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Pharmacological mechanisms of medicinal plant extracts in the treatment of dermatological diseases: *in vitro, in vivo* studies and clinical trials

Abstract

Dermatological diseases are common inflammatory affections of the skin. In recent times, interest in herbal medicine for the treatment of dermatological diseases has become more than necessary due to the side effects of conventional drugs and their ineffectiveness. To this end, the use of herbal medicine is a promising approach. The objective of this review is to list scientific articles and reviews on plant extracts or plant formulations used in the treatment of dermatological diseases including acne, psoriasis, dermatitis and wounds which are the most common affections. The following scientific databases were consulted: PubMed, Inari, science direct, Google scholar, Web of Science and Scopus. This review provides evidence that herbal medicines will be emerging and promising treatments for dermatological conditions. However, better quality evidence and standardized methodologies are needed to support and further investigate the efficacy, safety and security of these plants.

Keywords: skin diseases, phytotherapy, medicinal plants, plants extracts, acne, psoriasis, wounds

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Introduction

The skin is the largest organ in the body and plays a crucial protective role against external aggression. Injuries, burns and dermatological diseases can lead to severe impairment of this barrier.[1] Dermatological diseases constitute a considerable burden with psychological, social and financial consequences for patients, their relatives and society.[2] About 41.3 million people suffered from skin and subcutaneous tissue diseases and thus these skin diseases occupy the 18th place among the most prevalent diseases in the world (Karimkhani et al., 2017). Moreover, human dermatological diseases represent a serious public health problem in the intertropics, especially in Africa.

Psoriasis is a common chronic inflammatory skin disease characterized by clinical manifestations of erythema, scaling and itching. Although the pathology of psoriasis is still unclear, most research has revealed hereditary components, as well as environmental factors, that act on the immune system. Currently, Western medicine generally uses glucocorticoids, immunosuppressant's and targeted immune modulators as therapy, but these methods have relatively limited efficacy and the condition often relapses after withdrawal of the drugs. Also, Acne, another skin diseases affects 85% of adolescents and can continue into adulthood.

The psychological, social and emotional impairments resulting from acne have been estimated to be equal to and in some cases greater than those of diabetes, arthritis, epilepsy and asthma. Acne vulgaris can cause scarring, leading to lifelong self-esteem problems. These patients are prone to depression and are more likely to be unemployed. Currently there is no effective treatment for acne and the available drugs have serious side effects. The same applies to the Wound healing which is a process of recovery of damaged tissue by replacing damaged dysfunctional cell structures. Natural compounds for wound, psoriasis treatment have been widely used for centuries. Many published works have reviewed natural compounds used for dermatological diseases, separating the approaches according to different categories such as characteristics, bioactivities and modes of action. However, current studies provide analyses of natural compounds from plants or animals only.

The conventional care and management of dermatological diseases have a substantial economic cost for health care systems worldwide. There is no doubt that the scientific valorization of medicinal plants effective against these dermatological affections will have a substantial positive impact on the environment, the quality of life and the economy in both developed and developing countries.

The current growing interest in the use of medicinal plants as a safe alternative and candidate molecule in synthetic drugs has legitimised research on the pharmacological properties of plants (Rodrigues et al., 2019). This review describes the recent progress of herbal medicine in the treatment of dermatological diseases such as acne, psoriasis and wounds. This review aims to identify through the available literature the pharmacological properties of medicinal plants used to treat acne, psoriasis and wounds using the scientific basis.

Methods

The search terms used included acne, wound healing, psoriasis combined with the terms "herbal medicine", "medicinal plants,"phytotherapy", "plants extracts" based on recent literature available in six electronic databases including Scopus, Web of Sciences, PubMed, Google Scholar, Science Direct and Hinari. Articles, reviews of *in vitro* or *in vivo* studies and clinical evaluations of plant extracts or plant formulations were considered.

Acne

Acne is a dermatological condition of the pilosebaceous follicle that affects 9.4% of the world's population.[3] It is a condition that represents one of the most frequent reasons for consultation in dermatology.[4] The condition usually attacks adolescents with a prevalence of over 80% worldwide.[3,4] Acne is characterised by the appearance of pimples, nodules, pus blisters, cysts, and scars on the body, usually on the face and chest. The affection can cause an acute

purulent infection, which easily spreads to the subcutaneous tissues, subjecting the skin to extensive damage.[5] This common inflammatory disease causes emotional, psychosocial distress and psychiatric disorders including depression, emotional isolation, and even suicide in extreme cases.[6,7]

The pathogenesis of acne involves several pathophysiological factors: sebaceous hyperplasia and hyperproduction, hyperkeratinisation of sebaceous ducts, bacterial colonisation and proliferation, mainly by Cutibacterium acnes, and inflammatory response.[8] The anti-acne effects of these medicinal plants exhibit several mechanisms: antibacterial, anti-inflammatory, antioxidant and anti-androgenic activities.In sebaceous glands, the enzyme 5 α-reductase type I reduces androgens to dihydrotestosterone, a more potent androgen, which stimulates lipogenesis and sebocyte proliferation and differentiation.[9] Thus, in general, this review shows that plant extracts inhibit this enzyme and limit hyperseborrhoea. C. acnes is an anaerobic gram-positive commensal bacterium that stimulates inflammatory and immune responses by several mechanisms.[10,11]

In the follicle, fatty acids induce the production of several cytokines involved in inflammation and keratinocyte proliferation.[12] To evaluate cosmetic formulations for the treatment and prevention of acne, *in vitro*, *ex vivo* and *in vivo* models are used. These different available models provide new opportunities for research on biologically active materials, drugs and pharmaceuticals as well as cosmetics for the treatment of acne.[13]

Phytotherapy of acne

Ethanolic and aqueous extracts of the rhizomes of some turmeric species (Curcuma aromatica, Curcuma amada, Curcuma zedoaria) and the bark of Adina cordifolia exhibit anti-acne effects in vitro by inhibiting C. acnes and in vivo in rats (Karadi et al., 2012). Glycyrrhiza glabra flavonoid-containing gel showed anti-acne properties by modulating metabolites closely related to hyperseborrhea, inflammatory response, hyperkeratosis and most importantly by restoring the skin microbiome.[14,15] *Ocimum basilicum* extract inhibits C. acnes proliferation and suppresses Cutibacterium acnes-induced inflammation in vivo.[16] Hamamelis virginiana bark has potential anti-acne activity through its antioxidant, anti-cutibacterium acnes and anti-inflammatory activities on human keratinocytes.[17] Extracts of *Chamaecyparis obtusa* significantly reduced the number of inflammatory lesions in acne patients.[18] Topical tree oil at 5% is effective for mild to moderate acne.[19]

Punica granatum extract attenuates C. acnes-induced ear oedema in Wistar rats.[20] *Scutellaria baicalensis* extract also attenuates C. acnes-induced ear oedema in Wistar rats confirming antioxidant and anti-inflammatory activities in vitro.[20] *Ocimum basilicum* leaves, crushed in the palm and the juice applied to the face once daily, were found to be as effective as a combination of oral tetracycline 500 mg twice daily and topical sulphur.[21] *Ocimum gratissimum* leaf oil lotion is more effective than placebo and 1% clindamycin. In addition, it is enhanced by increasing concentrations of Aloe verra gel.[22] Ethanolic extract (0.01%) of Angelica dahurica suppressed neutrophil chemotaxis, comparable to the effect of erythromycin (0.01%). *Rhizoma coptidis* extract (0.01%) showed better anti-lipogenesis activity than retinoic acid (0.01%).[23]

Acne-N-Pimple cream comprising Leuns culinaris powders with extracts of Aloe barbadensis, Arographis paniculata, and Salmalia malabarica produced a significant reduction in the number of blackheads and whiteheads, number of pustules and inflammation in acne patients.[24] *Thymus vulgaris* essential oils have also demonstrated in vivo anti-acne properties in mice that confirmed its antimicrobial activities against *Cutibacterium acnes* and anti-inflammatory activities.[25] *H. virginiana* bark, potentially possesses anti-acne activity mediated by antioxidant, anti-cutibacterium acnes and anti-inflammatory activities on human keratinocytes.[17]

Hydroalcoholic extracts *of Mitracarpus scaber,Aloe buettneri* and *Hannoa udulata* have bactericidal and bacteriostatic properties on *Cutibacterium acnes* and staphylococcus aureus,two main bacteria responsible of acne.[26] Essential oils of *Anthemis aciphylla* obtained by hydrodistillation showed a weak to moderate inhibitory effect against *S. aureus* and *S. Epidermidis*.[27] The extracts of duzhong and *yerba mate* also reduced the secretion of pro-inflammatory cytokines such as TNF-α, IL-8 and IL-1β.[28] The aerial parts of balsamina, showed remarkable testosterone 5-alpha-reductase inhibitory activity.[29] The 50% ethanolic extract of *Rosa multiflora* reduces testosterone production by inhibiting 5α-reductase. A stable water-in-oil emulsion containing sea buckthorn extract decreased sebum secretion from the skin.[30] The anti-oxidant and anti-bacterial effects of *Lygodium japonicum* and *Polygonum aviculare* against *C. acnes*.[31]

Essential oils of *Tamarix bovena* inhibit facial flora and could be used in acne products.[32] *Ocimum basilicum* leaves, crushed in the palm and the juice applied to the face once a day, have been found to be as effective as a combination of oral tetracycline 500 mg twice a day and topical sulphur.[21] However, there is little clinical evidence for the efficacy and safety of these herbs in the treatment of acne and other skin infections. The main activities of antiacne plants are summarised in Table 1.

Table 1 The anti-acne activities of plants and their biological effects

Plants	Family	Pharmacological activities
Adina cordifolia	Rubiaceae	
Curcuma aromatica, Curcuma amada, Curcuma zedoaria	Zingiberaceae	Anticutibacterium acnes activity Karadi et al.,
Glycyrrhiza glabra	Fabaceae	Antiacné activity Ruan et al.,[14]
Ocimum basilicum	Lamiaceae	Anticutibacterium acnes activity Zhang et al.,[16]
Thymus vulgaris	Lamiaceae	Anticutibacterium acnes Antiinflammatory. Abdelhamed et al.,[25]
Hamamelis virginiana	Hamamelidaceae	antioxidant, anti-cutibacterium acnes and anti-inflammatory Piazza et al.,[17]
Aloe buettneri	Liliaceae	Anticutibacterium acnes Kombate et al.,[26]
		Antioxydant and antinflammatory, Metowogo et al., Kombate et al.,[26]

Table Continued...

Plants	Family	Pharmacological activities
Mitracarpus scaber	Rubiaceae	Anticutibacterium acnes and Antioxydant Kombate et al.,[26]
Hannoa udulata	Simaroubaceae.	
Rosa damascene	Rosaceae	Anticutibacterium acnes
Eucommia ulmoides Oliv	Eucommiaceae	Anti-inflammatory effect Tsai et al.,[28]
Ilex paraguariensis	Aquifoliaceae	
Abies koreana	Pinaceae	Anti-inflammatory and antibacterial activities against skin pathogens Yoon et al.,[75]
Momordica balsamina	Cucurbitaceae	Inhibits 5-alpha-reductase Ishiguro et al.,[29]
Rosa multiflora	Myrtaceae	
Lygodium japonicum	Lygodiaceae	Anti-inflammatory and antibacterial activities against skin pathogens (Gou et al.,[31]
Polygonum aviculare	Polygonaceae	
Curcuma aromatica, Curcuma amada, Curcuma zedoaria, Adina cordifolia	Zingiberaceae	Antiacne activity Karadi et al.,
Thymus vulgaris	Lamiaceae	Aniacne in mice Abdelhamed et al.,[25]
Hamamelis virginiana	Hamamelidaceae	Piazza et al.,[17]
Chamaecyparis obtusa	Cupressaceae.	Inflammatory acne lesions were reduced
Glycyrrhiza glabra	Fabaceae	Antiacné Ruan et al.,[14]
Punica granatum		Antiacne Lee et al.,[20]
Hippophae rhamnoides	Elaeagnaceae	Anti-sebum secretion effects Akhtar et al.,[30]
Azadirachta indica	Meliaceae	Anti-inflammatory effets and antioxydant effects Jain and Basal[69]
Mesua ferrea	Calophyllaceae	Antiinflammatory,antioxidant and antibacterial activities Nakyai et al.,[71]

Psoriasis

Psoriasis is a common autoimmune disease Krueger et al.,[33] as the most common genetic skin condition, it manifests mainly as progressively enlarging and scaling psoriatic plaques, accompanied by pustules and spots.[34] The first lesions appear in the uppermost layer of the dermis, the papillary dermis. The blood vessels swell and bend, and lymphocytes and lymphocytes become more abundant. To date, psoriasis patients have not had access to a cure for the affection. Some preparations inhibit the action of immune factors or suppress the effects of psoriasis. The current therapeutic substances have some disadvantages, including patient frustration with the ineffectiveness of the drugs and possible side effects - mood swings, diarrhoea and vomiting. There is a lack of an effective, long-term treatment plan in the fight against psoriasis.

There is a great need for the continued development of new, safe and effective treatments for psoriasis. Among the many active compounds that have been studied for the relief of psoriasis, plant extracts and specific phytochemicals from natural resources have received much attention in recent decades. Several studies evaluating psoriasis therapy based on natural sources have revealed potential activity, including antiproliferative effects, reduction of itching and reduction of inflammatory cytokine levels. Natural substances, compared to drugs, do not cause patient frustration, mood swings, diarrhoea and vomiting, which is the positive aspect of their use. To date, most reports of the antiproliferative efficacy of natural compounds in the treatment of psoriasis are based on laboratory or animal work. Some studies suggest the use of natural products in the treatment of psoriasis solely on the basis of their ability to inhibit keratinocyte proliferation.

The results of in vitro cell studies, in vivo animal tests, and clinical trials offer much information about the success of natural products in the treatment of psoriasis. All the studies discussed in this review reveal the benefits of the substances used without side effects. In addition, the researchers observed the improvement of the immune system response, as well as the reduction of oxidative stress after treatment. Further in vitro, in vivo and clinical trials may confirm the findings that natural substances could be a potential and useful candidate for improving clinical outcomes in patients treated with systemic, conventional or immunobiological therapies.

Phytotherapy of psoriasis

In vitro research shows that Aloe vera extract (from the gel and leaf) can affect various pro-inflammatory pathways, such as inhibiting NF-κB, MAPK and PI3K signalling and reducing the production of iNOS, IL-6 and IL-1β in macrophages, or decreasing prostaglandin E2 levels via COX blockade. The research was conducted in a psoriatic model of HaCaT cells stimulated by TNF-α. The research used doses of 20, 40 and 80 μg/mL of Aloe Vera for 24 h, to test the cell viability of HaCaT cells stimulated with 10 ng/mL of TNF-α.[35] The scientists conducted in vitro and in vivo tests on HaCaT cells and mice, which were stimulated with IMQ to create a psoriatic model. *Artemisa capillaris* extract can potentially inhibit the extensive proliferation of keratinocytes and induce their apoptosis. The plant can presumably reduce leukocyte influx by decreasing ICAM-1 expression and decreasing nitric oxide levels via inhibition of Inos production.[36] According to the results, all variables, including erythema, desquamation and thickness, were significantly reduced where the formulated ointment was applied.*Rehmannia glutinosa* extract showed antipsoriatic activities in a mouse model of psoriasis.[37]

Rehmannia glutinosa extract showed antipsoriasis activities in a mouse psoriasis model.[37] Reduced inflammation in vitro on THP-1 and RAW264.7 cells, where LPS was used to induce psoriasis-like

skin inflammation.[38] *Salvia miltiorrhiza* may also have antipsoriatic capabilities,[39](Tang et al.,2018;) as it possesses anti-inflammatory, antioxidant, antiproliferative properties.[40] *Capsicum annum* contains the molecules of which capsaicin can inhibit NF-κB and AP-1 signalling, influencing inflammation[98] and reducing redness and itching in psoriasis patients.[41] *Curcuma longa* can fight psoriasis. thanks to curcumin can potentially fight psoriasis because Curcumin can influence or even disrupt the signal transduction between TNF-α and its receptor through direct binding, thus suppressing the inflammation induced by this cytokine.[42]

Scientists claim that curcumin is a potential molecule that can be used to treat psoriasis due to its immunomodulatory effects.[43] *Mallotus phillippinensis* contains rottlerin which is a potent suppressor of keratinocyte proliferation by preventing elevation of basal and hydrogen peroxide-stimulated NF-κB(Putic et al.,2010) and has potential antipsoriatic properties in vitro and *in vivo*[44] inhibits the proliferation of keratinocytes (HaCaT cells and NHEKs) and induces their apoptosis, but also significantly blocks the secretion of cytokines responsible for psoriasis, including TNF-α, IL-6, IL-17, IL-22 and IL-23. *Hypericum perforatum* contains quercetin which possesses anti psoriatic activities in vivo in psoriatic models and IMQ-stimulated mice that TNF-α, IL-6 and IL-17 levels were significantly decreased after administration of different doses of quercetin.[45] In vivo Apigenin from many plants decreased the level of IL-6 and IL-12 in mice[46] while the levels of these cytokines are high in psoriasis.

Wound healing

Wound healing is a highly controlled process, which involves a sequence of complex steps. This healing pathway includes the phases of hemostasis, inflammation, proliferation and remodeling. Today, various drugs are used to heal wounds. Recent evidence suggests that plants can prevent or repair various types of destructive cellular damage, including chronic wounds. Several phytochemicals such as polyphenols, alkaloids, flavonoids, terpenoids and glycosides have synergistic effects, including the stimulation of fibroblast proliferation, the main step in wound healing. In addition, the mechanism involves the induction of collagen synthesis, migration and re-epithelialization and their antimicrobial, antioxidant, anti-inflammatory and immuno modulatory actions. Similarly, the use of phytochemicals has shown promising results in the management of chronic wounds. Natural active ingredients contained in medicinal plants have immuno regulatory activity and control inflammatory responses, and can affect coagulation, inflammation, epithelialization, collagenisation and wound contraction.[47,48] This review summarizes the medicinal plants used for wound healing, clarifies their mechanisms of action.

Phytotherapy of wound

Turmeric longa helps to increase fibroblast migration, granulation tissue formation and collagen deposition: these activities contribute to tissue epithelialisation; the increased production of TGF-β also enhances wound healing by stimulating wound contraction and granulation tissue remodeling.[49] *Aloe gel* can be considered as the most traditional phytotherapeutic agent for wound healing.[50,51,52] Extracts from *Origanum dictamnus* L. leaves and *Rosa gallica* flowers have also shown healing properties(Tsioutsiou et al.,2016). St. John's wort extract has shown its healing activity by increasing the percentage of fibroblasts and promoting the synthesis of collagen I which plays a fundamental role in wound repair.[53] *Agrimonia eupatoria* L. herba as a species for the treatment of skin wounds is supported by a large number of clinical results that prove its efficacy. The hydroalcoholic extract of *Adonsonia digitata* was evaluated and showed healing activities in rats.[54]

A hydroalcoholic extract of Moringa oleifera seeds has healing activities.[55] *Feijoa sellowiana* fruit extract is a valuable source of antioxidant and anti-inflammatory activities and that it can enable damaged tissues to heal (Otaghvar et al., 2022). *Persicaria odorata* leaf extract possess ecicasant antibacterial properties which are useful in biomedical applications (Lubis et al., 2022*). Lavandula stoechas* and *Mentha pulegium* ointments at 5 and 10% significantly accelerate the wound healing process and constitute scientific evidence of *M. pulegium* in wound treatment.[56]

Toxicity of plants extracts and their bioactive components

Many people are now interested in medicinal plants and their various applications. However, the evidence base for the use of medicinal plants has remained largely understated with little or no scientific data on the safety of plants. Essential oils from plants for example are continually tested for their pharmacological effects of interest to the skin. However, they have toxic effects on patients.[57] Five groups of toxic compounds have been identified in plants. These are alkaloids, glycosides, terpenoids, protides and phenolics especially esssential oils.[58]

Dermocausticity: Topical application may cause skin irritation such as redness or burning. Essential oils rich in phenols, aromatic aldehydes and terpenes are skin and mucosa irritants. They are dermocaustic biochemical substances.[59] They induce a chemical skin burn more or less immediately.[57]

Hypersensitisation: Any essential oil can be the source of allergic reactions. These are mainly skin contact allergies. Sesquiterpene lactones, cinnamic aldehyde and sesquiterpenes are the main molecules responsible for allergic reactions.[60] Extracts of Curcuma longa have shown respiratory, allergic and immunological disorders.[60]

Photosensitisation: The cutaneous application of essential oils containing coumarins, especially furocoumarins or psoralens, can trigger erythematous reactions under sunlight exposure. The basic safety precaution is to avoid significant sun exposure for six hours after application.[61]

Neurotoxicity and abortifacient risk: The main concerns in the use of plants are the cause of abortion, modulation of reproductive hormones, maternal toxicity, teratogenicity and embryonic fetotoxicity.[62] Essential oils containing ketones are tricky to handle because of their potential neurotoxicity (risk of convulsions and seizures) and the abortion risks associated with their use. The toxicity of these molecules varies according to the route of administration, the dose used and the place of application, as well as the tolerance threshold of each patient.[63]

Hepatotoxicity: Some plant extracts exhibited hepatotoxicity effects.[64] These toxicity effects reported in plant extracts and their components depend on their usage circumstances. It is essential to integrate the notion of 'efficacy-toxicity' duality: any therapeutically active substance is potentially toxic, depending on the unit dose, the daily dose, the route of administration and the patient's state of health. This is the reason why the use of plant extracts requires knowledge and care, and certain precautions must be respected for their safety. This study could be an important source of information on the toxicity of medicinal plants used by the public.[65-75]

Conclusion

At the end of this study, it appears that plants are used to treat dermatological deseases. Currently, the emerging field of herbal

medicine in the management of dermatological conditions is overcoming the limitations of conventional therapeutic approaches. Herbal treatment shows several promising advantages in the treatment of severe skin conditions over conventional treatments. Research on plants used for dermatological diseases has shown that some plants that usually have side effects have lesser side effects compared to conventional therapies. It would be important to conduct toxicological studies on these plants and especially to set up serious research programmes on plants used to treat dermatological diseases. This review provides in-depth and up-to-date research on the anti-acne, anipsoria and healing properties of medicinal plants.

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Conflicts of interest

Authors declare there is no conflict of interest.

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