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Review

A review of phytotherapy of *Acne vulgaris*

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Abstract

Acne vulgaris (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. This disease remains a common condition in industrialized societies, with many mainstream treatment options available. There are many acne products on the market, and making an appropriate selection can be daunting.

Common therapies that are used for the treatment of acne include topical, systemic, hormonal, herbal and combination therapy. Topically used agents are benzoyl peroxide, antibiotics and retinoid. Systemically used agents are antibiotics and isotretinoin. However, all such treatments carry risks and none is completely satisfactory. Natural alternatives are gaining greater research support, and have much to offer clinically in this disorder.

This review focuses primarily on herbal treatments for acne that show scientific evidence of clinical efficacy, as well as the more common herbs shown to be useful in the treatment of this dermatologic disorder.

Key words: *Acne vulgaris*, acne treatment, herbal therapy, phytotherapy of acne

Introduction

Acne is a chronic disease of the pilosebaceous follicle that causes polymorph cutaneous lesions, among them comedones, papules, cysts, pustules, and abscesses which, after regression, may leave scars (Ramos-e-Silva and Carneiro, 2009). It is one of the most common skin diseases encountered by community physicians and dermatologists. Acne can present at any age, from neonates to mature adults, but is most prevalent and severe during adolescence, reaching a peak at the age of 14-17 years in females and 16-19 years in males (Lucky, 1998; Williams and Layton, 2006; Rivera, 2008).

The distribution of acne corresponds to the highest density of pilosebaceous units (face, neck, upper chest, shoulders, and back). Acne classification, scarring, acne rosacea, chloracne, acne associated with polycystic ovary syndrome, infantile acne and acne inversa have been reviewed elsewhere (Jacob et al., 2001; Shalita, 2004; Meixner et al., 2008).

Depending on the appearance different types of acne can be distinguished: *a)*. *blackheads*, which are open comedones, where the top of accumulated sebum in the follicle opening oxidise and appears gray or black; *b)*. *whiteheads*, which are closed comedones, where the follicle opening is clogged with trapped sebum and sealed by normal colored skin; *c)*. *cystic acne*, tender, hard, purplish lumps often larger, and fluid-filled inflammatory swellings deep in the skin; *d)*. *acne scars*, after healing of cystic acne small, depressed pits (acne scars) and pigmentation is left behind; *e)*. *acne rosacea*, features redness (caused by dilatation of small blood vessels); *f)*. *acne pimples*, mainly on the cheeks and forehead, common in women in middle life

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and *g). acne vulgaris*, different kind of pimples and blemishes (papules, pustules, nodules) which are pus-filled and inflamed firm spots below the skin (Shalita, 2004).

However, the term acne in medical circle is correlated to common acne (*Acne vulgaris*). In addition to adolescent acne, drugs are a relatively common cause of eruptions resembling acne. The most common are steroids, androgenic hormones, certain anti-convulsives, anti-tuberculosis drugs, lithium, and others. Exposure to iodides, bromides, and chlorines has also been reported to cause acne (Valeyrie-Allanore et al., 2007). Drug-induced acne or acneiform dermatoses that can have a sudden onset *e.g*. within one day of drug administration can be resolved after the drug is stopped. Acneiform dermatoses have an unusual lesion distribution, such as inflammatory papules and pustules that are small and uniform in size (monomorphic), and can lead to secondary comedones of which the earliest histological event is spongiosis followed by lymphocytic and neutrophilic infiltrates, respectively (Plewig and Jansen, 1998; Momin et al., 2009). Therefore, although the initial causes are different, the pathogenesis of *Acne vulgaris* can be similar.

The pathophysiology of acne is slowly unraveling, and although many factors remain undetermined, a better understanding of the mechanisms involved has led to an improvement in acne management over the last two decades. Four key factors have been identified in the etiology of acne: increased sebum production, follicular hyperkeratinization, colonization of the pilosebaceous unit with *Propionibacterium acnes (P. acnes)* and the production of inflammation (Kurokawa et al., 2009). Sebum hypersecretion in deformed follicles leads to formation of microcomedones, and the follicular hyperproliferation of microcomedones causes inflammation, and comedones in both open and closed types (black and white comedones) appearing in papules, pustules, nodules and cysts. The resulting skin condition with sebum enrichment is prone to the anaerobic growth of *P. acnes*, which is the main causative microorganism in acne. In addition, *Staphylococcus epidermidis* and *Pitryosporum ovale* are present in acne lesions. Proliferation of these microorganisms, mainly *P. acnes*, leads to inflammatory lesions and severe acne (Leyden, 2001; Zaenglein and Thiboutot, 2006; Morelli, 2007).

Common acne treatments

Acne needs to be managed aggressively from the outset using a combination of treatments directed against each of the relevant factors.

Generally, the choice of acne therapy is largely determined by the severity and extent of the disease. According to the type and severity, acne is often graded on a scale from mild-to-moderate inflammation, featuring predominantly comedones, erythematous papules to papulo-pustules, to moderate-to-severe papulo-nodular, nodulo-cystic and scarring inflammatory states (Olutunmbi et al., 2008). However, defining optimum treatment strategies remains difficult as significant variability exists between individuals, both in terms of clinical presentation (disease duration, predisposition to scarring and post inflammatory hyperpigmentation) and response to previous treatments.

In approximately 60% of cases, acne is a self-limiting condition that can be managed with combination treatment followed by topical maintenance therapy (Thiboutot et al., 2009). In other cases, acne follows a chronic course that requires treatment for a prolonged period. Even mild acne can persist for 4-6 years, and in severe cases, the natural history could be in excess of 12 years (Gollnick et al., 2008). The reason as to why acne becomes chronic in some patients is not well understood, and predicting which patients will have persistent and/or refractory acne is very difficult. Factors that link to poor prognosis include early onset, hyperseborrhea, truncal acne and scarring (Dreno et al., 2006). A logical understanding of the pathophysiology of acne and the impact of therapies on these etiological factors should form the foundation of any treatment selection.

For mild and moderate acne, over-the-counter (OTC) and prescription medications may be the only treatment required. The most frequently used topic substances in acne treatment are retinoids, benzoyl peroxide, antibiotics, antiseborrheic medications, salicylic acid, alpha hydroxy acid, azelaic acid, nicotinamide, and keratolytic soaps (Gollnick and Krautheim, 2003; Ramos-e-Silva and Carneiro, 2009). Oral medications are used in severe cases, when an inflammatory component is present and in topical resistant cases. The most frequently prescribed are antibiotics, isotretinoin, and hormones. In very severe inflammatory cases it may be necessary to use systemic corticoids. Systemic treatment can be used even in mild cases, if there is intolerance to the topical treatment or where topical therapy has failed. Basic topical and systemic protocols may include several therapies, used according to the severity of each case (Auffret, 2000; Usatine and Quan, 2000; Bershad, 2001; Oberemok and Shalita, 2002).

However, these drugs produce a number of potential side effects and development of resistance to frequently used antibiotics. This leads to treatment failure with previously used successful therapy. Therefore, an alternative for the treatment of acne have been studied and developed and as a result natural approaches to combating acne and its disfiguring effects have gained popularity. Numbers of conventional and novel herbal cosmetics are useful to treat damaged skin (Amit et al., 2007; Ashawat et al., 2007; Chanchal and Swarnlata, 2008).

Acne can be cured by herbs either consuming internally or externally or with both. Topical herbal treatment is preferable choice of consumers as ease of application and it surpasses the bitter taste of herbal formulation (when taken internally). Because herbs are safe, efficacious and the added advantage of multi functionality, herbs are increasingly being used in mainstream cosmetic

products, including acne-fighting compositions (Aburjai and Natsheh, 2003; Chanchal and Swarnlata, 2008; Kumar et al., 2008). Although some of the herbs are scientifically explored for their efficacy in treatment of acne but still many herbs are remain untouched by scientist.

This review focuses on the benefits of some herbs for the treatment of *Acne vulgaris.* The purpose of this study is to open new avenues and set trends for the improvement of medicinal uses of herbs for acne treatment and also reflects the traditional knowledge which provides the base for clinical research to be carried out to explore the active compounds which are responsible for anti-acne activities.

Herbal therapy of acne

The quest for medications and cosmetic measures to combat acne continues to be a major research and development initiative in the pharmaceutical and cosmetic industries. Number of herbs with a history of use in traditional cultures has entered in the growing cosmetic market.

Herbal formulations which contain many herbal extracts and have negligible adverse effects compared with modern medicines are commonly indicated for moderate and severe forms of acne. The efficacy of these agents in acne treatment is not only based on antimicrobial activity but also on their possessed antioxidant and anti-inflammatory properties by which they inhibit neutrophile migration and generation of reactive oxygen species. Also, various herbs are used in acne due to their skin detoxification property. Herbal extracts or oils may be used as monotherapy or in combination therapy. Till now, there are certain herbal extracts such as ***Angelica dahurica,*** *Melaleuca alternifolia, Azadirachta indica*, *Rhizoma coptidis* and *Psidium guajava,* that are proved to be more effective that antibiotics and retinoids in acne therapy (Kumar et al., 2008). Below some herbs are discussed in details for their potential efficacy in acne treatment.

Arctium lappa (Great burdock)

Burdock root extract has strong antibacterial and estrogenic effect and therefore it is used for treatment of different skin conditions like eczema, psoriasis, and acne.

The root of the burdock plant has been used in its native haunts, which include much of Africa and Europe, to improve immunity and overall health for at least 3,000 years. Like the honeybee, it has followed civilization. The plant produces a burr that gets stuck on people's clothing, and in this manner it has been carried to every continent. In recent years, the burdock has come to be considered a weed, despised by lawn owners for its tenacious growth habits.

The plant is a biennial, meaning that in its second year it blooms and then dies. Burdock spends its first year of life working industriously to store all the necessary elements to bloom the following year. The root is considered to be the most important part of the plant. It is usually plucked from the ground in the autumn of the plant's first year just as leafs started to fall.

The root contains lignans including arctigenin, glyco-

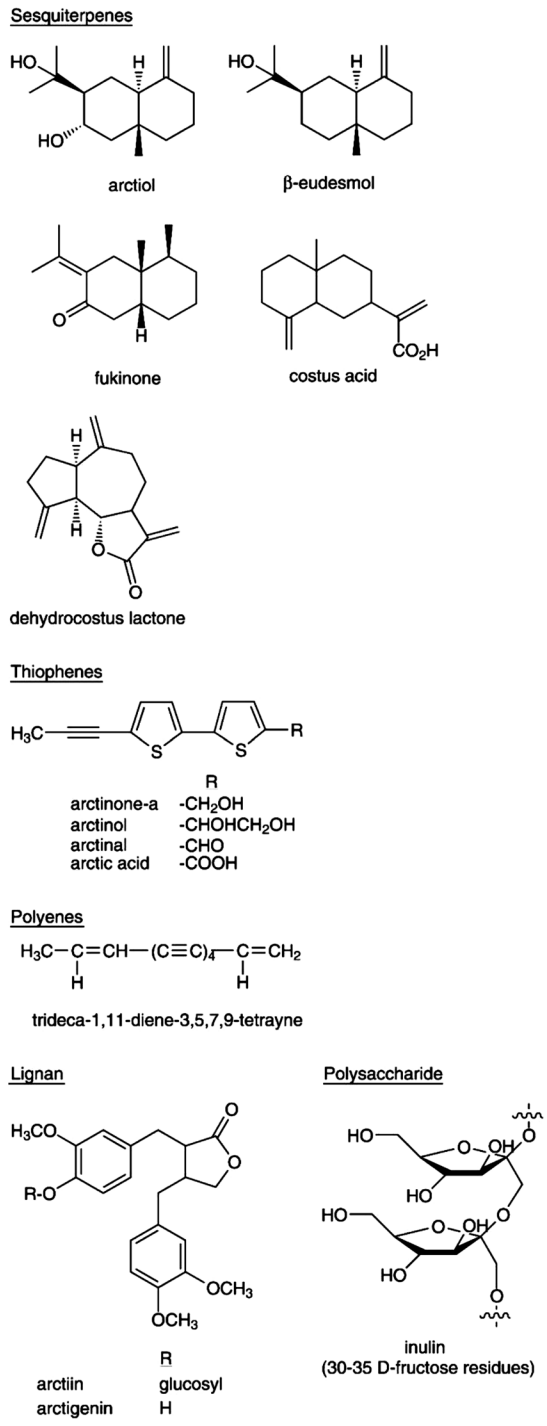


Fig. 1. Main constituents of *Arctium lappa* (Great burdock) (http://www.medicinescomplete.com/mc/herbals/current/images/HrbburdockC001_default.png).

side arctiin, and matairesinol, polyacetylenes including tridecadienetetraynes, tridecatrienetriynes, and a sulfur containing arctic acid (Fig. 1) (Park et al., 2007). It also contains amino acids including alpha guanidino-n-butyric acid, inulin, organic acids, fatty acids, and phenolic acids (Wang and Yang, 1993; (Community herbal monograph on *A. lappa, radix*, EMA/HMPC/246763/2009 Corr.1).

In general, burdock has the ability to gently stimulate health and, as a consequence, to improve the appearance of the skin. Elements contained in the plant improve the digestion and absorption of food, which makes the body stronger and better able to fight with infections. Furthermore, one of main attributes of burdock is its detoxification ability. The elimination of toxic substances *via* the urine is also aided by the burdock due to its mild diuretic property. Beyond its general health-stimulating abilities and like many other members of the daisy family, chamomile, elecampane, and calendula included, burdock is also considered to be one of the best tonic correctives of skin disorders. Burdock is a classic remedy for skin conditions which result with dry, scaly skin and cutaneous eruptions, eczema, psoriasis, dermatitis, boils, carbuncles, sties and chronic acne. Whereas calendula is only used externally to improve the skin's appearance, burdock has been recommended for internal (burdock tea, tincture, fluid extract, capsules) and external use (ointment, mask) in skin disorders.

Biological activities and pharmacological functions reported for burdock include anti-inflammatory, anticancer, antidiabetic, diuretic, antimicrobial, antiviral and free radical scavenging activities (EMA, HMPC, 2009). The Committee for herbal medicinal products from European Medicines Agency (EMA) besides use as an adjuvant in minor urinary tract complaints and for improvement of appetite, recommended root from this plant for treatment of seborrhoeic skin conditions (Community herbal monograph on *A. lappa, radix*, EMA/HMPC/246763/2009 Corr.1).

Its antibacterial (Pereira et al., 2005; Gentil et al., 2006), anti-inflammatory (Lin et al., 1996; Zhao et al., 2009) and antioxidant properties are particularly beneficial in acne treatment. Studies have shown that burdock root is able to inhibit the growth of the acne causing *P. acnes* bacteria which is found naturally in sebum. Also, burdock is rich with essential fatty acids, which contribute in regenerative processes in the skin. Burdock root is also able to regulate the function of the sebaceous glands, which are responsible for sebum production; the natural oil which builds inside clogged pores to create acne blemishes. On the other hand, in traditional Chinese medicine acne or eczema are seen as symptoms of system intoxication. Therefore, burdock and its clinically proven ability to act as a diuretic could effectively resolve problems affecting the skin.

Oenothera biennis (Evening primrose)

Evening primrose oil (EPO) made from the seeds of *O. biennis* is a fixed oil extremely rich in essential fatty acids playing an important role in prostaglandin synthesis of human body. Prostaglandins help to regulate the action of several hormones like estrogens and have anti-inflammatory action. EPO has been used for a wide range of skin conditions such as eczema, psoriasis, and acne. It is also used as a dietary source of essential fatty acids and in the production of soaps and cosmetic ingredients. EPO has demonstrated significant effect in treatment of other diseases like asthma, rheumatoid arthritis, breast problems and metabolic disorders (Bayle and Usatine, 2009; Coffey, 1993; Hederos and Berg, 1996; Horrobin, 2000; Williams, 2003; Worm and Henz, 2000).

O. biennis is a member of evening primrose family (Onagraceae). It is found in fields, roadsides, prairies and waste places in the United States and south Canada, but it is widely naturalized elsewhere in temperate and subtropical regions. *O. biennis* is a biennial with large yellow flowers. In its first year, it forms a rosette of basal leaves. A tall flowering stem is formed in the second year. Plants produce one or two new flowers every evening.

Although the entire plant is edible, the flowers are added in salads, leaves eaten like greens, and the roots boiled like potatoes, it is primarily a minor oilseed crop used to produce the EPO. Seeds from *O. biennis* contain 14% of EPO which usually contains 50 - 70% *cis*-linoleic acid (LA) and 7-10% *cis*-gamma-linolenic acid (GLA) (Fig. 2). Wild varieties of *O. biennis* contain highly variable amounts of LA and GLA. However, extensive crossbreeding has produced a commercial variety that consistently yields oil with 72% LA and 9% GLA. Also found are *cis*-6,9,12-octadecatrienoic acid, small amounts of oleic, palmitic, and stearic acids and steroids (campesterol, and beta-sitosterol). Mucilage and tannin in the plant parts have been also analyzed (http://www.drugs.com/npp/evening-primrose-oil.html).

GLA is essential for healthy skin functioning and is produced in human body from LA. Metabolites formed from GLA improve cellular membrane function and restore the skin lipid barrier, leaving it more hydrated, moisturized and protected from injury or stress. Because of its ability to dilute sebum production, EPO is effective at calming acne flare-ups, hydrating the skin at the same time. The use of EPO for acne treatment has become an all-natural alternative for those suffering from this skin condition. The use of EPO for acne treatment can be accomplished both externally (pure oil, creams, lotions) and internally (soft gelatin capsules) (http://www.cancer.org/docroot/ETO/content/ETO_5_3X_Evening_Primrose.asp?sitearea=ETO; http://www.herbs2000.com/herbs/herbs_evening_primrose.html).

There are also evidences that EPO may benefit patients with eczema (Bayle and Usatine, 2009; Coffey, 1993; Hederos and Berg, 1996; Horrobin, 2000; Williams, 2003; Worm and Henz, 2000). An improvement in clinical condition of children's atopic eczema was observed after four weeks of oral treatment with EPO (Biagi et al.,

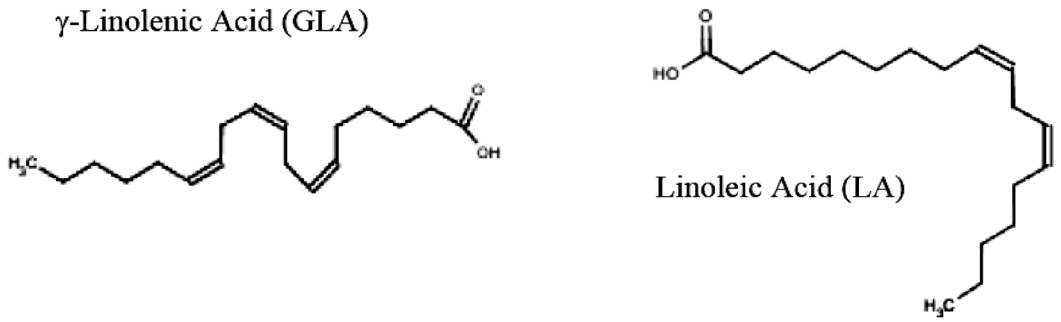


Fig. 2. Major constituents of evening primrose oil.

1988). Other workers have reported that EPO oral supplementation could significantly improve skin problems in patients undergoing hemodialysis mainly due to the assumption that abnormalities in plasma composition of essential fatty acids may be associated with the etiology of uremic skin symptoms, like dryness, pruritus and erythema. After six weeks of therapy with EPO, significant increase in plasma dihomo-gamma-linolenic acid, a precursor of anti-inflammatory prostaglandin E1 was observed, suggesting that oral supplementation with EPO could restore deranged plasma essential fatty acids and ameliorate skin symptoms (Yoshimoto-Furuie et al., 1999). Other workers have reported that the EPO therapeutic effect in atopic dermatitis patients with dry scaly skin lesions was associated with the normalization of serum gamma-interferon levels (Yoon et al., 2002).

Topical treatment with EPO was also beneficial in treatment of atopic dermatitis. A meta-analysis of randomized, placebo-controlled clinical trials of Efamol® (pure evening primrose oil) in atopic eczema have shown that the oil has a simultaneous, beneficial effect on itch/pruritis, crusting, edema and redness (erythema) that becomes apparent between 4 and 8 weeks after treatment was initiated (Morse and Clough, 2006). It is also important to notice that the use of EPO for management of atopic dermatitis is considered as safe and effective (Sanapati et al., 2008).

EPO has been also studied for its ability to calm and reduce inflammation due to the fact that in the human body GLA is converted to powerful prostaglandins that have potent anti-inflammatory and anti-irritant activities, protecting the skin from the damaging effects of UV radiation that lead to inflammatory skin conditions as well as skin aging. Studies on immunomodulatory and antiinflamatory activities showed that EPO proved useful effects in old age when delta-6-desaturation (delta-6-desaturate acts in the metabolism of linoleic and alpha-linolenic acid) activity decreases (Biagi et al., 1988; Charnock, 2000). Animal studies have shown that EPO stimulates COX-1 expression in some tissues (Fang et al., 1997), reduced platelet hyperaggregabilty in rabbits fed an atherogenic diet (De La Cruz et al., 1997) and GLA modulate the level of serum interferon-gamma, monocyte chemotactic protein-1 and tumor necrosis factor-alfa which may be a worthwhile line of treatment in certain human diseases (Dirks et. al., 1998; Ismail et al., 2008). Also, experiments were performed to see the effect of *O. biennis* oil on antioxidant potential, given with hyperlipemic diet to New Zealand rabbits. It was observed that glutathione peroxidase activity reduced and the activities of glutathione reductase and transferase increased (De La Cruz et al., 1999). Also, EPO has shown antimicrobial activity against *Staphylococcus aureus* (Borchardt et al., 2009).

Viola tricolor (Heartsease)

Heartsease is a small plant of creeping and ramping habit, reaching at most 15 cm in height, with flowers about 1.5 cm in diameter. It grows in short grassland on farms and wasteland, chiefly on acid or neutral soils. It is usually found in partial shade. It flowers from April to September. The flowers can be purple, blue, yellow or white. They are hermaphrodite and self-fertile, pollinated by bees.

Viola tricolor herba cum flore contain different classes of secondary metabolites such as:

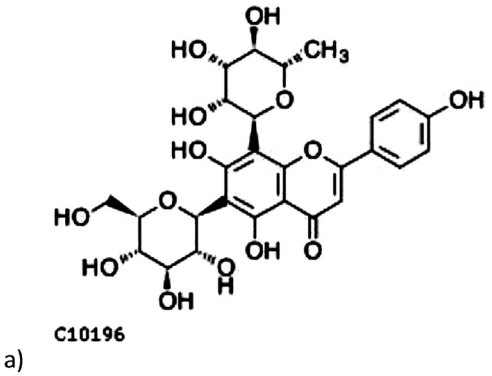
- Flavonoids. The quantity of flavonoids in the herb *Viola tricolor* and *Viola arvensis* was found to be 2.1% and 1.3%, respectively. The main flavonoids of *Viola tricolor* are violanthin and rutin (quercetin 3-rutinoside) (Fig. 3), together with quercetin, luteolin and luteolin 7-glucoside. Other flavonoids: apigenin mono-C-glucosides: vitexin and isovitexin (saponaretin), luteolin mono-C-glucosides: orientin and isoorientin, and scoparin (3'-O-methylluteolin 8-Cglucoside), and few other O- or C-glycosides (Assessment report on *Viola*, EMA/HMPC/131735/2009).
- Sixteen flavonoid glycosides have been separated from the methanol extract of wild pansy by microliquid chromatography: four flavonol O-glycosides of kaempferol, quercetin, and isorhamnetin; nine flavone C-glycosides of luteolin, chrysoeriol and apigenin, and three flavone C, O-glycosides of apigenin (Toiu et al., 2007; Vukics et al. 2008a; Vukics et al. 2008b; Vukics, 2009).

- Polysaccharides. The mucilage content in wild pansy herb is about 10%. Hydrolysis of polysaccharides results in glucose (35.1%), galactose (33.3%), arabinose (18.1%), rhamnose (8.4%), uronic acid (6.2%) and xylose (5.1%) residues (Assessment report on *Viola*, EMA/HMPC/131735/2009). The water soluble fraction of polysaccharides is composed of glucose, galactose and arabinose residues (2:1.8:1.1) and galacturonic acid, rhamnose and xylose. The pectin fraction contains galacturonic acid, glucose, and galactose (Assessment report on *Viola*, EMA/HMPC/131735/2009). According to Deters, the polysaccharides of wild pansy are mainly composed of galactose, glucose, galacturonic acid (34:29:27), whereas arabinose, rhamnose and mannose are minor components (7:2:1) (Deters et al., 2005).
- Phenolic acids. The content is about 0.18%, including *trans*-caffeic, *p*-coumaric, gentisic, protocatechuic, phydroxybenzoic, *p*-hydroxyphenylacetic, and vanillic acids, and 0.06% to about 0.3% salicylic acid and its derivatives, such as methyl salicylate and violutoside (violutin, glucosidoarabinoside of methyl salicylate), and monotropitoside (primveroside of methyl salicylate) (Assessment report on *Viola*, EMA/HMPC/131735/2009).
- Volatile oil. The content is reported with 0.0086%, containing methyl salicylate as a principal constituent (Assessment report on *Viola*, EMA/HMPC/131735/2009).
- Carotenoids. In wild pansy flowers occurs *cis*-violaxanthin (Szabolcs and Toth, 1970). Yellow blossoms yield carotenoids (9.69 mg/g dry weight), mainly 9-cis-violaxanthin (51.3%), all-*trans*-violaxanthin (29.6%), 13-*cis*-violaxanthin (1.7%), 15-*cis*-violaxanthin (0.6%), antherexanthin.
- Anthocyanins. Main pigment which is responsible for the violet colour of flowers of *Viola tricolor* is composed essentially of violanin (ca 33%), a derivative of delphinidin with D-glucose, L-rhamnose, p-coumaric acid, and 2.7 to 4% of potassium (Assessment report on *Viola*, EMA/HMPC/131735/2009).
- Cyclotides (macrocyclic peptides) and other constituents (Assessment report on *Viola*, EMA/HMPC/131735/2009).

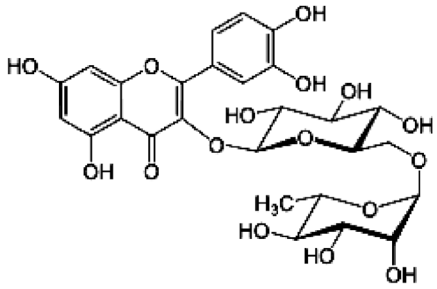
The traditional use of heartsease goes back to ancient times. Heartsease preparations were used during the Middle Ages mainly as a remedy for various skin ailments and were mentioned according to Madaus (1938) by Lonicerus 1564; Hieronimus Bock 1565, Matthiolus (1501-1577) and Andreas Caesalpinus (died 1602). Its therapeutic activity is presented in Madaus "Lehrbuch der Biologischen

Heilmittel" (1938) and Jaretzky's "Pharmakognosie" (1937). The traditional use of heartsease in different diseases has been thoroughly documented in several handbooks and in folk tradition (Allen and Hatfield, 2004; Assessment report on *Viola*, EMA/HMPC/131735/2009). Laboratory experiments have confirmed that *Viola* extract exerts antimicrobial activity against gram positive and gram negative bacteria as have anti-inflammatory and other beneficial effects.

Antioxidant activity. Mantle et al. (2000) compared relative antioxidant activities of different British medicinal plants, *Viola tricolor* L. included. Antioxidative activity of the plants was tested through competitive scavenging of the ABTS (2,2`azinobis-(3-ethylbenzthiazoline-6-sulfonic acid)), presented in terms of mM Trolox equivalent – mM TE) or O_2 radicals (estimated as superoxide dismutase – SOD activity) *in vitro*. Antioxidant activity (mM TE/g dry weight) of fresh tissue *Viola tricolor* leaf was 1.46±0.32, whereas for flowers was 1.43±0.26. This activity was quite potent, as comparable extracts of *Ginkgo biloba* gave values of 0.62 and 0.61 mM TE/g dry weight, respectively (Vukics et al., 2008b). Therefore, authors concluded that heartsease, especially its flower, is a promising source of natural antioxidants. In addition, a significant correlation was found between the flavonoid content and antioxidant activity.



a)



b)

Fig. 3. Main flavonoids in *Viola tricolor herba cum flore* a) Violanthin, b) Rutin.

Antibacterial activity. The infusion, decoction and ethanol extract of *Viola tricolor* herb displayed significant inhibitory activity against *Staphylococcus aureus, Bacillus cereus, Staphylococcus epidermidis* and *Candida albicans* and moderate activity against *Pseudomonas aeruginosa, Enterococcus faecalis, Escherichia coli* and *Klebsiella pneumoniae*. The dichloromethane, ethyl acetate and methanolic fractions obtained by partitioning of Soxhlet of dried plant material, showed the lower activity. The higher activity of the extracts containing complexes of components of the plant, relative to that of the fractions comprising compounds of different polarity, suggested a synergism in antibacterial action between compounds of heartsease (Witkowska-Banaszczak et al., 2005).

Anti-inflammatory activity. The anti-inflammatory activity of the tincture from *Viola tricolor* aerial parts was tested in acute inflammation induced with oil of turpentine (i.m. 0.6 ml/100 g b.w.) in male Wistar rats. The results were compared with those from a positive control group with experimental inflammation and with those of a group treated with diclofenac (30 mg/100 g b.w.). *Viola tricolor* extract (50 mg tincture/100 g b.w.) significantly reduced polymorphonuclear leukocytes and monocytes percentages and the activation of circulating phagocytes (Toiu et al., 2007).

Experimental preclinical data confirmed antioxidant, antibacterial and anti-inflammatory activity of heartsease in different skin conditions. Results from *in vitro* antimicrobial activity of *Viola tricolor* extracts support the traditional use of heartsease even though the effects are relatively weak compared to standard antibiotics.

None clinical studies were published on mono-preparations of heartsease. Randomized, double-blind, vehicle controlled study of an ointment composed of *Mahonia aquifolium, Viola tricolor* and *Centella asiatica* was performed on 88 patients between 18-65 years of age with mild to moderate atopic dermatitis. They were treated for 4 weeks with an ointment containing *Mahonia aquifolium, Viola tricolor* and *Centella asiatica* alcohol extracts (5g of each /100 g of ointment). After 4 weeks of topical treatment the primary (erythema, oedema/papulation, oozing/crust, excoriation and lichenification) and secondary (pruritus, global assessment of effectiveness and tolerability) endpoints were evaluated. No significant differences were observed between ointment containing *Mahonia aquifolium, Viola tricolor* and *Centella asiatica* alcohol extracts and the base. However, a sub-analysis indicated that the formulation might be useful under conditions of cold and dry weather (Klövekorn et al., 2007).

According to European community herbal monograph, indication for traditional use of *herba cum flore* of *Viola tricolor, V. arvensis* and *V. vulgaris* is for symptomatic treatment of mild seborrhoeic skin conditions (Community herbal monograph on *Viola tricolor, herba cum flore*, EMA/HMPC/131734/2009).

Vitex agnus castus (Chaste tree)

Vitex agnus castus (Verbernaceae) commonly known as chaste tree, chaste berry, or monk's pepper is a native of the Mediterranean region. It is a small deciduous tree that grows in Asia, Europe and North America. It bears slender spikes of violet blue, 8-10 cm flowers. Locally, the plant is used as insect repellent and insecticide. A wide range of medicinal applications are also shown by other plants of this family as berries are considered as tonic supplement for male and female reproductive system.

No single constituent has been identified as being the active one, in fact, with the exception of agnoside, all constituents are found in other plants. The total sum of constituents appears to generate a synergistic effect.

- Flavonoids: castican, orientin, isovitexin, vitexin.
- Iridoid glycosides: agnuside (the reference constituent for standardization), aucubin.
- Volatile oil (0.8-1.6%): terpenoids (cineole, sabinene, limonene, camphene), α- and β-pinene.
- 3-Ketostaroids: *Vitex* has been found to contain 3-ketosteroids (probably progesterone and 17-α-hydroxyprogesterone) by thin-layer chromatography (Russo and Galletti, 1996).

The flowers and leaves may also possibly contain progesterone, 17-hydroxyprogesterone, testosterone, and epitestosterone although further research is needed. Other constituents in the flowering tops include flavonoids (particularly C-glycosides), and iridoids (aucubin, agnuside, eurostoside), 3-ketosteroids, essential oils (0.8-1.6%): *o*-cymol, β-famescene, *a*- and β-pinene, cineol, sabinene, limonene (Fig. 4) (Russo and Galletti, 1996).

Very often, acne flare-ups are related to the impending onset of menstruation. This particular type of acne highlights the fact that acne is often affected by hormone balance in the body. Much work has focused on the potential negative impact of androgenic hormones on acne; estrogen and progesterone can definitely also be involved. *Vitex* and *Serenoa repens* (saw palmetto) are most commonly used herbs for addressing hormonal issues that arise in acne. Studies have shown that the whole fruit extract of *Vitex* increases progesterone levels and decreases estrogen levels by acting upon follicle-stimulating hormone and luteinizing hormone levels in the pituitary gland, and decreases exceedingly high premenstrual prolactin levels *via* dopaminergic mechanisms (Bone, 1994). This may explain the benefit of *Vitex* in improving hormonal acne conditions.

In one placebo controlled trial of males and females, after 3 months of treatment with *Vitex*, both groups experienced a 70% improvement in their acne. This was significantly better than the placebo. However, it should be noted that if *Vitex* is given to patient who does not have a relative progesterone deficiency, acne condition could be worse, and in fact may be initiated by *Vitex* use (Gardiner, 2000).

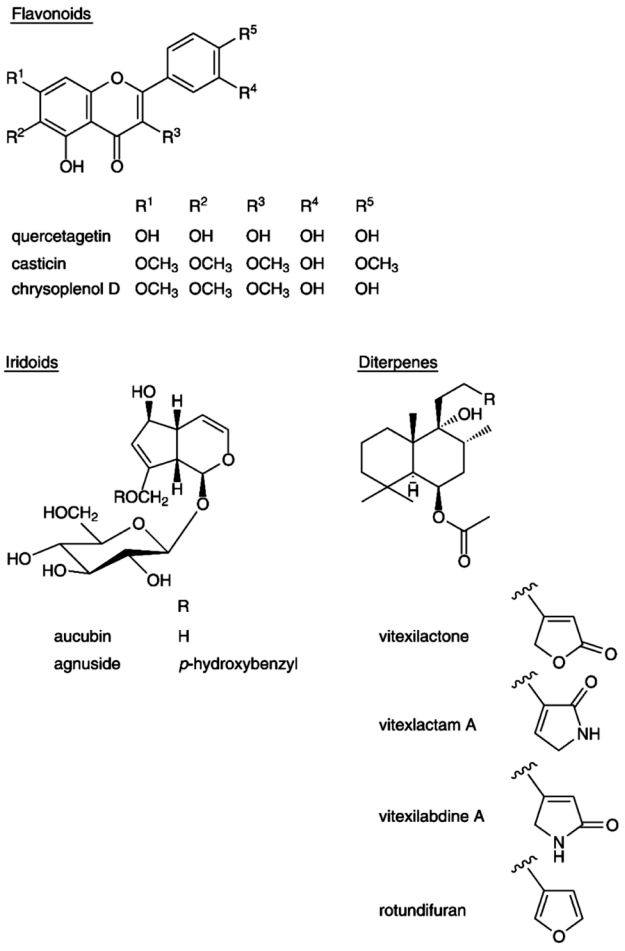


Fig. 4. Main constituents of *V. agnus castus.* (http://www.medicinescomplete.com/mc/herbals/current/images/Hrbagnus_castusC001_default.png)

Preliminary German research also confirmed that chaste tree can be effective in moderate hormonal acne. For optimal anti-acne effects, chaste tree should be taken throughout the menstrual cycle. *Vitex* is often used together with vitamin B6, which has also proven to be quite helpful for resolving hormonal acne, although one comparative trial found that *Vitex* was superior to vitamin B6 for helping patients with symptoms of premenstrual syndrome (Yamell and Abascal, 2006).

As it was mentioned previously, conditions such as acne and seborrhoea (excessive secretion of sebum) result from the action of androgens on the skin. The severities of these effects are dependent upon androgen production by the ovary or adrenal gland and the bioavailability of androgen to peripheral tissues. This in turn is related to transport of plasma androgens by specific binding proteins and to peripheral metabolism of testosterone and androstenedione to the more potent dihydrotestosterone (DHT) (Reed and Frans, 1988). An effective anti-androgen is one which blocks the androgen receptor-mediated actions of testosterone and DHT on skin. Although no actual clinical data are available, *Serenoa repens* (saw palmetto) extract is believed to be beneficial for topical use in anti-acne formulations. *In vitro* studies have shown that saw palmetto extract could inhibit both isoforms of the 5-alpha-reductase (enzyme that catalyze the conversion of testosterone to DHT), as well as binding of testosterone or DHT to androgen receptor (Bayne et al., 2000).

Other well-documented anti-androgenic herb is *Glycyrrhiza glabra* (licorice), although it also has not been studied for acne in clinical trials. Other hormone-balancing herbs may have a role in *Acne vulgaris*, including but not limited to, *Medicago sativa* (alfalfa), *Chamaelirium luteum* (false unicorn root), *Verbena* spp. (vervain), and *Mitchella repens* (partridge berry) (Yarnell and Abascal, 2006).

Among hormone-like effects in treatment of acne, the antibacterial activity of extracts of *Vitex* was tested against clinical isolates and drug resistant bacterial strains. The minimum inhibitory concentrations (MICs) of the extracts ranged between 0.312 and 5 mg/ml. Among all the extracts, the ethyl acetate was found to be most active against all the tested bacterial species (Methicillin resistant *Staphylococcus aureus* (0.312 mg/ml), carbapenem resistant *Acetobacter baumannii* (0.625 mg/ml), ciprofloxacin resistant *E.coli* (0.625 mg/ml), *Proteus vulgaris* (2.5 mg/ml), *Salmonella typhi* (5 mg/ml), *Escherichia coli* (2.5 mg/ml), *Enterococcus durans* (0.625 mg/ml) and *Pseudomonas aeruginosa* (2.5 mg/ml)). Compare to standard streptomycin ethyl acetate extract showed good activity against all the three tested drug resistant bacteria. The present study indicates that the plant contains potential anti-bacterial components such as flavonoids, terpenoids and steroids that may be of use for development of phytomedicine for the therapy of tested bacterial diseases. The results of this study demonstrated that, ethyl acetate extract from the leaves of *Vitex agnus-castus* showed dominant antibacterial activity against potent clinical pathogens (Arokiyaraj et al., 2009). Research studies also confirmed the antifungal activity of seeds of *Vitex negundo* (Sathiamoorthy et al., 2007; Shaukat et al., 2009) and antioxidant and anti-inflammatory activities of methanol extract of the plant standardized on the content of flavonoids (Kulkarni et al., 2008), which effects could be also beneficial in treatment of various skin diseases.

Hamamelis virginiana (Witch hazel)

Hamamelis virginiana L. is a winter-flowering shrub, commonly known as witch hazel that is native from Nova Scotia, Canada to Texas and Florida in the U.S. It is best known for its decorative and fragrant yellow flowers and its bright yellow fall foliage.

Native Americans first learned how to use witch hazel for medicinal purposes when they used the extract to relieve bleeding, swelling, bruising and discomfort of external wounds. Hamamelis virginiana was also used in sweat

lodges to soothe sore muscles. Native Americans also considered it as an astringent and purifier and a remedy for treating tumors. Throughout American history, uses for witch hazel have included treating insect bites and stings, rashes, hemorrhoids, sores, diarrhea and dysentery. Today, the external use of witch hazel is well known for the astringency associated with the tannin content of its leaves and bark.

The main characteristic constituent of *Hamamelis virginiana* is hamamelitannin (Fig. 5), a mixture of the α- and β- forms of (2´, 5-di-O-galloyl-hamamelose), its molecular structure bears two gallate moieties and a sugar unit, hamamelose (Tourino et al., 2008). Wang et al. (2003) developed an HPLC method for the determination of hamamelitannin, catechins, and gallic acid from witch hazel bark, twig and leaf. The concentrations in the bark for hamamelitannin, gallic acid, (+)-gallocatechin, and (+)-catechin were 4.77, 0.59, 0.22, and 0.39% (*w/w*), respectively. Hamamelitannin and catechins were also detected in the leaves at concentrations of < 0.04% (*w/w*).

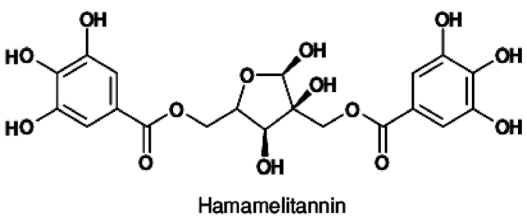


Fig. 5. Main tannin of *Hamamelis virginiana* bark.

According to Vennat et al. (1992), proanthocyanidins, phenolic acids and flavonoids have been identified in leaf extracts. Hydroxycinnamic acids and flavonoids (e. g. myricetin, leucodelphinidin, quercetin, kaempferol, and gallic acid) are found mainly in the leaves of *Hamamelis virginiana.* Phenolic compounds from leaves of *Hamamelis virginiana* were studied by Sagareishvili et al. (1999), where kaempferol, quercetin, trifolin, kaempferol 3-O-β-D-glucuronide, quercetin 3-O-β-D-glucuronide were isolated.

According to Engel et al. (1998), the composition of the volatile fraction obtained by water distillation from the leaves and bark of *Hamamelis virginiana*, and determined in detail by GC-MS, consists in about 175 (leaves) and 168 (bark) identified compounds or at least partly characterized on the basis of a computerized database (SeKoMS). The dominating substances were represented by a homologous series of alkanes, alkenes, aliphatic alcohols, related aldehydes, ketones, and fatty acid esters. Significant differences in the terpenoid and phenylpropanoid patterns of the products obtained from the bark and leaves are apparent: whereas the product of bark distillation was found to typically contain phenylpropanoids and mainly sesquiterpenoids, that obtained from the leaves included some distinct monoterpenoids detected in comparably higher amounts. The chemical composition of the volatiles, when taken together with the absence of specific accumulation sites of lipophilics, emphasizes the definition "volatile fraction" rather than essential oil (Assessment report on *Hamamelis virginiana*, 2009).

Extracts from witch hazel bark have long been used in therapy of skin diseases and in cosmetic formulas (skin lotions, nourishing creams, pre- and after-shaves, etc.). When applied topically, witch hazel could significantly reduce bacteria grow, thus preventing inflammation and acne formation. Also, the tannin content in witch hazel has strong astringent as well as antioxidant properties. These astringent properties are cleansing to the skin, while minimizing the size of skin pores. Unlike many harsh commercial acne formulations, it is gentle, non-irritant and non-drying when used to tone and cleanse acne-infected or acne-prone skin. Furthermore, it helps to prevent any further infection from occurring. The tannins in witch hazel tighten pores and swollen veins, as well as reduce inflammation. The anti-inflammatory properties are further increased by the flavonoids and procyanadins, as well as resin, in the witch hazel plant.

Many acne treatments can irritate the skin, causing soreness, inflammation and dryness. Witch hazel, being a natural product, is well suited for skin care, because it does not disrupt the pH of the skin, which tends to cause irritation (Assessment report on *Hamamelis virginiana*, 2009).

Hamamelis extracts and isolated chemical constituents have shown anti-inflammatory activity *in vitro* and *in vivo*. It was found that polyphenols isolated from hamamelis stem and twig bark inhibited the synthesis of platelet activating factor in human polymorphonucleocytes (PMNs). Dimeric galloylated proanthocyanidins showed the strongest effects. The synthesis of leukotriene B4 in PMNs was inhibited by the tested substances. Oligomeric proanthocyanidins had stronger activity than hamamelitannin (Hartisch et al., 1997). According to Deters et al. (2001), polysaccharides and proanthocyanidins from hamamelis bark could influence on human skin keratinocyte proliferation and differentiation of cultured human keratinocytes, and influence on irritated skin. While the polysaccharide fraction, consisting mainly of arabinans and arabinogalactans, did not have effect human keratinocytes, the proanthocyanidins strongly increased the proliferation of the cells, while the differentiation was not influenced significantly. Within a preliminary cumulative *in vivo* study on SLS-irritated skin, proanthocyanidins were proven to reduce transepidermal water loss and erythema formation. Furthermore, a clinical scoring indicated that procyanidins can influence irritation processes significantly.

An aqueous ethanolic extract of hamamelis bark (ethanol 70%) showed a significant anti-inflammatory effect (43% inhibition of oedema; $p<0.05$) in the croton oil ear oedema test in mice when applied topically at 250μg per ear. This effect was shown to be mainly due to proanthocyanidins of molecular weight ≥ 3kDa (69% inhibition at

250μg per ear; $p<0.05$) obtained from this extract subjected to ultrafiltration and identified by TLC, HPLC. Proanthocyanidins also exhibit significant antiviral activity against Herpes simplex virus type 1. In addition, the UV-concentrate displayed radical scavenging properties, inhibited α-glucosidase as well as human leukocyte elastase (HLE). With the exception of the antioxidant potential and the inhibition of HLE-action the lower molecular fraction possessed weaker activities and contained mainly hamamelitannin, catechin, and unidentified constituents (Erdelmeier et al, 1996).

An aqueous extract of the leaves of *Hamamelis* inhibited the growth of *Escherichia coli* (MIC 0.4 mg/ml), *Staphylococcus aureus* (MIC 0.4 mg/ml), *Bacillus subtilis* (MIC 1.1mg/ml) and *Enterococcus faecalis* (MIC 3.0mg/ml). Aqueous extracts of the bark inhibited the growth of *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Enterococcus faecalis* (MIC for all 10.0 mg/ml) (WHO monograph on *Hamamelis*, 2004).

Eucaliptus globulus

Two products from eucalyptus are in medicinal and commercial use, essential oil and dried extract, both obtained from leaves of *Eucaliptus globulus* Labill. (Myrtaceae). There are several hundred species of eucalytpus, most of them native to Australia. Like the Tea Tree, preparations of *Eucalyptus* have been an important part of traditional medicine of Australia's Aboriginal people for thousands of years. Eucalyptus essential oil is primarily produced from the leaves of the Blue Gum Eucalyptus (*Eucalyptus globulus*), although other species of eucalyptus are also used.

The primary component of eucalyptus essential oil is eucalyptol (1.8-cineol). Eucalytpol is a monoterpene molecule and it constitutes up to 90% of eucalyptus essential oil. In pure form, eucalyptol is a clear, colorless liquid that has a strong camphor-like smell. In addition to eucalyptus oil, eucalyptol is found in the essential oil of many other plants, although usually at lower concentrations. Eucalytpol is volatile and flammable and has a lower boiling point than water. It is also toxic to most animals when ingested in high quantities. Secondary components of eucalyptus essential oil are alpha-pinene, limonene, globulol and terpinen-4-ol (the primary component of tea tree oil). Several of these secondary components are known to have antibacterial and anti-inflammatory properties, but most of the activity of eucalyptus oil is attributed to its primary component, eucalyptol. On the other hand, the *Eucalyptus globulus* extract is one of the best-selling products today, manufactured from leaves of Blue Gum Eucalyptus and standardized on 25% of total chlorogenic acid (http://www.herb-extract.com/plant-extract/563839.html).

In traditional medicine, eucalyptus leaves have been used to prepare compresses, poultices, teas, etc. Eucalyptus essential oil and eucalyptol are both used extensively in modern medicine. Eucalyptol is toxic to many types of bacteria and is one of the active ingredients in antibacterial mouthwashes. Eucalyptol also has anti-inflammatory and cough suppressant properties, and is an ingredient in many cough drops. Inhalation of eucalyptol vapors is an effective short term analgesic and decongestant. Eucalyptus oil is a natural insect repellent for pests like mosquitoes (although it attracts certain types of bees).

There is little direct research into the effectiveness of eucalyptus essential oil in the treatment of acne. However, it is certainly possible that eucalyptus essential oil would be helpful in treating acne because of its antibacterial and anti-inflammatory properties (Athikomkulchai et al., 2008; Takahashi et al., 2004). The essential oil of *E. globulus* has a strong antimicrobial activity, especially against *Streptococcus pyogenes*, *Escherichia coli, Candida albicans, Staphylococcus aureus, Acinetobacter baumannii,* and *Klebsiella pneumonia* (Ghalem and Mohamed, 2008; Tabanca et al**.,** 2001).

Essential oils of *Eucaliptus* species produced anti-inflammatory effects, demonstrated by inhibition of rat paw edema induced by carrageenan and dextran, neutrophil migration into rat peritoneal cavities induced by carrageenan, and vascular permeability induced by carrageenan and histamine (Silva et al., 2003).

Recent studies have shown that eucalyptus essential oil is effective against *P. acnes*, the primary bacteria in acne infections. It was reported that eucalyptus oil has similar antibacterial capabilities as benzoyl peroxide, a commonly used topical OTC medication for acne treatment (Athikomkulchai et al, 2008). Additionally, the anti-inflammatory properties of eucalyptus oil may also be beneficial in acne condition. However, like most topical acne treatments, topical application of eucalyptus do not necessarily deliver enough active ingredients to the site of infection. Even though eucalyptus oil is effective against *P. acnes in vitro*, there is no real evidence that topically applied eucalyptus oil penetrates effectively into the follicle and sebaceous glands and its efficacy in the treatment of acne is unproven, at this time. It is also important to notice that topical applications of high concentration eucalyptus oil can produce side effects (Darben et al., 1998).

The second important product from eucalyptus is leaf dried extract. It contains gallic acid, ellagic acid, glucosides of quercetin and kaempferol, tannin dimer, oenothein B, and a new gallotannin with structure 1,2,3,6-tetra-O-galloyi-beta-D-galactose (Amakura et al., 2009). The extract demonstrate strong antibacterial activity against *Staphylococcus aureus, Streptococcus pneumonia* and *Haemophilus influezae* as well as on other gram positive (*C. pyogenese, S. aqueous, S faecalis, B. stecrothermohplus, S. epidermis, B. cereus, B. polymyxa, B. anthracic, B. subtilis* and *C. sporogenes*) and gram negative bacteria (*K. pneumonia, P. aeruginosa, E. coli* and *P. fluorescents*) (Salari et al., 2006; Egwaikhide et al., 2008).

Eucalyptus bark extract represent also interesting nat-

ural substance with specific chemical composition that include polygalloyl glucoses, catechin, epicatechin, ellagic acid, quercetin-3-O-rhamnoside and isorhamnteine glucosides and poses antioxidant activity (Vázquez et al., 2008).

Melaleuca alternifolia (Tea-tree)

Melaleuca alternifolia, Narrow-leaved Tea-tree, is a species of tree or tall shrub in the plant genus *Melaleuca*. Native to Australia, it occurs on the north coast and adjacent ranges of New South Wales. It grows along streams and on swampy flats, and is often the dominant species where it occurs. Characteristic of the myrtle family Myrtaceae, it is used to distil essential oil. It is the primary species for commercial production of Tea-tree oil (TTO, melaleuca oil), an essential oil with antibacterial (Carson et al., 2006) and antifungal activity (Hammer et al., 2003). More recently, the scientific community has confirmed that TTO has tremendous medicinal benefits and it is recognized as an excellent natural remedy for hundreds of bacterial and fungal skin ailments. Therefore it is used in a range of herbal medicine products and in cosmetic and toiletry products (deodorants, shampoos, soaps and lotions).

TTO is toxic if ingested in large amounts and if used topically in high concentrations may cause skin irritation (Hammer et al., 2006). No deaths have been reported.

TTO is a pale yellow color to nearly colorless and clear essential oil with a fresh camphoraceous odor. TTO should not be confused with tea oil, the sweet seasoning and cooking oil from pressed seeds of the tea plant *Camellia sinensis* (beverage tea), or the tea oil plant *Camellia oleifera*.

TTO is composed of terpene hydrocarbons, mainly monoterpenes, sesquiterpenes, and their associated alcohols. According TTO required chemical composition, as per ISO 4730 (2004), its chemical composition comprises terpinen-4-ol (30-48%), γ-terpinene (10–28%), α-terpinene (5–13%), 1.8-cineole (0–15%), α-terpinolene (1.5–5%), α-terpineol (1.5–8%), α-pinene (1–6%) and p-cymene (0.5–8%) (Tea-tree oil, http://chemicalland21.com/lifescience/foco/TEA%20TREE%20OIL.htm).

Given the scope for batch-to-batch variation, it is fortunate that the composition of oil sold as TTO is regulated by an international standard for "Oil of *Melaleuca*—terpinen-4-ol type," which sets maxima and/or minima for 14 components of the oil. Notably, the standard does not stipulate the species of *Melaleuca* from which the TTO must be sourced. Instead, it sets out physical and chemical criteria for the desired chemotype. Six varieties, or chemotypes, of *M. alternifolia* have been described, each producing oil with a distinct chemical composition. These include a terpinen-4-ol chemotype, a terpinolene chemotype, and four 1.8-cineole chemotypes. The terpinen-4-ol chemotype typically contains levels of terpinen-4-ol of between 30 to 40% and is the chemotype used in commercial TTO production (Homer et al., 2000). Despite the inherent variability of commercial TTO, no obvious differences in its bioactivity either *in vitro* or *in vivo* have been noted so far. The components specified by the international standard were selected for a variety of reasons, including provenance verification and biological activity. For example, with provenance, the inclusion of the minor components sabinene, globulol, and viridiflorol is potentially helpful, since it may render the formulation of artificial oil from individual components difficult or economically untenable. With biological activity, the antimicrobial activity of TTO is attributed mainly to terpinen-4-ol, a major component of the oil. Consequently, to optimize antimicrobial activity, a lower limit of 30% and no upper limit were set for terpinen-4-ol content. Conversely, an upper limit of 15% and no lower limit were set for 1.8-cineole, although the rationale for this may not have been entirely sound. For many years cineole was erroneously considered to be a skin and mucous membrane irritant, fuelling efforts to minimize its level in TTO. This reputation was based on historical anecdotal evidence and uncorroborated statements (Williams and Home, 1988; Williams et al., 1990; Williams et al., 1993), and repetition of this suggestion appears to have consolidated the myth.

Recent data, do not indicate that 1.8-cineole is an irritant. Although minimization of 1.8-cineole content on the basis of reducing adverse reactions is not warranted, it remains an important consideration since 1.8-cineole levels are usually inversely proportional to the levels of terpinen-4-ol (Brophy et al., 1989), one of the main antimicrobial components of TTO (Carson and Riley, 1995; Raman et al., 1995; Carson et al., 2006).

Antimicrobial activity of TTO has received the most attention. The few earlier reports of the antibacterial activity of the TTO (Walsh and Longstaff, 1987; Low et al., 1974) have been reviewed (Carson et al., 1993; Christoph et al., 2000; Lis-Balchin et al., 2000; Messager et al., 2005) and in general previously obtained results were confirmed.

In the last two decades, many reports describing the antimicrobial activity of TTO appeared in the scientific literature. Although there was still a degree of discrepancy between the methods used in the different studies, the MICs reported were often relatively similar. A broad range of bacteria have now been tested for their susceptibilities to TTO. While most bacteria are susceptible to TTO at concentrations of 1.0% or less, MICs in excess of 2% have been reported for organisms such as commensal skin staphylococci and micrococci, *Enterococcus faecalis*, and *Pseudomonas aeruginosa* (Hammer et al., 1996). Few researchers published lower value of MIC (0,25%) of TTO for *Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Salmonella choleraesuis, Shigella flexneri, Bacillus subtilis, Listeria monocytogenes, Staphylococcus aureus, S. saprophyticus*, and *S. xylosus* (Harkenthal et al., 1999).

TTO is for the most part bactericidal in nature, although it may be bacteriostatic at lower concentrations. The activ-

ity of TTO against antibiotic-resistant bacteria has attracted considerable interest, with methicillin-resistant *Staphylococcus aureus* (MRSA) receiving the most attention thus far. Several groups have evaluated the activity of TTO against MRSA, beginning with Carson et al. (1995), who examined 64 MRSA isolates from Australia and the United Kingdom, including 33 mupirocin-resistant isolates. The MICs and minimal bactericidal concentrations (MBCs) for the Australian isolates were 0.25% and 0.5%, respectively, while those for the United Kingdom isolates were 0.312% and 0.625%, respectively (Carson et al., 2006). Using a TLC-bioautographic technique Raman et al. (1995) investigated the antibacterial activity of TTO and isolated terpine-4-ol, alfa-terpineol and alfa-pinene, against *Staphylococcus aureus*, *S. epidermidis* and particularly against *P. acnaes*. The obtained results supported the use of TTO in acne treatment, demonstrating that terpinene-4-ol was not the sole active constituent of the oil. Among antibacterial, *in vitro* investigation of TTO against dermatophytes and filamentous fungi shown inhibitory and fungicidal activity (Hammer et al., 2002).

The mechanism of action of TTO against bacteria has now been partly elucidated. Prior to the availability of data, assumptions about its mechanism of action were made on the basis of its hydrocarbon structure and attendant lipophilicity. Since hydrocarbons partition preferentially into biological membranes and disrupt their vital functions, TTO and its components were also presumed to behave in this manner. This premise is further supported by data showing that TTO permeabilizes model liposomal systems. In previous work with hydrocarbons not found in TTO and with terpenes found at low concentrations in TTO, lysis and the loss of membrane integrity and function manifested by the leakage of ions and the inhibition of respiration were demonstrated. Treatment with TTO sensitized *S. aureus* cells to sodium chloride and produced morphological changes apparent under electron microscopy. Furthermore, no cytoplasmic membrane damage could be detected using the lactate dehydrogenase release assay, and only modest uptake of propidium iodide was observed after treatment with TTO (Carson et al., 2006; Cox et al., 2000).

In parallel with the characterization of the *in vitro* antimicrobial activity of TTO, the clinical efficacy of the oil has also been the subject of investigation. One of the first rigorous clinical studies assessed the efficacy of 5% TTO in the treatment of acne by comparing it to 5% benzoyl peroxide (Bassett et al., 1990). The study found that both treatments reduced the numbers of inflamed lesions, although benzoyl peroxide performed significantly better than TTO. The benzoyl peroxide group showed significantly less oiliness than the TTO group, whereas the TTO group showed significantly less scaling, pruritis, and dryness. Significantly fewer overall side effects were reported by the TTO group (27 of 61 patients) than by the benzoyl peroxide group (50 of 63 patients). Few years ago, Enshaieh et al. (2007) confirmed the efficacy of 5% topical TTO gel in treatment of moderate *acne vulgaris* in a randomized, double-blind placebo-controlled study. The efficacy of TTO in dental applications, for the eradication of MRSA carriage, in the possibility of using TTO in handwash formulations for use in hospital or health care settings and as a mouthwash in the treatment of oropharyngeal candidiasis, has been also evaluated in numerous clinical studies (Carson et al., 2006).

Numerous recent studies support the anti-inflammatory activity of TTO. Research studies performed over the last decade have demonstrated that TTO affects a range of immune responses, both *in vitro* and *in vivo*. For example, the water-soluble components of TTO can inhibit the lipopolysaccharide-induced production of the inflammatory mediators tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and IL-10 by human peripheral blood monocytes by approximately 50% and that of prostaglandin E_2 by about 30% after 40 h (Hart et al., 2000). Further examination of the water-soluble fraction of TTO identified terpinen-4-ol, α-terpineol, and 1.8-cineole as the main components, but of these, only terpinen-4-ol was able to diminish the production of TNF-α, IL-1β, IL-8, IL-10, and prostaglandin E_2 by lipopolysaccharide-activated monocytes. The water-soluble fraction of TTO, terpinen-4-ol, and α-terpineol also suppressed superoxide production by agonist-stimulated monocytes but not neutrophils (Brand et al., 2001). In contrast, similar work found that TTO decreases the production of reactive oxygen species by both stimulated neutrophils and monocytes and that it also stimulates the production of reactive oxygen species by nonprimed neutrophils and monocytes (Caldefie-Chézet et al., 2004). Human studies on histamine-induced wheal and flare provided further evidence to support the in vitro and animal data, with the topical application of neat TTO significantly reducing mean wheal volume but not mean flare area (Koh et al., 2002). Work has now shown that terpinen-4-ol, but not 1.8-cineole or α-terpineol, modulates the vasodilation and plasma extravasation associated with histamine-induced inflammation in humans (Khalil et al., 2004).

Ocimum sanctum (Holi basil)

In traditional systems of medicine, different parts (leaves, stem, flower, root, seeds and even whole plant) of *Ocimum sanctum* Linn. (known as Tulsi in Hindi), a small herb seen throughout India, have been recommended for the treatment of bronchitis, bronchial asthma, malaria, diarrhea, dysentery, skin diseases, arthritis, painful eye diseases, chronic fever, insect bite etc. The *Ocimum sanctum* has also been suggested to possess antifertility, anticancer, antidiabetic, antifungal, antimicrobial, hepatoprotective, cardioprotective, antiemetic, antispasmodic, analgesic, adaptogenic and diaphoretic actions (Mondal et al., 2009; Singh et al., 2007).

Eugenol (1-hydroxy-2-methoxy-4-allylbenzene), the active constituent present in *Ocimum sanctum*, has been

found to be largely responsible for the therapeutic potentials of the plant. Although because of its great therapeutic potentials and wide occurrence in India the practitioners of traditional systems of medicine have been using *Ocimum sanctum* for curing various ailments. A rational approach to this traditional medical practice with modern system of medicine is, however, not much available (Prakash and Gupta, 2005).

Chemical composition of *O. sanctum* means presence of volatile oil (0.4-0.8%) containing chiefly eugenol app. 21% and ß-caryophyllene 37% (eugenol content reaches maximum in spring and minimum in autumm). A number of sesquiterpenes and monoterpenes such as bornyl acetate, ß-elemene, methyleugenol, neral, ß-pinene, camphene, α-pinene etc. are also present as constituents of the oil. Besides, triterpene component ursolic acid, sterols (campesterol, cholesterol, stigmasterol, ß-sitosterol) and methyl esters of common fatty acids are also key constituents of the plant oil (*Ocimum sanctum*, http://101herbs.com/ocimum_sanctum.html).

From fresh leaves and stems of *O. sanctum* and further purification of the obtained extract, the few phenolic compounds were isolated: cirsilineol, cirsimaritin, isothymusin, isothymonin, apigenin, and rosmarinic acid, and appreciable quantities of eugenol (Kelm et al., 2000).

Gupta et al. (2007) isolated three new compounds, ocimumosides A and B and ocimarin (Fig. 6), were isolated from an extract of the leaves of holy basil, together with eight known substances, apigenin, apigenin-7-*O*-β-D-glucopyranoside, apigenin-7-*O*-β-D-glucuronic acid, apigenin-7-*O*-β-D-glucuronic acid 6″-methyl ester, luteolin-7-*O*-β-D-glucuronic acid 6″-methyl ester, luteolin-7-*O*-β-D-glucopyranoside, luteolin-5-*O*-β-D-glucopyranoside, and 4-allyl-1-*O*-β-D-glucopyronosyl-2-hydroxybenzene, and two cerebrosides.

In order to establish the therapeutic uses of *O. sanctum* in modern medicine, in last few decades several Indian scientists and researchers have studied the pharmacological effects of steam distilled, petroleum ether and benzene extracts of various parts of the plant and eugenol on immune system, reproductive system, central nervous system, cardiovascular system, gastric system, urinary system and blood biochemistry and have described the therapeutic significance of *O. sanctum* in management of various ailments. These pharmacological studies have established a scientific basis for therapeutic uses of this plant (Prakash and Gupta, 2005).

The most studies on biological effects are based on antimicrobial activity of *O. sanctum* essential oil (Dey and Choudhari, 1984; Mondal et al., 2007). The essential oil of *O. sanctum* has been effective against gram-positive and gram-negative bacteria and the properties were comparable with the effectiveness of clove oil. It also exhibited significant antimicrobial activities against some of the clinical isolates and multi-drug resistant Neisseria gonorrhoeae (Mondal et al., 2009). A comparative investigation has shown that the oil of sweet basil (*O. basilicum*) was even more effective against the *P. acnes*, in comparison to the oil of holy basil (*O. sanctum*), but both oils could be recommended for use in micro-emulsion formulations for acne skin care (Viyoch et al., 2006).

The aqueous and methanolic suspension of *O. sanctum* has shown to inhibit acute as well as chronic inflammation in rats. The test was conducted by carrageenan induced paw edema, croton oil induced granuloma and exudates, at a dose of 500 mg/kg, bw/day (Godhwani et al., 1987). The oils extracted from fresh leaves (essential oil) and seeds (fixed oil) of *O. sanctum* have shown anti-inflammatory effects on experimental animals hind paw edema induced by carrageenan, serotonin, histamine and prostaglandin-E-2. These experimental rats were administered with essential oil (200 mg/kg, bw), and fixed oil (0.1ml/kg, bw) before injection of phlogistic agents and was compared with standard drug flurbiprofen. It was noted that extracts could significantly reduce the edema when compared with the saline treated control. However, its effect was less than the standard drug (Singh and Agarwal, 1991).

The mechanism of action of the anti-inflammatory effects of *O. sanctum* could be the cyclo-oxygenase and lipooxygenase pathways (Singh et al., 1996; Singh and Majumdar, 1995; 1997). In order to compare the anti-inflammatory effects of fixed oils of various species of *Ocimum v.s. O. sanctum, O. basilicum, O. americanum,* which possess varying proportions of unsaturated fatty acids (par-

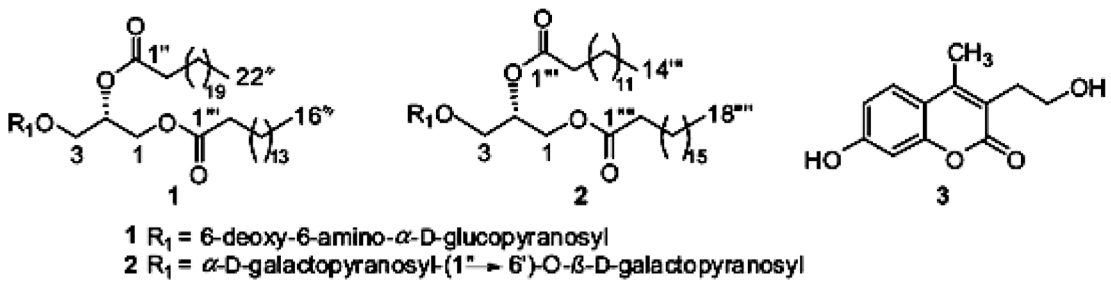


Fig. 6. Structures of ocimumosides A (1) and B (2) and ocimarin (Gupta et al., 2007).

ticularly linolenic acid) showed different response against phlogistic agent induced paw edema. *Ocimum basilicum* possess highest percentage of linolenic acid (21%) and offered maximum inhibition of paw edema (72.42%), *O. Sanctum* fixed oil containing 16.63% linolenic acid provided 68.97% inhibition while *O. americanum* offered least paw edema inhibition (Singh, 1998). Fixed oil of *O. sanctum* can inhibit enhanced vascular permeability and leukocyte migration as evidenced by carrageenan induced inflammatory stimulus (Singh et al., 1996). Extract of seeds from three plants including *Ocimum sanctum* have been studied for anti-inflammatory effects of carrageenan, leukotrine and arachiodonic acid induced paw edema in rats. *Ocimum sanctum* seed oil showed maximum percentage inhibition of leukotrine induced paw edema (Singh et al., 2008). According to Prakash and Gupta (2005), eugenol, active constituent of the *O. sanctum* essential oil, has been found as largely responsible for the therapeutic potentials of the plant. Anti-inflammatory activity of the eugenol isolated from the essential oil of *O. sanctum* was studied in Wistar rats by using carrageenan induced Hind paw edema method (Thakur and Pitre, 2009). The isolated eugenol and anti-inflammatory drug paracetamol (positive control) exhibited significant activity when compare with cararageenan control.

Calendula officinalis (Marigold)

Calendula officinalis, or (pot) marigold, is a common garden plant belonging to the Asteraceae family. Native to Southern Europe, *Calendula* grows up to 60 cm in height and produces large yellow or orange flowers. Like many other members of the Asteraceae family, which include daisies, arnica, chamomile, and yarrow, calendula is now cultivated throughout the world and is valued for its culinary and medicinal uses. The flowers are the part of the herb used medicinally (mainly because of its antibacterial, anti-inflammatory and antioxidant properties) either in

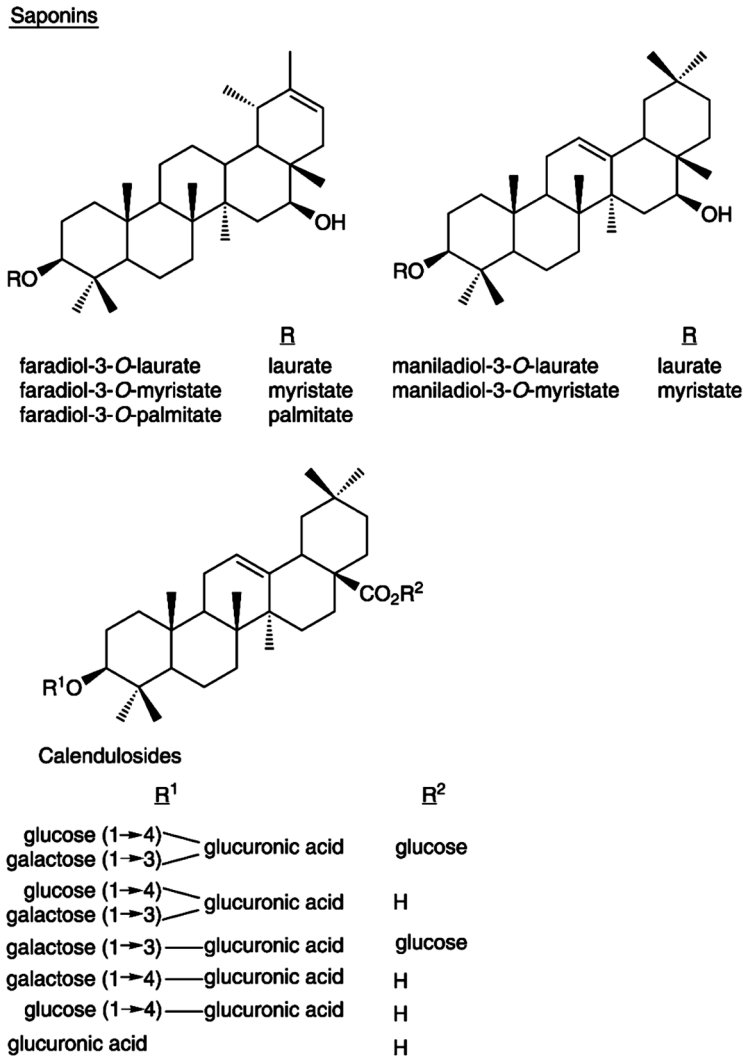


Fig. 7. Saponins of *Calendula officinalis* (http://www.medicinescomplete.com/mc/herbals/current/images/HrbcalendulaC001_default.png).

the form of infusions, tinctures, liquid extracts, creams or ointments, or in one of a number of skin and hair products available as OTC or cosmetics.

A number of phytochemical studies have demonstrated the presence of several classes of chemical compounds in flowers or in other organs of marigold, the main ones being terpenoids, flavonoids, coumarines, quinones, volatile oil, carotenoids and amino acids (Muley et al., 2009). Various terpenoids and sterols have been reported from the petroleum ether extract of *C.officinalis* flowers such as: sitosterols, stigmasterols, diesters and monoesters of taraxasterol, lupeol, erythrodiol, ursadiol, faradiol, arnidiol, calenduladiol, oleanolic acid saponins (calenduloside AH) and oleanane triterpene glycoside (calendulaglycosides) (Fig. 7). One new triterpenic ester of olanane series isolated from the flowers was cornulacic acid acetate (Naved et al., 2005).

Various flavonoids have been isolated from the ethanol extract of the inflorescence of *C. officinalis*. They include quercetin, isorhamnetin, isoquercetin, narcissin, calendoflaside, calendoflavoside, calendoflavobioside, rutin, isoquercitrin neohesperidoside, and different glycosides of isorhamnetin and quercetin (Muley et al., 2009; Vidal-Oliver et al., 1989). Different quinones, volatile oil, carotenoids, carbohydrates, lipids and other constituents were also identified in marigold flowers (Muley et al., 2009).

For centuries, marigold flowers have been used to treat a number of clinical conditions, specifically, different dermatological disorders. Whilst the many chemical constituents within marigold and the numerous actions of the plant suggest that marigold may be effective in treating a myriad of complaints. However, there is currently insufficient clinical evidence to support the use of pot marigold in conditions other than cutaneous lesions.

Marigold is considered a mainstay in alternative medicine for the treatment of inflammation, to speed wound healing and as an antiseptic. Available in topical herbal forms and as a homeopathic preparation, the anti-inflammatory (Braga et al., 2009; Chandran and Kuttan, 2008; Chandran et al., 2009; Della Loggia et al., 1994; Ukiya et al., 2006) and anti-bacterial (Lauk et al., 2003) properties of marigold may be helpful for treating dermatological conditions including acne (Muley et al., 2009).

Calendula officinalis flower extract have been proved for possessing significant anti-inflammatory activity against carrageenan and dextran-induced acute paw edema. In recent study conducted on flower extracts to find out mechanism involved in this, it was found that TNF-alpha production by macrophage culture treated with lipopolysaccharide was inhibited by *C. officinalis* extract. *C. officinalis* also contains flavonoids, which accounts for its anti-inflammatory impact (Preethi et al., 2009). Different hydroalcoholic extracts of marigold possesses proven antimicrobial, antifungal and antiviral properties against *Staphylococcus aureus* and *Streptococcus fecalis Prophyromonas gingivali*s, *Fusobacterium nucleatum, Capnocytophaga gingivalis, Veilonella parvula, Eikenella corrodens, Peptostreptococcus micros* and *Actinomyces odontolyticus, Staphylococcus aureus, Sarcina lutea, Escherichia coli, Klebsiella pneumonia* and *Candida monosa* on one hand, and on the other hand, the aetiology of acne.

Calendula off. is available in a number of ointment, cream and salve preparations in a variety of strengths. *Calendula* oils and infusions are also widely available in health-food stores and through online sources. *Calendula off*. is also commonly available in tea and liquid tinctures which can be applied directly to the acne prone areas of the skin.

Conclusion

Much disparate and introductory research exists on the effects of herbs on multiple aspects of acne. A comprehensive approach combining multiple herbs as well as lifestyle and dietary changes has helped people with acne in preliminary clinical trials. The continued resistance of mainstream dermatology to the possibility of this approach does not optimally serve patients who might be significantly helped by natural therapies. There are sufficient pilot data to warrant larger trials on various herbal medicines in isolation and combined with each other and other natural therapies. The data are also sufficient to support a recommendation for use of these herbs in clinical practice. Overall, herbal medicine has much to offer to improve our ability to deal with the complex issues acne presents.

However, an appropriate delivery system should be developed to impart their efficacies in addition to the standardization of these herbs. Furthermore, an optimized and effective dose should be evaluated prior to the development of preparations in order to avoid irritation or allergy in subjects with hypersensitive skin. Strict quality control will ensure their safety and efficacy. In addition, combination treatment should be conducted as it was found to be more effective than the application of a single product with regard to synergistic effects on the pathogenesis of acne.

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Резиме

Фитотерапија на *Acne vulgaris*

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Клучни зборови: *Acne vulgaris*, третман на акни, фитотерапија на акни

Acne vulgaris (акне) е една од најчестите дерматози во современото општество. Акне е хронична полиморфна болест на пилосебацеалните структури на кожата, што вклучува абнормалности во продукцијата на себум и се карактеризира со појава на инфламаторни (папули, пустули, нодуси) и неинфламаторни (отворени и затворени комедони) лезии. *Propionibacterium acnes* и *Staphylococcus epidermidis* се значајни фактори во патогенезата на инфламаторните облици на акни, иако акне не претставува бактериска инфекција.

Денес на пазарот се присутни голем број лекови и козметички производи за третман на акни, при што се прифатени четири основни принципи: елиминирање на алтерираниот начин на кератини за цијанафоликулот, намалување на интрафоликуларната популација на *Propionibacterium acnes* или генерирањето на екстрацелуларните инфламаторни агенси и намалување на секрецијата на себум.

Третманот на акни вклучува локална и/или системска терапија, директна интралезиона терапија со кортикостероиди, фитотерапија и нивни комбинации. При локалната терапија најчесто се користат бензоил пероксид, локални антибиотици и ретиноидна киселина. Системската терапија опфаќа примена на антибиотици и орални ретиноиди. Изборот на третманот зависи од стадиумот на болеста, но истиот често е проследен со одредени несакани ефекти.

Во последните години, примената на хербалните преработки во третманот на акни добива сè поголема научна потврда и се смета како ефикасна алтернатива на конвенционалната терапија.

Целта на овој труд е да даде сèопфатен преглед, базиран на научни докази, на растителните суровини и на фитопрепаратите со потврдена клиничка ефикасност што се користат во третманот на акни.