

A COMPREHENSIVE REVIEW ON HERBAL APPROACHES AGAINST ACNE VULGARIS

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ABSTRACT

Acne vulgaris affects about 85% of teenagers and may continue to adulthood. There are about two million visits to physicians per year for teenagers and the direct cost of acne treatment in the US exceeds \$1 billion per year. Acne is a cutaneous pleomorphic disorder of the pilosebaceous unit involving abnormalities in sebum production and is characterized by both inflammatory (papules, pustules and nodules) and non-inflammatory (comedones, open and closed) lesions. *Propionibacterium acnes* and *Staphylococcus epidermidis* are common pus-forming microbes responsible for the development of various forms of, acne vulgaris. Common therapies that are used for the treatment of acne include topical, systemic, hormonal, herbal and combination therapy. It is the sequelae of the disease that are the distinguishing characteristics of acne in skin of color, namely post-inflammatory hyperpigmentation and keloidal or hypertrophic scarring. Although the medical and surgical treatment options are the same, it is these features that should be kept in mind when designing a treatment regimen for acne. This review focuses on the treatment of acne using various drug delivery systems. Many herbal drugs are used for the treatment of acne vulgaris. Though they have very few numbers of clinical trials, many successful results have been recorded. There are many types of herbal drugs which act against acne vulgaris and some of those are:- Aloe Vera, Amaranth, Arnica, Asparagus, Barberry, Basil, Birch, Bittersweet nightshade, Brewer's yeast, Burdock, Calendula, Celandine, Chaste tree, Chaste berry, Coriander, Cur cumin, Green Tea, Guggul, Jojoba oil, Kali bromatum, Labrador tea, Lavender, Liquorice, Mint, Neem, Orange peel, Pine, Poplar, Rhubarb, Rose, Saw palmuto, Soapwart, Stinging nettle, Tea tree oil, Thyme, Turmeric, Usnea Barbara, Viola, Walnut, Willow bark.

KEYWORDS: Acne Vulgeris, Pathophysiology, Causes of acne, Medicinal plants, Herbal medicines.

INTRODUCTION

Acne vulgaris (or simply acne) is an infectious disease and one of the most prevalent human diseases. It is characterized by different areas of scaly red skin (seborrhea), pinheads (papules), blackheads and whiteheads (comedones), large papules (nodules), and sometimes scarring (pimples). Severe acne is usually inflammatory; however it may also be non-inflammatory. In acne, the skin changes, due to changes in pilosebaceous unit skin structures including hair follicles and their associated sebaceous glands. These changes usually require androgen stimulation.^[1] Acne vulgaris is usually due to an increase in body androgens, and occurs more often in adolescence during puberty, regardless of sex. Acne is usually seen on the face, upper part of the chest, and the back of subjects who possess greater numbers of oil glands.^[2] Acne vulgaris is a most common chronic inflammatory skin disorder of pilosebaceous unit that affect areas containing the largest

oil glands, including the face, back, and trunk.^[3-5] It is almost a universal disease occurring in all races and affecting 95% of boys and 83% of girls. Acne vulgaris is generally characterized by formation of seborrhea, comedone, inflammatory lesions and presence of bacteria *Propionibacterium acnes*, *Staphylococcus epidermidis* and *Staphylococcus aureus* in the follicular canal and sebum production.^[6] *P. acnes* have been described as an obligate anaerobic microorganism. It is implicated in the development of inflammatory acne by its capability to activate complements and by its ability to metabolize sebaceous triglycerides into fatty acids, which chemotactically attract neutrophils. On the contrary, *S. epidermidis*, an aerobic organism, usually involves in superficial infections within the sebaceous unit. When the chemicals produced by *P. acnes* destroy the cellular structure of skin cells, *Staphylococcus aureus*, grows causing acne lesions. These factors provide a potential target for treatment. *P. acnes*, *S. epidermidis* and *S. aureus* are the target sites of antiacne drugs.^[7] With the

excessive use of antibiotics for long periods has led to the increased resistance in acne causing bacteria i.e. *P. acnes*, *S. epidermidis* and *S. aureus*. The development of antibiotic resistance is multifactorial, including the specific nature of the relationship of bacteria to antibiotics, how the antibacterial is used, host characteristics, and environmental factors. To overcome the problem of antibiotic resistance, medicinal plants have been extensively studied as alternative treatments for diseases.^[8] The incidence of women exposed to oral tretinoin, a known teratogen, during pregnancy has been increasing, possibly the result of direct-to-consumer drug advertising. These and other concerns, including cost, underscore the need for safer, effective, more-inexpensive approaches, including those offered by herbal medicine. All forms of acne involve one or more of these pathophysiologic factors are Hyperkeratinization of the follicular epithelium with comedone formation, increased sebum production, Bacterial proliferation of *Propionibacterium acnes* (*P. acnes*), and Local immune hypersensitivity causing inflammation.^[9]

Acne may be classified according to predominance of specific skin lesions.^[10]

Comedonal (non-inflammatory) – mild
Papular (inflammatory) – mild-to-moderate
Pustular (inflammatory) – moderate
Nodulocystic– severe

This order also follows increasing severity, with cutaneous scarring as the ultimate result.

Pathophysiology

The pathogenesis of acne vulgaris is multifactorial. The key factor is genetics. Acne develops as a result of interplay of the following 4 factors:

- 1) Follicular epidermal hyper proliferation with subsequent plugging of the follicle.
- 2) Excess sebum production.
- 3) The presence and activity of the commensal bacteria *Propionibacterium acnes*.
- 4) Inflammation.^[11,12]

Causes of acne vulgaris

Infectious contribution

Staphylococcus aureus and *Propionibacterium acnes* have been attributed to acne vulgaris. However, their exact contributions in the acne process are not entirely clear. There are sub-strains of *P. acnes* in normal skin and some others in long-term acne complications. Therefore, it is unclear whether these strains are involved in this condition or they are pathogenically acquired. Resistance of *P. acnes* to commonly used drugs has been shown to be increasing.^[1] These strains are able to change, perpetuate, or adapt to the abnormal oil production, inflammation and inadequate sloughing of acne pores. Infection with *Demodex*, which is a parasitic mite, has been shown to be associated with the development of acne. However, eradication of the mites has not improved acnes.^[13]

Dietary contribution

The relationship between diet and acne is unclear as there is no good quality evidence. However, a high level of glycemic diet has been shown to be associated with worsening of acne vulgaris. A positive correlation between the use of milk, chocolates or salt, and increase in the severity of acne vulgaris has also been suggested. However, the contribution of chocolates is disputable, as they can be made with different amounts of sugar, with or without milk. A relationship between obesity and acne has also been reported.^[14]

Genetic contribution

For specific subjects, the predisposition to acne might be explained by a genetic component. This suggestion has been supported by some studies that have evaluated the rate of acne among first degree relatives, as well as twin studies. There are varieties of genes, which have been attributed to acne, such as polymorphisms in *IL-1 α* , *TNF- α* , and *CYP1A1* amongst others.^[15]

Hormonal changes

Hormonal changes, such as puberty and menstrual cycles, seem to contribute to formation of acne vulgaris. An increase in some sex hormones, especially in androgens during puberty and pregnancy, cause the follicular glands to produce more sebum. The use of anabolic steroids usually has similar effects. The hormones, which have been attributed to acne vulgaris, consist of testosterone, dehydroepiandrosterone and dihydrotestosterone, as well as insulin-like growth factor 1. Development of acne vulgaris in adult women might be due to an underlying condition such as Cushing syndrome, polycystic ovary syndrome or hirsutism.^[16]

Psychological contribution

Some scientific researchers have indicated that acne severity is correlated with an increase in stress level and stress has been listed as a factor attributed to acne flare. However, the connection between stress and acne vulgaris has been debated by some other studies.^[17]

Anxiety and stress

Mental stress can affect your levels of some hormones, such as cortisol and adrenaline, which in turn can make acne worse. Again, stress can make some people binge-eat. Experts believe the culprits are most likely the hormone levels, rather than the binge-eating.

Hot and humid climates

When it is hot and humid we sweat more. This can make the acne worse. Oil based makeups moisturizing creams, lubricating lotions, and all makeup that contains oil can speed up the blocking of your pores.

Greasy hair

Some hair products are very greasy and might have the same effect as oil based makeup. Hair products with cocoa butter or coconut butter are examples squeezing the pimples - if you try to squeeze pimples your acne is

more likely to get worse, plus you risk scarring. Make-up and hair care products can clog pores. When shopping, look for the following acne-friendly terms on product labels: oil-free, non-comedogenic, or nonacnegenic.^[18]

Medical treatments

Topical or/and systematic treatments are used to treat acne. The response of patients to treatment is considerably different. Usually more than one treatment modality is employed to treat acne and best results are achieved when treatments are individualized on the basis of clinical evaluations. Retinoids are the mainstay of therapy in patients who only have comedones. They are capable of reducing inflammatory lesions and the number of comedones (40% - 70%). Other agents, including isotretinoin, oral antibiotics, topical antimicrobials, and hormonal therapy, have been shown to yield high response rates. Patients with mild to moderate severity, inflammatory acne with papules and pustules are recommended to be treated with topical

antibiotics combined with retinoids. For patients with moderate to severe inflammatory acne, oral antibiotics are the first-line therapy. However, oral isotretinoin is recommended for severe nodular acne, frequent relapses, treatment failures or severe psychological distress. Isotretinoin is the most effective drug and to avoid long-term topical or oral antibiotic therapy, which may cause bacterial resistance, this drug may be recommended. However, isotretinoin is a powerful teratogen, needing strict precaution for use among women of the childbearing age. Medicinal plants are also used for the treatment of acne and are discussed below.^[1,19]

Drugs used against acne vulgaris

Many Allopathic drugs and their combination therapies are used in the treatment of acne vulgaris like Adapalene, Retinoic acid containing drugs, Clindamycin, Benzoyl peroxide and many more are used in suitable formulations. But the problem with these drugs and their combination therapies is that they have recorded side effects.^[20]

Table 1: Acne type and drug name.

Acne type	Drug name
(Mild acne) Comedonal	Isotretinoin Tretinoin Adapalene Azelaic acid
(Mild acne) Papulopostular	Benzoyl peroxide
(Moderate acne) Papulopostular	Oxytetracycline Minocycline Doxycycline Erythromycin Azithromycin
Nodular	Oral isotretinoin
Severe Acne	Spirolactone Oral contraceptive Corticosteroids

Medicinal plants with anti-acne activity

Herbal medicines are gaining increased popularity due to their advantages, such as better patient tolerance, long history of use, fewer side-effects and being relatively less expensive.^[21] Furthermore, they have provided good evidence for the treatment of a wide variety of difficult to cure diseases.^[22-32] These plants are used alone or in combination with synthetic drugs to treat diseases.^[33-38] More importantly, other than consumption as preventive or treatment remedy, they might be accompanied with synthetic drugs to reduce their side effects.^[22,39-45] With no exception, botanical drugs are also used accompanied by other methods or alone to treat acne vulgaris. Many medicinal plants with anti-inflammation and antibacterial activities are used in different ways in the treatment of acne and other infective diseases.^[46-51] *Matricaria recutita*, *Calendula officinalis* and *Triticum aestivum* are commonly used species of these plants.^[52] Creams or aqueous infusions made from plants including astringents and composites such as tannins are used

topically on skin after cleansing or a steam bath. *Hamamelis virginiana* has tannins and extraction of epidermis is commonly used to treat acne because it is very safe for topical prescription. Other plants containing tannins are white oak's bark (*Quercus alba*), walnut's leaf (*Juglans regia*), *Agrimonia eupatoria*, *Syzygium cuminum*, *Syzygium cuminum*, *Ledum latifolium*, *Alchemilla mollis*, *Lavandula angustifolia*, *Verbascum thapsus*, *Krameria triandra*, *Rheum palmatum*, *Hypericum perforatum* and *Rumex crispus*.^[53] Other plants that are traditionally used topically or as a depurative include *Bellis perennis*, *Viola tricolor*, *Elymusrepens* and *Taraxacum officinale*. Topical use of horsetail depurative (*Equisetum* species) is recommended due to the high amount of silicic acid and yellow milk of *Aloe ferox* fresh leaves because of anthranoids.^[52] *Vitex agnus-castus* is used for acne before menstruation. The whole fruit extract acting on follicle stimulating and luteinizing hormone levels in the pituitary gland led to an increase in progesterone and

decrease in estrogen levels through the dopaminergic mechanism, declining the level of premenstrual prolactin. German Commission E has recommended daily intake of 40 mg Vitex agnus-castus extract for the treatment of acne. Pregnant and nursing women should not use this plant. Adverse side effects such as gastrointestinal disturbances and skin rashes have been reported.^[54,55] In addition to the traditional use of herbal medicines as anti-acne, antibacterial activities of some plants in order to determine their potential as acne herbal treatment have been investigated.^[56] An anaerobic pathogen, *P. acnes*, plays an important role in acne pathogenesis and seems to begin the inflammatory process through stimulating the production of reactive oxygen species (ROS) and release of inflammatory and proinflammatory cytokines.^[57] Interestingly, the inhibitory effect of licorice (*Glycyrrhiza glabra*) is not associated with bacterial resistance induction of the growth of *P. acnes* in vitro.^[58] Screening of plant extracts for anti-bacterial and yeast activity has shown that usnic acid, an effective substance of *Usnea barbata*, has strong inhibition effect on the growth of *P. acnes*. The growth of bacteria was inhibited at $\geq 1\mu\text{g/mL}$ concentrations. In addition, *U. barbata* was found to have a wide range of anti-oxidative and antibacterial properties suggesting that it may be a promising substance in acne treatment.^[59] A four-week clinical trial compared the essence of *Ocimum gratissimum* at four different levels (0.5-5%) and four different bases by placebo and standard treatment (benzoyl peroxide, 10%). Two percent essence of *O. gratissimum* in a hydrophilic base (alcohol or cetomacrogol) reduced skin lesions faster than standard therapy, without any side effects, while 5% concentration was effective but with skin irritation.^[56] A study reported that topical application of *O. gratissimum* essence was superior to placebo and clindamycin 1%. In this study, topical yellow Aloe vera was not solely effective in acne treatment, however, showed a synergistic interaction with *O. gratissimum*.^[60] Topical use of 50% Aloe vera gel with tretinoin cream was well tolerated during eight weeks in a randomized double-blind clinical trial with 60 patients suffering from mild-moderate acne and was significantly more effective than tretinoin and vehicle.^[61] German Commission E has confirmed the topical use of *Solanum dulcamara* and edible use of *Saccharomyces cerevisiae* because of their antibacterial effect as acne remedy.^[62] In China, *Lemna minor* has been used topically to treat acne. A clinical trial noted that consumption of gugulipid, standardized extraction of oleoresin of an Indian herbal plant named *Commiphora mukul*, for three months, was effective in treating acne. Interestingly, the patients with oily skin respond remarkably to gugulipid. It should be noted that the aforementioned studies had a number of methodological limitations, for instance, there were only 10 individuals in each group (and without placebo), thus there was not enough power to determine significant differences between the medicines.^[54] Use of 2% lotion of green tea (*Camellia sinensis*) topically, during six weeks among 20 patients suffering from mild to

moderate acne, was found to be effective compared with pretreatment. Tannins and flavonoids of green tea may possess an anti-acne effect, since they seem to have an antiseptic effect while tannins also have an anti-inflammatory effect.^[62]

In Western traditional medicine the root of *Mahonia aquifolium* or *Berberis aquifolium* has been used to treat chronic skin rashes (pustule). The main effective substances of *Mahonia* extracts include two alkaloids of Protoberberine, namely Jatrorrhizine and Berberine, which have inhibited the in vitro growth of *Staphylococcus coagulase*, *P. acnes* and *Candida* species. Berberine (100 $\mu\text{mol/ml}$) in an animal model inhibited fat production in Sebaceous by 63%.^[63] Berberine alkaloid is a bitter substance with anti-fat production and anti-inflammatory effect on 3T3-L1 fatty cells, and its anti-fat production effect, has been related to down regulation of fat production enzymes and transcription factors. However, the exact mechanism of Berberine and herbs enriched in Berberine is still unknown.^[64] Tea tree oil (TTO) has a broad spectrum of antibacterial properties and reduces skin inflammation due to inhibition of histamine release. Five percent tea tree oil and 5% benzoyl peroxide improved acne in a three-month single-blind clinical trial on 124 patients, however, the effect of tea tree oil began slowly and a few patients in the tea tree oil group showed skin complications.^[65] While the mentioned study had no placebo group, a 45-day double-blind, randomized trial with 60 patients showed the efficacy of 5% topical gel of tea tree oil on mild to moderate vulgaris acne. The efficiency of tea tree oil gel for the total numbers of acne lesions and intensity index of acne was found to be 3.55 and 5.75 times higher than the placebo, respectively.^[66] Gluconolactone is made of a polyhydroxy acid formed by *S. boulardii*. The results of a double-blind clinical study on 150 patients with topical usage of a 14% gluconolactone solution showed the removal of inflamed acne lesions, which was significantly superior when compared to the placebo and comparable with 5% benzoyl peroxide, however, with less adverse side effects.^[67] The plants, which have gained more popularity for the treatment or prevention of Acne vulgaris during the past two decades, are presented with more details below.

Achyranthes aspera

This medicinal plant is traditionally used for the treatment of Acne vulgaris, eruptions of the skin, boils, scabies and other skin diseases. Saponin, alkaloid and non-alkaloid fractions obtained from the leaves of this plant have enormous inhibitory effect on the Epstein-Barr virus early antigen activation in Raji cells, with the most inhibitory activity (96.9%; 60% viability) observed for the non-alkaloid fraction, which contains non-polar compounds. In the in vivo two-stage mouse skin carcinogenesis test the total methanolic extract possessed a pronounced anti-carcinogenic effect (76%). The results revealed that the leaf extract and the non-alkaloid fractions were valuable antitumor promoters in

carcinogenesis. The plant has abortifacient properties in rodents and also has contraceptive activity, which might be due to its potent estrogenic activity.^[67]

Allium cepa

Onion extract gel has shown the ability to improve the appearance of scars in patients with seborrheic keratosis. This extract gel has been shown to improve the scar's appearance by improving its redness, softness and texture at excision site four, 6 and 10 weeks after the extract usage.^[76] In another study, the antimicrobial and antifungal properties of a *A. cepa* and *A. sativum* were revealed against *Malassezia furfur*, *Candida albicans* and some other *Candida* sp, as well as some strains of dermatophytes and *Acne vulgaris* microbes. The results indicated that *A. cepa* and *A. sativum* might be promising in the treatment of bacterial and fungal-associated infections.^[68]

Commiphora mukul (Guggul)

Guggul extracts appear to have anti-inflammatory and antibacterial properties that may benefit acne patients. Research suggests guggulipid reduces sebum secretion and blocks bacterial metabolism of triglycerides that promote the development of acne. The cholesterol-lowering effects of guggul appear to work best when combined with a non Western, Indian diet. Those patients with oily skin responded much better to the guggulsterone treatment.^[69]

Azadirachta indica

In a study, conducted on an anti-acne formulation prepared from herbal extracts, it was revealed that ethanol extract of *Azadirachta indica*, *G. glabra*, *Andrographis paniculata*, *Ocimum sanctum*, and green tea possessed the potential for inhibiting acne. In this study the anti-acne formula successfully acted against *Propionibacterium* and *Staphylococcus epidermis* [70]. Aqueous extract of *Azadirachta indica* leaves also possess chemopreventive potential against murine skin carcinogenesis. Skin tumors have been shown to enhance the expression of proliferating cell nuclear antigen in comparison to the control group. In this study, skin tumors exhibited high level of lipid peroxidation.^[71]

Curcuma longa (Turmeric)

Turmeric's primary biologically active component is curcumin. Research has shown that curcumin has potent antioxidant, woundhealing, and anti-inflammatory properties, which may prove to be therapeutic against acne. Turmeric is considered safe in amounts found in foods and when taken orally and topically in medicinal quantities. It may cause atopic dermatitis in some people. However, pregnant women should not take medicinal amounts of turmeric because it could stimulate the uterus. Topically turmeric may cause the skin to temporarily stain yellow—especially in people with light skin tones. When used as a topical remedy, it is typically mixed with water or honey to a pasty consistency and

applied directly to the skin. Orally, dried turmeric can be mixed into liquid and consumed.^[72]

Cannabis sativus

The seed oil of *Cannabis sativus* is useful for the treatment of acne rosacea, seborrheic dermatitis, eczema, dermatitis, psoriasis and lichen planus. The leaves powder of this plant is very useful as a wound and sore dressing. *Cannabis sativus* extract is externally useful to relieve pain in itchy skin. The seed oil strengthens the skin and makes it more resistant to bacterial, fungal and viral infections.^[73]

Serenoa repens (Saw palmetto)

Saw palmetto is considered an anti-androgenic substance because it inhibits the enzyme necessary to convert testosterone to dihydrotestosterone (DHT). DHT influences sebum production by the sebaceous glands, and lowering DHT levels may help reduce the excess oils that contribute to the development of acne. In fact, when excessive androgen hormones are suspected in acne cases (e.g., in females with polycystic ovary syndrome) herbal clinicians often look to saw palmetto as a first-line regimen. Oral use of saw palmetto is generally considered safe.^[74]

Tea tree oil

Extracted from the leaves of the tea tree, studies have confirmed tea tree oil's antibacterial activity against harmful microbes without damaging normal, healthy skin microbes. This includes inhibiting growth of the gram positive bacteria associated with acne *Propionibacterium acnes*. In laboratory experiments it's even been shown to kill *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) and actively inhibits herpes simplex virus. Tea tree oil constituents also have anti-inflammatory properties. Clinical studies have demonstrated the effectiveness of tea tree oil in the fight against acne.^[75]

Echinacea angustifolia and Echinacea purpurea

The extract of *Echinacea purpurea* has been shown to readily kill *P. acnes*, which is the main cause of acne vulgaris. In cell culture models, *P. acnes* induced substantial secretion of several pro-inflammatory cytokines, such as IL-6 and IL-8. However, the *E. purpurea* was able to completely reverse this effect to normal levels. Hence, *E. purpurea* provided a safe two-fold benefit to acne patients by inhibiting bacterial-induced inflammation and inhibiting the proliferation of organism.^[40] *Echinacea* has also been used to treat other skin problems such as psoriasis, skin wounds, burns, ulcers, herpes and hemorrhoids.^[62]

Barberry

Barberry's main bioactive constituent is the alkaloid berberine. Berberine exhibits anti-inflammatory, antibacterial, and androgen-inhibiting properties. Preliminary studies show that it can inhibit the skin cell processes that form comedones in acne, and in animal

model research, berberine suppressed sebum production by over 60%. Laboratory studies show that two other barberry alkaloids, berberine and jatrorrhizine, exert antibacterial effects against a number of different bacteria, including *Propionibacterium acnes* (*P. acnes*). When used as recommended, berberine alkaloids from barberry are considered nontoxic. However, if consumed in large quantities they can cause severe, even fatal, poisoning. Pregnant or nursing women and newborn infants should not consume any herb that contains berberine because it can cause a severe, potentially fatal form of jaundice. Other herbs that contain berberine are goldenseal and yellowroot. Topical use of barberry can cause skin irritation, but creams containing berberine have been used for 20 days without adverse side effects.^[76]

Rosmarinus officinalis

Rosmarinus officinalis is a household plant, which is grown in many parts of the world. It is used as a beverage drink, flavoring food, as well as in cosmetics. *Rosmarinus officinalis* contains rosmarinic acid. Chronic UV exposure has manifestations such as photo-cancers and photo aging. Aqueous extract of *R. officinalis* is effective in prevention of photo damage induced by UV radiations due to its antioxidant effect.^[71] Infections are also associated with oxidative stress. Therefore, the compounds, which possess antioxidant properties, might be beneficial in this way, regardless of their antibacterial activity. *Rosmarinus officinalis* oil has also been effective against *P. acnes*, a type of bacteria that causes acne. In a study, the antibacterial properties of *R. officinalis* essential oil was evaluated against *P. acnes* in which significant changes were reported in size and morphology of *P. acnes* in response to treatment.^[77]

Melaleuca alternifolia

Melaleuca alternifolia or tea-tree is a tree or tall shrub in the plant genus *Melaleuca*. It is native in Australia, and occurs in north coast and adjacent areas of New South Wales. It also grows on swampy flats and along streams and where it occurs, it is often the dominant species. Tea tree oil is a broad-spectrum agent against Gram-positive and Gram-negative bacteria and even *S. aureus* resistant to methicillin and yeasts such as *C. albicans* in vitro. Its mechanism of action has been attributed to monoterpenes, which cause disruption of the plasma membrane barrier. Other than antimicrobial activity, tea tree oil has monocyte activators and anti-inflammatory activities. Topical use of low concentrations of tea tree oil has anti acne activity with low side effects. It is effective in chronic infectious wounds and osteomyelitis.^[78]

Eucalyptus globulus, E. viminalis* and *E. maculata

In one study, the leave extractions of 29 *Eucalyptus* species were examined for anti-microbial activities. Extractions of *Eucalyptus globulus*, *E. maculata* and *E. viminalis* were able to inhibit the growth of six gram-positive bacteria including *P. acnes*, *S. aureus*,

Enterococcus faecalis, *Bacillus cereus* and *Alicyclobacillus acidoterrestris*, and a fungi, *Trichophyton mentagrophytes*, yet they did not show a strong inhibitory activity against gram-negative bacteria. A component of *E. maculata* (8-desmethyl-eucalyptin) also had strong inhibitory activity against the above-mentioned microorganisms. The authors concluded that *Eucalyptus* extracts and some components isolated from this plant had an inhibitory effect on microorganisms causing acne and Athlete's foot infection, as well as some fungal infections.^[72]

Case study and clinical trials

Purim has hepatoprotective herbs, which help to eliminate various toxins present in the blood and improve digestion and blood circulation. It has also anti-inflammatory and antibacterial properties. Clarina cream acts topically as an astringent, anti-inflammatory and antibacterial agent. In an experimental trial *Aloe barbadensis* exhibited topical anti-inflammatory activity equivalent to hydrocortisone. *Alternanthera sessilis* contains very high amounts of carotene, which is a potent antioxidant. Clinical trials conducted using acne gels containing zinc showed that at the end of the test period there was a significant difference in the reduction of inflammatory and non-inflammatory lesions. The extract of *Rubiaceae cordifolia* has been shown to possess significant inhibitory properties in experimentally induced lipid peroxidation⁸. Borax, which is present in Clarina cream, acts as an astringent. Purim tablets contain different herbs. *Picrorrhizakurroa* has hepatoprotective and hepatic stimulant properties. In a randomised, double-blind placebo controlled trial in patients with acute viral hepatitis, a 375 mg extract was administered three times a day for 2 weeks. Inhibition of bilirubin, SGOT and SGPT was significant. *Andrographis paniculata* has andrographolide as an active principle, which acts as an anti-inflammatory agent. Studies have shown that *Eclipta alba* has potent hepatoprotective activity, the mechanism of action being the regulation of the levels of hepatic microsomal drug metabolising enzymes. *Tinospora cordifolia* is found to possess immunomodulatory activities. *Saussurea lappa* has many active principals which act as an anti-inflammatory drug, it acts by inhibiting the production of inflammatory mediators and the proliferation of lymphocytes. *Embeliaribes* was found to be effective as an analgesic by oral, i.m. and i.v. routes and the results are comparable with morphine. In a study on the wound healing properties of *Curcuma longa*, it was observed that there was faster wound closure of punch wounds in curcumin-treated animals in comparison with untreated controls. Biopsies of the wound showed re-epithelialization of the epidermis and increased migration of various cells including myofibroblasts, fibroblasts, and macrophages in the wound bed. Multiple areas within the dermis showed extensive neovascularization. *Azadirachta indica* has antibacterial activity against a variety of micro-organisms such as *Staphylococcus*, *Enterococcus*, *Pseudomonas*,

Escherichia, Klebsiella, Salmonella and Mycobacterium. A study was done to assess various plants for antibacterial properties. Among them Cassia fistula showed significant antibacterial activity against various bacteria¹⁷. The growth curve of Staphylococcus aureus in a liquid medium with and without bakuchiol, the main component of Psoralea corylifolia also displayed the antibacterial properties of the herbal ingredient in vitro. Significant symptomatic relief was noted with 4 weeks of treatment with Clarina cream and Purim tablets, administered concurrently. The results in this clinical trial show that Clarina cream and Purim tablets can be safely given to patients with acne.^[79]

Digestive herbs for acne

A 23-year-old male patient with mild-to-moderate papulopustular acne on the face, back, and chest that had not responded to systemic erythromycin treatment sought naturopathic care. He also complained of having claylike stools. He was a vegan (and had been for 7 years) except for occasional dairy-product intake and was in a stressful educational program. He used no medication but was taking a multivitamin and vitamin C. Blood tests revealed that he had low grade macrocytic anemia. Stool fecal-fat analysis indicated elevated fecal-fat levels. Celiac disease was excluded by a negative serum antiendomysial antibody test. The initial treatment for this patient included:

- Increasing omega-3 fatty acid-rich foods in his diet, particularly (Linum usitatissimum) flax oil
- An elimination/challenge diet (which revealed that he had various negative reactions to dairy products, avocados, and chocolate)
- One intramuscular (IM) vitamin B12 shot weekly for 6 weeks.

After 3 months on this protocol, the patient had a moderate reduction in number of acne lesions and his anemia was resolved, but his stools had not improved much. Therefore, a bitter tincture formula containing 50 percent Gentiana lutea (gentian) root, 30 percent Taraxacum officinale (dandelion) leaf, and 20 percent Mahonia aquifolium (Oregon grape) root was prescribed at a dose of 2 droppers-full before meals. The patient also decided to start eating fish and began taking 6 g of fish oil per day. Three (3) months of this program led to a near-total resolution of all lesions as well as normalization of his stools. The bitters were discontinued after 1 more month, and the acne remained almost entirely resolved. After 1 year that was associated with a severe time of stress, some of his acne lesions recurred, but these were reduced when his stress passed. Reinstating bitters, occasional use of topical tea tree (Melaleuca alternifolia) oil in jojoba (Simmondsia chinensis) oil, and stress reduction were sufficient to control these episodes. After 4 years of this treatment, the patient would often go for months with no lesions, and acute outbreaks would consist of no more than 4–5 lesions on his back and face. Vitamin B12 has been reported to exacerbate acne in some cases, but this

patient was vitamin B12-deficient and, clearly, the vitamin was indicated (and it did not exacerbate his acne). This is an instance that illustrates the value of individualized medicine.^[80]

CONCLUSIONS

Many plants seem to have inhibitory effects on the growth of bacteria, fungi and viruses in vitro. Also, some plants have been shown to have anti-inflammatory and anti-fat properties. However, there are a few clinical evidences about the effectiveness and safety of these plants in the treatment of acne and other skin infections. For this reason, chemical drugs seem to still be the first choice in the treatment of acne and skin infections. However, the efficacy and safety of synthetic drugs are under question in the treatment of acne and other skin infections. Some plants reviewed in this paper have shown promising results. Hence, they might possibly be used alone or as adjuvant with other therapeutic measures or in mild to moderate situations. Possible contact sensitization especially in topical or oral use should be considered. Some plants, especially the roots of mountain grapes, tea tree oil, Saccharomyces, and perhaps Ocimum basilicum due to their effectiveness and safety can be compared to alternative treatments with synthetic drugs for mild to moderate acne. Further clinical studies validated with controls are required to use plants particularly the three species of eucalyptus (E. globulus, E. maculata, E. viminalis), G. glabra, U. barbata, L. minor, green tea, mountain grape root (M. aquifolium) and gluconolactone of S. bulderi, and guggulipid to treat acne. Efficacy and clinical safety trials of H. perforatum, C. sativum, B. serrata, U. barbata, R. officinalis and green tea are also essential in bacterial skin infections. Mechanism of action of these plants is another important subject, which should be addressed. Phenolic compounds derived from plants have been shown to possess antibacterial activity. Most of the presented plants in this review article possess these compounds. However, in most cases it is not known how much these compounds are responsible for their anti-acne activity. It should be noted that a lot of other plants have phenolic compounds. Hence, if these compounds are solely responsible for the observed anti-acne activities, all plants with phenolic compounds should have anti-acne properties, which worth examining.

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