase inhibitory activity in B16F10 murine melanoma cells, which was in accordance with melanin reduction. In addition, *P. atlantica* samples significantly reduced ROS in melanoma cells. Polyphenols and flavonoids possess antioxidant effects and can be attributed to the anti-melanogenic effect of this plant (44).

Distilled leaves of *P. lentiscus* were dried and extracted with ethyl acetate. The main separated phenolic compounds were QM, MM, and kaempferol-3-O-rhamnoside. According to a transdermal diffusion study, MM penetrated the membrane barrier at a greater rate than other compounds. Comparatively to kojic acid, MM, and QM inhibit mushroom tyrosinase. Inhibition of elastase by MM and QM was significant, but lower than that of ethyl acetate extract. Epigallocatechin gallate was used as a positive control for the elastase activity assay. Intracellular tyrosinase inhibitory and cytotoxicity assays on skin melanoma cells (B16) showed that ethyl acetate extract, QM, and MM have considerable inhibitory activities compared to the positive control kojic acid at non-cytotoxic concentrations (13, 37).

Discussion

It was found that *Pistacia* genus has been investigated in several dermatological disorders, including wounds, hyperpigmentation disorders, cutaneous leishmaniasis, and AD. Twenty studies have been conducted on wounds, mainly burn wounds, and two studies on diabetic wound models. Both diabetic ulcer studies were on *P. atlantica*.

According to the chemical compounds in the mentioned plant parts, different mechanisms could be involved in wound healing. Generally, in the healing process of wounds, there are three parallel phases, including inflammatory, proliferative, and remodeling phases (51,52).

The most studied plant parts were seeds and fruits. Oleoresin, the hull, and plant leaves have also been investigated.

The main compositions of seed oil in this genus are unsaturated fatty acids. *P. vera* (53), *P. atlantica* (54), and *P. lentiscus* (55) have been reported with remarkable contents of oleic acid, linoleic acid, and linolenic acid followed by other saturated fatty acids and triglycerides. Linoleic and oleic acids have been shown to have pro-inflammatory effects during the wound-healing process by increasing VEGF-alpha and IL-1β levels, in vitro. Also, oleic acid stimulates the generation of cytokine-induced neutrophil chemo-attractants in inflammation 2 alpha/beta (CINC-2alpha/beta) that might accelerate the wound healing (56). Moreover, it has been shown that in wound healing, oleic acid modulates the immune response (57).

Oleoresins of the *Pistacia* genus have also been studied in wound healing experimental models. The most prominent chemicals in their EOs are α-pinene and β-pinene. It has been indicated that alpha-pinene promotes wound healing by generating scars with sufficient tensile strength, speeding up wound closure, acting as an adhesive of primary intention, and forming collagen (58). Also, some studies have shown antibacterial activity for these monoterpenes (22,59) which can be effective in wound healing. α-Pinene was also shown with moderate anti-inflammatory activity, in vivo (60), and contributed to wound healing by providing anti-inflammatory effect in chronic wounds (61) with prolonged inflammatory response (62). In case of dermatitis, anti-inflammatory effects of *P. lentiscus* resin preparation has also been shown via the regulation of total IgE levels, lymphocyte proliferation in LNs, and cytokine production. It also decreased the production of IL-33, TSLP, and TARC levels, *in vitro* (14)

Pistacia atlantica hull extract has also been reported with remarkable amounts of total phenolic content, flavonoids, phenolic acids, resulting in higher antioxidant activities compared to another parts of the fruits, including shell and kernel (63). Furthermore, various studies have reported that the *P. lentiscus* leaves have significant amounts of phenolic compounds in addition to EO contents similar to other parts of the plant (64,65). In wound treatment, polyphenols are becoming increasingly popular due to their antimicrobial properties, regenerative capabilities, and antioxidant properties (66).

It has been indicated that regulating redox balance through the modulation of antioxidant levels that results in maintaining ROS in non-toxic levels could accelerate healing rate of wounds (67,68). In diabetic wound healing, oxidative stress regulation is also crucial (69). Phenolic compounds have been shown to affect oxidative stress, inflammatory process, re-epithelialization, and angiogenesis. They could mediate several factors and act on macrophages, fibroblasts, endothelial cells, as well as inflammatory cytokines (70). Some of the mentioned mechanisms have been demonstrated in two studies reporting the healing effect of *P. atlantica* resin oil and its hull extract administered topically on wounds in streptozotocin-induced diabetic animals (23,40).

Among other areas studied regarding the dermatological effects of *Pistacia* sp., we can point out their effects on tyrosinase enzyme activity as well as on cutaneous leishmaniasis. According to the available literature, among the different plants of this genus, *P. atlantica* and then *P. lentiscus* species have the most evidence regarding wound healing. Also, species of *P. atlantica*, *P. vera*, and *P. Khinjuk* are considerable in terms of anti-leishmaniasis effects. Although there are several *in vitro* studies on anti-leishmaniasis activity of plants in *Pistacia* genus (71,72) *P. khinjuk, P. vera and P. atlantica have* been especially evaluated in cutaneous leishmaniasis *in vitro* and *in vivo* (16,41,42). Some findings revealed that *P. khinjuk* initiated the production of nitric oxide compared to untreated macrophages (41). Also, an *in silico* study proposed two compounds from *P. atlantica*, 3-methoxycarpachromene and masticadienonic acid as inhibitors of *L. infantum* trypanothione reductase, which has a crucial role against virulence of these parasites (73).

Conclusion

In general, *Pistacia* species might play a role in dermatological disorders management, especially in wound-healing. The main chemical compounds that have had a potential for therapeutic effects are α-pinene, β-pinene, and triterpenoid compounds found in the EOs of these plants, unsaturated fatty acids in their oils, and also the phenolic compounds found in the prepared extracts. This genus probably provides new therapeutic preparations for skin disorders as adjuvant therapy. Nevertheless, more human clinical studies should be conducted to found the optimum drug delivery methods and dosages that would be helpful for different dermatological conditions. The herbs reviewed in this study illustrate a great potential for the development of prescription or over-the-counter dermatology medications from botanical compounds and extracts in particular from the genus *Pistacia*.

Authors' contributions

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Conflict of interests

There is no conflict of interest.

Ethical considerations

Not applicable.

Funding/Support

There was no financial support for the conduct of this review paper.

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