



THERAPEUTIC PROPERTIES OF MEDICINAL PLANTS: A REVIEW OF THEIR DERMATOLOGICAL EFFECTS (PART 1)

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ABSTRACT

Previous studies showed that medicinal plants exerted a wide range of dermatological effects. These plants included: *Adiantum capillus-veneris*, *Agrimonia eupatoria*, *Allium sativum*, *Aloe vera*, *Ammannia baccifera*, *Ammi majus*, *Ammi visnaga*, *Bauhinia variegata*, *Bellis perennis*, *Bidens tripartite*, *Bryophyllum calycinum*, *Caesalpinia crista*, *Calamintha graveolens*, *Calendula officinalis*, *Calotropis procera*, *Capparis spinosa*, *Capsicum annum*, *Capsicum frutescens*, *Carthamus tinctorius*, and *Cassia occidentalis*. This review was designed to highlight the dermatological effects of these medicinal plants.

Key words: *Adiantum capillus-veneris*, Dermatological effects, Dermatitis.

INTRODUCTION

Plants are a valuable source of a wide range of secondary metabolites, which are used as drugs with different pharmacological activities. Herbal medicine was used extensively in dermatology for the treatment of acne, wound and burn, viral, fungal, bacterial, parasitic infections, dermatitis, psoriasis, vitiligo, alopecia, skin cancer and other skin complaints [1-50]. This review will highlight the dermatological effects of the medicinal plants.

Adiantum capillus-veneris

The hair growth-promoting activity of a preparation of the *Adiantum capillus-veneris* was evaluated on albino mice using a testosterone-induced alopecia model. *Adiantum capillus-veneris* solution was applied topically to the back skin of animals and hair growth was evaluated by visual observation and histological study of several skin sections via various parameters as follicle density (number of follicles/mm) and anagen/telogen ratio. After 21 days, a patch of diffuse hair loss was seen in animals received testosterone while animals treated with *Adiantum capillus-veneris* showed less hair loss as compared to those treated with testosterone only. The follicular density observed in the *Adiantum capillus-veneris* -treated group was 1.92 ± 0.47 , compared to 1.05 ± 0.21 in testosterone-group and 2.05 ± 0.49 (follicles/mm) in finasteride-treated animals.

Anagen/telogen ratio was significantly affected by *Adiantum capillus-veneris*, which was 0.92 ± 0.06 as compared with 0.23 ± 0.03 and 1.12 ± 0.06 for testosterone and finasteride treated groups, respectively [51].

Agrimonia eupatoria

Prepared ethanolic extract ointment showed wound healing activity in rats in contrast with fucidin ointment and aqueous extract ointment, hence the wound healing was completed in 10 days by using the ethanolic extract ointment, while the healing was completed in 12 and 14 days for the aqueous extract and fucidin ointments respectively, in comparison with the untreated wound which needed more than 16 days for healing completion [52].

The successful treatment of cutaneous porphyria in a group of 20 patients receiving agrimony infusions has been described. An improvement in skin eruptions together with a decrease in serum iron concentrations in urinary porphyrins was noted [53].

Allium sativum

A randomized placebo-controlled double-blinded study show that 5 h after the administration of garlic powder a significant increase in capillary skin perfusion occurs by 55% in the healthy volunteers. The increased erythrocyte velocity results from vasodilation of

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precapillary arterioles which increases diameter of erythrocyte column by an average of 8.6% [54]. Chicken skin wounds exposed to aged garlic extract show an increase in the re-epithelialization and dose-dependent neovascularization [55].

In vivo and *in vitro* studies showed that garlic extract reduces footpad lesions in leishmania mexicana-infected BALB/c mice by inducing IFN-gamma production from T cells as a Th1 immunomodulator. *In vitro*, extract decreased macrophage infection via induction of nitric oxide production [56].

The activation of nuclear transcription factor kappaB which linked with psoriasis. This transcription factor can be interrupted by diallyl sulfide, S-allylmercaptocysteine and ajoene [57].

Allium sativum contains ajoene, which exerted antifungal activity. 34 patients treated topically with 0.4% ajoene cream once a day for tinea pedis, 79% were cleared within 7 days, while others were cleared within 14 days. In a 3-month follow-up, all participants were free of fungus [58].

The topical use of garlic gel in a double-blinded randomized controlled trial was significantly increase the therapeutic efficacy of topical betamethasone valerate in alopecia areata and it can be an effective adjunctive topical therapy for alopecia areata [59].

The application of chloroform extracts of garlic result in the complete resolution of cutaneous warts without recurrence after 3–4 months in a placebo-controlled trial [60].

Diallyl disulfide from garlic (*Allium sativum*) has been shown to have an antiproliferative effect on human tumor cells including those of skin. The consumption of garlic and related sulfur compounds has been reported to inhibits N-methyl-N-nitrosourea induced mammary cancer, dimethylhydrazine induced colon cancer, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone induced lung cancer, 1,2-dimethylhydrazine induced hepatic cancer, 7,12-dimethyl benz[a]anthracene and benzo[a]pyrene-induced skin cancer and carcinogen-induced stomach cancers in experimental animals [61-66].

Garlic oil increased glutathione (GSH) peroxidase activity in isolated epidermal cells incubated in the presence or absence of the potent tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA), and inhibited the sharp decline in the intracellular ratio of reduced (GSH)/oxidized (GSSG) glutathione caused by TPA. According to these findings, it was postulated that the inhibitory effects of garlic oil on skin tumor promotion may result from their enhancement of the natural GSH-dependent antioxidant protective system of the epidermal cells [67].

Aloe vera

Aloe vera gel enhanced wound healing. It reduced wound diameter (induced on both sides of the vertebral column) by 62.5% in mice receiving 100 mg/kg/day orally and 50.80% in animals receiving topically 25% *Aloe vera* [68]. Many studies showed that aloe hasten wound healing

cause by burns, frostbite, electrical injuries, caustic chemicals and surgery. It stimulated the activity of macrophages and fibroblasts which increase both collagen and proteoglycan synthesis and promote tissue repair. It also enhanced collagen deposition and cross-linking in granulation tissue in wounds and improved scar strength compared with topical antibiotic medication [69-72]. Acemannan also accelerated wound healing and reduce radiation induced skin reactions [73-74].

Aloe vera was recently found to be a potential treatment for psoriasis. In a double-blind placebo-controlled study, 60 patients with slight to moderate plaque psoriasis were treated topically with either 0.5% hydrophilic aloe cream or placebo. The aloe treated group showed statistically significant improvement (83.3%) compared with the placebo group (6.6%). There were no adverse effects reported in the treatment group [75].

Ammannia baccifera

The application of leaf extracts of *Ammannia baccifera* L cream to the infected wound in rats, it improved the healing activity and reduced the risk of further infection. The application of ethanolic leaf extracts of *A. baccifera* was found to improve the different phases of wound repair, including collagen synthesis and maturation, wound contraction and epithelialization [76].

Ammi majus

Numerous studies have assessed the efficacy of Fructus *Ammi majus* and xanthotoxin for the treatment of vitiligo, psoriasis, and hypopigmentation tinea versicolor [77-84].

Experimentation with *Ammi majus* extracts was started in Egypt by El Mofti [79-80]. This followed by the work of Sidi and Bourgeois who used *Ammi majus* Linn, in six patients with vitiligo, five men and one woman. Their ages were from 30 to 50 years. *Ammi majus* Linn was used (a) by oral administration, (b) by local topical application at the affected sites followed by sun or ultraviolet lamp exposure, or, (c) by a combination of (a) and (b). Three of patients were subjected to the combined treatment, two only to topical treatment and one to treatment by mouth for 5 months, and then to the combined treatment. The repigmentation appeared in all patients as pigmented minute macules with hair follicles in their center. These macules were distributed over the leukodermic plaques and increased progressively in size until they joined, forming larger islands. This was particularly distinct in the lesions on the trunk and on the extremities. On the face the repigmentation developed more rapidly and appeared to be progressing more from the periphery towards the center [85].

Many clinical trials were carried out to investigate the efficacy of *Ammi majus* in vitiligo. Patient with leukodermis took oral *Ammi majus* powdered fruits with exposing the affected patches to direct sunlight for 1 hour developed symptoms of itching, redness, oedema, vesiculation and oozing in the leukodermic patches. Within few days, the affected skin gradually started to display deep brown pigmentation [86].

In two small group of patients (eight patients each) with leukoderma treated with oral (0.05 g of *Ammi majus* three time daily) or liniment 1 g/100 ml, applied to the skin, with daily exposure of leukodermic areas to the sun for 0.5 hour or to UV light for 2 minutes, gradually increasing to 10 minutes, the leukodermic skin areas were inflamed and vesiculated, and the leukodermic areas began to show normal pigmentation [78].

However *Ammi majus* and its furanocoumarins constituents showed good results in many other clinical studies, 70% of the patients treated with an oral dose of 0.6 mg/kg bw of xanthotoxin 2 hours before exposure to sunlight three times per week with calcipotriol ointment in a randomized double-blind study, showed significant improvement [87].

Xanthotoxin with exposure to either UV-A or UV-B radiation for the treatment of plaque psoriasis in 100 patients appeared effective in reducing the number of plaques [88]. Oral administration of 0.6 mg/kg bw of xanthotoxin with two UV-A radiation dosage regimens was used for treatment of patients with moderate–severe chronic plaque psoriasis. 42% of patients were clear 1 year after treatment and the treatment regimens were well tolerated [89].

Many other similar results were obtained in assessment of *Ammi majus* and its furanocoumarins in the treatment of psoriasis, vitiligo and tinea versicolor by many authors [78, 83, 90-91].

Ammi visnaga

A double-blind, placebo-controlled study of 60 people indicated that the combination of oral khellin (which is the main constituent of *Ammi visnaga*) and natural sun exposure caused repigmentation in 76.6% of the treatment group, in comparison, no improvement was seen in the control group receiving sunlight plus placebo [92].

A subsequent placebo-controlled study of 36 patients of vitiligo, showed that a topical khellin gel plus UVA caused repigmentation in 86.1% of the treated cases, as opposed to 66.6% in the placebo group [93].

Bauhinia variegata

Excision and incision wound models in albino Wistar rats, were used to evaluate the wound healing activity of the ethanolic and aqueous extracts of root of *Bauhinia variegata* at dose of 200 and 400 mg/kg bw. Both aqueous and ethanolic extracts of root of *Bauhinia variegata* at both doses produced significant wound healing by excision and incision wound models, which was comparable to that of standard (framycetin) in excision wound model [94].

The methanolic extract of stem bark of *B. variegata* (at a dose of 500 and 1000 mg/kg bw) exerted anticancer effects in skin papilloma model against 7, 12-dimethylbenz (a) anthracene and croton oil induced skin carcinogenesis in mice. It was effective in decreasing the rate of tumor incidence and the cumulative number of papillomas. Tumor yield and tumor burden were also

found to be reduced. The depleted level of glutathione was restored in *B. variegata* bark extract treated groups [95].

Bellis perennis

Bellis perennis was used as skin lightening drug (BelidesTM, *Bellis perennis* flower extract). It affected the metabolic pathways involved in melanin synthesis. It inhibited tyrosinase, transcriptional control of tyrosinase expression, reduced pro-melanogenic mediators endothelin, and α MSH (melanin stimulating hormone), as well as reducing melanosome transference keratinocyte [96].

The wound healing activity of *Bellis perennis* flowers was evaluated in Wistar albino rats. Dried *Bellis perennis* flowers were extracted with ethanol, then fractioned with n-butanol and an ointment was prepared from the n-butanol fraction. Six wounds were created for each animal by using circular excision wound model. The first two wounds were treated topically with HOTBp (hydrophilic ointment treatment containing n-butanol fraction). The second two wounds were control group and not treated with anything. The third two wounds were treated only with HOT (hydrophilic ointment treatment without n-butanol fraction). Treatments were applied once a day and lasted for 30 days. Wound samples were excised on days 5th, 10th and 30th. The percentage of wound healing was calculated by Walker's formula after measurement of the wound area and the tissue samples were examined histopathologically. The percentages of wound closure (HOTBp: 100%; HOT: 85% and control: 87%) and histopathological observations showed that there were statistically significant differences between HOTBp, HOT and control groups ($p < 0.05$) at 30th day. The authors concluded that topically administered ointment prepared from the n-butanol fraction of *Bellis perennis* flowers has a wound healing potential without scar formation in circular excision wound model in rats [97].

Bellis perennis is the homeopath's first choice for deep tissue injury, it is also one of the top remedies for joint and muscular soreness, deep tissue injuries and sport accidents [98, 99].

Betula alba

Betulin enriched birch extracts produced an in vitro antiproliferative effect on four malignant human cell lines including A431 (skin epidermoid carcinoma). Furthermore, all of the bark extracts exerted a pronounced antiproliferative effect against human cancer cell lines [100].

Bidens tripartita

Clinically, 70% ethanol extract of the aerial parts of the plant and an ointment containing 2.5% of the extract were used by 53 patients with psoriasis. After one week of oral administration of the extract (20 drops three times daily) with application of the ointment to the affected areas of the skin once a day, desquamation of the skin was decreased, and a decoloration of the psoriatic plaques was observed. 29 of the patients were clinically recovered, 22 patients were clinically improved and failure of the therapy was recorded in 2 patients [101].

Bryophyllum calycinum

The ethanolic extract of the leaves of the plant was evaluated for its wound healing activity by using excision wound model in rats. The histological investigation showed that plant leaf ethanolic extract exhibited significant wound healing potential which could be attributed to the presence of steroid glycosides [102].

Caesalpinia crista

Butanol and water fractions of *Caesalpinia crista* hydroalcoholic extract produced significant orthokeratosis ($p < 0.001$). In relative epidermal thickness, a significant ($p < 0.05$) reduction with respect to control was observed in groups treated with retinoic acid, *Caesalpinia crista* decoction, butanol fraction of *Caesalpinia crista* decoction and water fraction of *Caesalpinia crista* hydroalcoholic extract. Maximum antiproliferative activity was shown by *Caesalpinia crista* hydroalcoholic extract (IC_{50} , 77.5 ± 12.7 $\mu\text{g/ml}$). In lipoyxygenase inhibition assay, water fraction of *Caesalpinia crista* decoction showed maximum activity with an IC_{50} value of 164.71 ± 4.57 $\mu\text{g/ml}$ [103].

The wound healing activity of different extracts of seed kernels of *Caesalpinia crista* was investigated in excision, incision and dead space wound models in albino rats. Ethyl acetate fraction of seed kernel of *Caesalpinia crista* has shown better wound healing activity in all models as compared to alcoholic extract and ether fraction. While petroleum ether extract, butanol fraction and butanone fraction has shown the least effective wound healing activity [104].

Calamintha graveolens

The essential oils were frequently used in aromatherapy, topical creams, homeopathic natural medicine, and food products. It alleviated acne symptoms systemically when taken orally [105].

Calendula officinalis

The effects of oral and topical application of *Calendula officinalis* flower extract on excision wounds were checked in rats. The percentage of wound closure was 90.0% in the extract-treated group, whereas the control group showed only 51.1% on the eighth day of wounding ($P < 0.01$). The days needed for re-epithelialization were 17.7 for the control animals; while, extract treatment at a dose of 20 or 100 mg/kg bw reduced the period to 14 and 13 days, respectively. A significant increase was observed in the hydroxy proline and hexosamine content in the extract-treated group compared with the untreated animals [106].

Surgically induced skin wounds in rats were treated with a 5% *Calendula* ointment in combination with allantoin. The drug combination was found to markedly stimulate physiological regeneration and epithelialization. This effect was attributed to more extensive metabolism of glycoproteins, nucleoproteins and collagen protein during the regenerative period in the tissues [107].

Effect of *Calendula officinalis* flower extract was investigated against experimentally induced thermal burns

in rats. Burn injury was made on the shaven back of the rats under anesthesia and the animals were treated orally with different doses of the flower extract (20 mg, 100 mg and 200 mg/kg body weight). The animals treated with the extract showed significant improvement in healing when compared with the control untreated animals. The indicators of the wound healing such as collagen-hydroxyproline and hexosamine contents were significantly increased in the treated group indicating accelerated wound healing in the treated animals. The acute phase proteins-haptoglobin and orosomucoid which were increased due to burn injury were found to be decreased significantly in 200 mg/kg body weight extract treated animals. The antioxidant defense mechanism, which was decreased in the liver during burn injury, was found to be enhanced in treated animals. The lipid peroxidation was significantly lowered in the treated group when compared to control animals. Tissue damage marker enzymes (alkaline phosphatase, alanine and aspartate transaminases) were significantly lowered in the treated groups in a dose dependant manner. The histopathological analyses of skin tissue also gave the evidence of the increased healing potential of the extract after burn injury [108].

The therapeutic efficacy of marigold (*Calendula officinalis*) extract was investigated in the epithelialization of lower leg venous ulcers. Twenty-one patients with 33 venous ulcers out of 34 patients were treated with (*Calendula officinalis* ointment) which applied twice a day for 3 weeks. The second group was a control group that consisted of 13 patients with 22 venous ulcers. In the control group, saline solution dressings were applied to ulcers for the same period. In the experimental group the total surface of all the ulcers at the beginning of the therapy was 67,544 mm^2 . After the third week the total surface of all the ulcers was 39,373 mm^2 (a decrease of 41.71%). In seven patients, complete epithelialization was achieved. In the control group the total surface of all the ulcers at the beginning of the therapy was 69,722 mm^2 . After the third week the total surface of all the ulcers was 58,743 mm^2 (a decrease of 14.52%). In four patients, complete epithelialization was achieved. There was a statistically significant acceleration of wound healing in the experimental group ($p < 0.05$) [109].

The photoprotective effect of the topical formulations containing marigold extract (ME) (*Calendula officinalis* extract) was studied in ultraviolet (UV) B irradiation-induced skin damage. The physical and functional stabilities, as well as the skin penetration capacity, of the different topical formulations were evaluated. In addition, the *in vivo* capacity to prevent/treat the UVB irradiation-induced skin damage in hairless mice and skin penetration capacity of the formulation was investigated. All of the formulations were physically and functionally stable. The gel formulation was the most effective for the topical delivery of ME, which was detected as 0.21 $\mu\text{g/cm}^2$ of narcissin and as 0.07 $\mu\text{g/cm}^2$ of the rutin in the viable epidermis. This formulation was able to maintain glutathione reduced levels close to those of nonirradiated animals, but did not affect the gelatinase-9

and myeloperoxidase activities which increased by exposure to UVB irradiation. In addition, gel formulation reduced the histological skin changes induced by UVB irradiation that appear as modifications of collagen fibrils [110].

The *in vivo* protective effect of *Calendula officinalis* extract against UVB-induced oxidative stress in the skin of hairless mice was evaluated by determining reduced glutathione (GSH) levels and monitoring the secretion/activity of metalloproteinases. An oral treatment of hairless mice with 150 and 300 mg/kg of *Calendula officinalis* maintained GSH levels close to non-irradiated control mice. In addition, this extract affected the activity/secretion of matrix metalloproteinases 2 and 9 (MMP-2 and -9) stimulated by exposure to UVB irradiation [111].

Calotropis procera

Topical preparation of *C. procera* was used for the treatment of eczema in 94 patients. The trials were conducted for nine months. The result was found encouraging, complete cure of all the signs and symptoms have been noted in 14 (14.89%) patients, excellent response was noted in 24 (25.53%) patients, good response in 33 (35.10%) patients, fair response in 10 (10.63%) patients. Two (2.12%) patients showed poor response to the treatment and 2 (2.12%) patients exhibited worsened condition [112].

The wounds healing effect of the latex of *Calotropis procera* was evaluated in rabbits. Animals were treated daily for 21 days. The wounds' diameters were measured on the day of wound creation, thereafter on days 7, 14 and 21 post wound creation. Biopsies of the wounds were taken on days 3 and 21 and viewed histologically. The wounds were found to be significantly ($p < 0.05$) reduced in groups treated with 50% latex in honey and triamcinolone, on day 7 post wound creation, while there was a significant ($p < 0.05$) reduction in wound surface area in all treated groups on days 14 and 21 post wound creation. Histological findings in untreated group showed thick bundle of collagen fibres some of which had broad based configurations, reminiscent of keloid. The group treated with 2ml of *Calotropis* latex revealed the presence of florid granulation tissues on day 3, while there was a marked reduction in quantity and size of collagen fibres on day 21 post wound creation which was comparable with what was seen for the triamcinolone-treated group [113].

Mice topically treated with Calo-protein, purified from the aqueous extracts of *C. procera* revealed antibacterial activity and significant wound healing after 14 days comparable to fusidic acid as positive control. This protein was devoid of cytolytic effect even at higher concentrations on skin cells after 24 h [114].

Capparis spinosa

When *Capparis spinosa* applied topically it afforded significant *in vivo* protection against UVB light-induced skin erythema in healthy human volunteers [115].

Capsicum annuum* and *Capsicum frutescens

The effectiveness of capsaicin was studied in the treatment of psoriasis. *In vitro*, capsaicin was found to inhibit phorbol ester-induced activation of transcription factors NF- κ B and AP-1 [116].

In 44 patients with moderate and severe psoriasis, 0.025% capsaicin cream showed a significant decrease in scaling and erythema during a 6-week [117].

However, a double-blind study of 197 patients with psoriasis treated with the capsaicin cream four times daily for 6 weeks showed significant decrease in scaling, thickness, erythema, and pruritus [118].

Carthamus tinctorius

It appeared that *Carthamus tinctorius* was sufficiently characterized for the maintenance of skin and hair when used as safflower seed oil 314 and 50 mg/day respectively [119]. The potential of hydroxysafflor yellow A-rich *C. tinctorius* extract (CTE) was examined on hair growth both *in vitro* and *in vivo*. The effect of CTE on cell proliferation and hair growth-associated gene expression in dermal papilla cells and keratinocytes (HaCaT) was determined. In addition, hair follicles from mouse neonates were isolated and cultured in media supplemented with CTE. Moreover, CTE was applied topically on the hair-shaved skin of female C57BL/6 mice, and the histological profile of the skin was investigated. *C. tinctorius* floret ethanolic extract promoted the proliferation of both dermal papilla cells and HaCaT and significantly stimulated hair growth-promoting genes, including vascular endothelial growth factor and keratinocyte growth factor. In contrast, CTE suppressed the expression of transforming growth factor- β 1 that is the hair loss-related gene. Furthermore, CTE treatment resulted in a significant increase in the length of cultured hair follicles and stimulated the growth of hair with local effects in mice [120].

The mixture of erythro-alkane-6,8-diols from the flowers of *C. tinctorius* markedly suppressed the promoting effect of TPA (12-O-Tetradecanoylphorbol-13-acetate) on skin tumor formation in mice following initiation with 7,12-dimethylbenz [a]anthracene [121].

Cassia occidentalis

The wound healing property of methanolic crude extract of *Cassia occidentalis* leaves and a pure compound chrysophanol isolated from it, was evaluated in excision, incision and dead space wound models. The parameters studied included rate of wound contraction and the period of epithelialization in excision wound model. Tensile strength in incision wound model and granulation tissue dry weight in dead space model were assessed along with histopathological examinations. Chrysophanol was found to possess significant wound healing property than methanol crude extract. This effect was evident by the decrease in the period of epithelialization, increase in the rate of wound contraction, skin breaking strength, granulation tissue dry weight content and breaking strength of granulation tissue. Histopathological study of the granulation tissue showed increased collagenation when compared to control group of animals [122].

The sun protection factor (SPF) for the flowers of *Cassia occidentalis* was studied. On comparison it was observed that *C. occidentalis* had high SPF value with antioxidant and antibacterial property. The results indicated that *Cassia occidentalis* flowers can be used as efficient antimelonyte agent for UV radiation hazards [123].

Chrozophora tinctoria

The inhibitory effect of *Chrozophora tinctoria* on mouse skin tumors was studied in vivo, tumor initiation was achieved by a single topical application of 7, 12-Dimethylbenze (a) anthracene (DMBA) (40 µg/100 µl acetane/mouse). After 7 days, tumor promotion was begun by twice-weekly topical application of Benzoyl peroxide (BPO) (20 mg/300 µl acetone/mouse) for a period of 32

weeks. Also before 4 hours of DMBA application , animals received a single topical dose of *Chrozophora tinctoria* extract (10 mg/gr carbopol gel/mouse). Results showed that there were higher yields of tumors in those animals receiving both DMBA and BPO. However, the *Chrozophora tinctoria* pretreated group showed complete inhibition of tumor incidence. The authors suggested that the antitumor effect of the plant was mediated by its scavenging of free radicals which play an important role in skin cancer [124].

CONCLUSION

The paper reviewed the dermatological effects of the medicinal plants to enhance their uses in the treatment of different skin diseases as a result of effectiveness and safety.

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