Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1895-1906 | ISSN:2251-6727

Novel Review on Anti-Acne Plant Medicines: Their Significance for Contemporary Therapies

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(Received: 04 February 2024 Revised: 11 March 2024 Accepted: 08 April 2024)

KEYWORDS

Acne; treatment; natural products; photodynamic therapy; cultivation; coastal communities

ABSTRACT:

Acne is a common but serious skin disease, which affects approximately 80% adolescents and young adults in 11–30 age group. from the beginning until their twenties, 50.9% of women and 42.5% of men still have this illness. The overuse of antibiotics has led to an alarming level of bacterial resistance. Therefore, the need of the hour is to find new lead molecules or bioactives and to strategically deliver the current medication to the site of action for improved therapeutic effect. Since the beginning of time, plants and products derived from them have played a crucial role in the health care system. Thus, the current review summarizes plants that have high potential and those that are currently used to treat acne. The most potent plant extracts against P. acnes are P. granatum, M. alba, A. anomala, and M. aquifolium, which have minimum inhibitory concentrations (MICs) between 4 and 50 µg/mL. Meanwhile, the aromatic oils of C. obovoides, C. natsudaidai, C. japonica, and C. nardus have MICs between 0.005 and 0.6 µL/mL, and phytomolecules like rhodomyrtone, pulsaquinone, hydropulsaquinone, honokiol, magnolol, xanthohumol lupulones, chebulagic acid, and rhinacanthin-C have MICs between 0.5 and 12.5. Novel approaches to delivering significant plant leads for the treatment of acne have also been explored.

Introduction

The advancing fields of neurodermatology and psychodermatology have long acknowledged the comorbidity of long-term skin diseases and mental health issues. Frequently, depression, anxiety, and other psychological aftereffects are linked to acne vulgaris, a common dermatological condition [1]. One of the most prevalent multifactorial chronic inflammatory diseases of the pilosebaceous follicles, acne is caused by a combination of factors such as immune system hypersensitivity, hormone imbalance, altered follicular keratinization, and sebaceous hyperplasia induced by androgen [2]. Even though acne doesn't have the same urgency as a life-threatening condition and doesn't affect one's general fitness, it can still have significant long-term effects, including the development of superficial and psychological scars that last a lifetime [3]. It damages one's self-esteem and causes emotional distress due to perceived impairment, which lowers one's self-esteem and causes physical, social, and psychological suffering [4,5].

Acne's clinical manifestations include inflammatory lesions (papules and pustules), noninflammatory lesions (open and closed comedones), and varying degrees of scarring from cyst formation [2]. The distribution of acne, which affects the face, neck, upper chest, shoulders, and back, is in line with the density of pilosebaceous units. Acne can be categorized as noninflammatory (comedonal acne only) or inflammatory (mild papular, scarring papular, and nodular) depending on the type of lesion. Acne can be classified as mild, moderate, or severe based on how severe it is. Mild acne is defined as having fewer than twenty open and closed comedones, fifteen inflammatory lesions, and fewer than thirty total lesions. comparable to severe acne, moderate acne is characterized by a large number of papules and pustules, acne comedones (20–100), inflammatory lesions (15–50), and total lesions (30–125). Extensive lesions, such as nodules and scarring along with cysts (>5), a total comedone count (>100), a total inflammatory count (>50), and a total number of lesions greater than 125 are indicative of severe acne [6, 7].

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JCHR (2024) 14(3), 1895-1906 | ISSN:2251-6727

1.1. Epidemilogy

The condition appears to have virtually no mortality, although there is frequently notable physical and psychological morbidity. In accordance with statistics, 85% of young adults in the world between the ages of 12 and 25, 8% of adults between the ages of 25 and 34, and 3% of adults between the ages of 35 and 44 suffer from some form of acne [8]. In their twenties, 42.5% of men and 50.9% of women, on average, still have the illness. According to recent research, 30% of women may experience acne for the duration of their fertile period [9]. Acne affects 40 to 50 million the Americans annually, and many adults still experience acne problems years after they first appeared as teenagers. According to a German population study, 46% of people aged 20 to 29 and 43% of people aged 30 to 39 had visible acne. At the age of 40 to 49, 3% of men and 5% of women in a different German study involving over 2000 adults still had prominent mild acne [10]. In a study involving 309 participants in southern India, there was a 4.9:1 difference between closed and open comedones. 186 patients (60.2%) had grade 1 acne vulgaris, while grades 2, 3, and 4 were reported in 85 (27.5%), 8 (2.6%), and 30 (9.7%) of the patients, respectively [11]. Acne is nearly 80% inherited in first-degree relatives and more severe in those with a favorable family history, according to recent research. There was a dose-dependent correlation between smokers' acne and their acne severity and frequency [12]. The cost of acne to society was not clearly defined, but its prevalence supported the high expenses that placed a significant financial strain on the community. According to a recent USA report, the annual cost of acne treatment and lost productivity is estimated to be $3 billion.

Kaempferia parviflora, a herbaceous species in the Zingiberaceae family, is also referred to as black ginger or "krachaidum" in Thai. It has long been utilized as an alternative medicine that promotes health because of its anti-inflammatory, anti-allergic, anticholinesterase, adaptogenic, and anti-obesity properties. Numerous flavonoids, including 5,7-dimethoxyflavone, 5-hydroxy-3,7,40-trimethoxyflavone, and 5-hydroxy-3,7dimethoxyflavone, are found in Kaempferia parviflora. This plant's extracts have shown effectiveness against malignancy and a range of other illnesses, including metabolic, sexual, and cognitive issues. It is yet unknown, nevertheless, whether Kaempferia parviflora extracts specifically work on acne vulgaris.

1.2. Pathophysiology of Acne.

A higher prepubertal androgen production is the initial pathophysiologic factor that leads to acne development. This is generally followed by unnatural pilosebaceous follicular keratinization and desquamation; increased sebocyte proliferation; enlarged sebaceous glands; increased secretion of acnes acnes; and perifollicular inflammation [13,14]. Androgens are necessary for seborrhea, sebocytic hyperplasia, and follicular hyperkeratinization [15,16].

This is widely acknowledged that sebum production and androgen levels are related in acne vulgaris. The primary cause of acne is the hypertrophy of sebaceous glands brought on by androgen, which results in an excess of sebum production [17]. Steroid metabolizing enzymes found in the sebaceous glands change dehydroepiandrosterone (DHEAS) into dihydrotestosterone (DHT). DHT receptor, activated by androgens, and the neuromodulator receptor, mainly substance P and corticotrophin-releasing hormone (CRH) receptor which are mainly activated by stress, recent molecular research has identified three other receptors that are expressed by the sebocyte and that control sebum production (Fig. 1) [20,21].

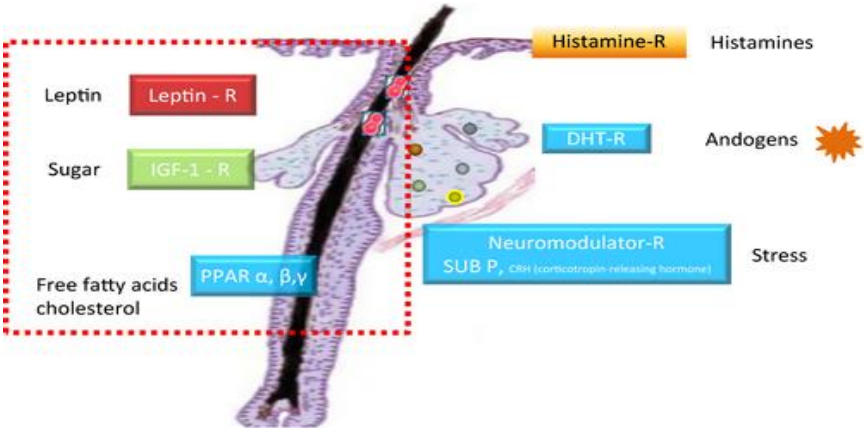

Figure 1: Receptors controlling sebum production (adapted from Zhang *et al.*7).

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JCHR (2024) 14(3), 1895-1906 | ISSN:2251-6727

Additionally, testosterone is converted to the more active DHT by two subtypes of 5-αreductase isozymes, namely type 1 and type 2, which are expressed in the scalp, chest, sebaceous glands, genitourinary tissue, and the dermis in addition to hair follicles [4]. Overproduction of sebum promotes cell turnover in the follicular canal and obstructs the pilosebaceous unit. Additionally, in the second factor of pathogenesis, inflammatory mediators and macrophages with Toll-like receptors (TLR2) expressed on their surface envelop pilosebaceous follicles. The activation of TLR2 results in the transcription of nuclear factor triggering, which in turn leads to the expression of cytokines, including IL-8, GM-CSF, and interleukin-1β. These cytokines initiate and propagate the inflammatory response, which in turn induces keratinocyte hyperproliferation [18]. The comedone is a thin-walled cystic lesion that forms when desquamated keratinocytes remain within the pilosebaceous unit. This plugging and obstruction of the follicles leads to the destruction of the follicle's normal architecture. The microcomedo wall eventually bursts due to the accumulation of keratinocytes and sebum, causing inflammation [19].

A developing comedone is a greasy plug made of bacteria, sebum, keratin, and the superficial layer of melanin that can look like a black or white head. "Black heads" or open comedones are comedones that break through the skin's surface and have a central black appearance (caused by tyrosinase oxidizing tyrosine to melanin). However, "white heads," or closed comedones, develop when the follicle becomes impactioned and distended due to improperly desquamated keratinocytes and sebum. These comedones remain beneath the skin's surface as closed follicles [19]. These lesions are representative of a papule, pustule, nodule, or cyst, depending on the severity of the underlying pathologic conditions.

1.3. Molecular Targets for Acne Treatment.

Human sebocytes express a broad spectrum of receptors considering they are highly metabolically and biologically active cells [22]. Numerous ligands attach to these receptors and cause a range of reactions that change the synthesis of lipids, cytokines, and cell division, all of which are eventually involved, either directly or indirectly, in the pathophysiology of acne. Following a review of the literature, potential ligands have been identified that, upon binding with their corresponding receptors, cause proliferation of cells, cytokine expression, and lipogenesis. Since each ligand (agonist) causes acne in a different way, acne needs a particular antagonist to bind to these receptors and eliminate acne. Before choosing a treatment, all of these pathways for acne treatment and management should be taken into account.

1.3.1. Neuropeptides Like neuropeptide Y, calcitonin gene-related peptide, and vasoactive intestinal polypeptide (VPAC), and substance P typically bind on VPAC receptors found on sebocytes of sebaceous glands. Binding results in the expression of cytokines, differentiation and proliferation of sebocytes, and upregulation of lipogenesis [17, 22,23].

1.3.2. PRAR ligands comprise leukotriene B4, a well-known natural ligand of PPARα receptors found in sebocyte microsomes, mitochondria, and peroxisomes (5-lipoxygenation product derived from arachidonic acid). 5-lipoxygenase inhibitors may be used to lessen lipogenesis and acne lesions because this ligand is known to stimulate lipogenesis in cultured human sebocytes.

1.3.3. Histamine bound to the histamine 1 receptor, causing SZ95 sebocytes to produce more squalene. Lipid peroxidation occurs as a result, with squalene peroxide being produced as a byproduct. Moreover, it triggers comedogenesis and inflammatory reactions, and it occasionally obstructs sebocyte differentiation and sebogenesis [22,24].

1.3.4. Fibroblast growth factor (FGF) FGF is an essential component in regulating epithelial proliferation and differentiation. It is secreted by keratinocyte-derived interleukin-1α stimulated fibroblast and binds on FGF receptor 2b present in suprabasal spinous layer of the epidermis and sebocytes. Additionally, androgen-mediated upregulation of FGFR2b signalling is possible, which eventually leads to follicular hyperkeratinization and sebaceous gland hypertrophy [25, 26].

1.3.5. Insulin in higher concentration and insulin like growth factors-1 activate the IGF-I receptor, which is expressed on the surface of sebocytes (SZ95). Lipid accumulation in sebocytes is enhanced by IGF-I in a dose-dependent manner. It is also known to activate androgen receptor signal transduction, adrenal and gonadal androgen synthesis, and 5α-reductase, which in turn promotes sebocyte proliferation [27, 28].

1.3.6. Corticotrophin releasing hormone and urocortin bind to human sebocytes' CRH-receptor 1 (CRH-R1), which in turn inhibits sebocyte proliferation, increases the expression of IL-6 and IL-8, upregulates 3-hydroxysteroid dehydrogenase, promotes lipogenesis and keratinocyte differentiation, and increases local inflammation [22, 29].

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JCHR (2024) 14(3), 1895-1906 | ISSN:2251-6727

1.3.7. β-Endorphin binds to μ opiate receptors on sebaceous glands, causing lipogenesis to be stimulated and a specific increase in fatty acid content in sebocytes that is comparable to linoleic acid.

1.3.8. α-Melanocyte stimulating hormone binds to the cellular surface of sebocytes at the melanocortin 1 and 5 receptors (MC-1R and MC-5R). In SZ95 sebocytes, MC-1R controls inflammation; in sebaceous glands involved in acne, this expression is more pronounced.

1.3.9. Retinoic acid (RA) and 9-cis retinoic acid are the ligands of the retinoid X receptors (RXRα) and retinoic acid receptors (RAR α and γ), which are the main retinoid receptors in human sebocytes and control cell differentiation and proliferation.

1.3.10. Vitamin binds to vitamin D receptors to cause time- and dose-dependent changes in lipid content, cell cycle regulation, proliferation, and the release of IL6 and IL8 by cultured sebocytes.

1.3.11. P. acnes moieties activate keratinocyte TLR receptors (TLR2,4,6). Keratinocytes release inflammatory cytokines (TNF-α, IL-6, and IL-8) in response to TLR activation.

1.3.12. Matrix metalloproteinases are found in sebum and come from sebocytes and keratinocytes. MMP-1, MMP-13, TIMP-1, TIMP-2, proMMP-9, and MMP13 are all found in sebum; the latter two of these decreased in tandem with clinical improvement when isotretinoin was administered. In HaCaT keratinocytes, the medication suppressed arachidonic acid, induced secretion, and MMP mRNA expression [30, 31].

1.3.13. Dipeptidyl peptidase IV and aminopeptidase N are ectopeptidases that interact with specific receptors to regulate sebocytes. APN and DP IV increase total neutral lipid synthesis, decrease terminal differentiation, and promote proliferation. Moreover, these enhanced P. acnes proliferation and IL-2 production stimulated T cells ex vivo and inhibited the expression of transforming growth factor-β1, an immunosuppressive cytokine [32].

Acne lesions may arise due to altered lipogenesis, sebum production, hyperkeratinization, sebocyte proliferation/differentiation, and cytokine expression. The effective treatment of acne is contingent upon the precise elucidation of the pathogenic mechanism. Due to their direct or indirect involvement in the pathophysiology of acne, these mentioned targets may be taken into account when evaluating the antiacne potential of the leading active ingredients in the near future.

2. Difficulties Associated with Acne Treatment

Acne treatment is a well-established procedure that needs to be personalized for every patient. The foundation of any disease treatment is an appropriate therapeutic approach following diagnosis. The main issue with choosing an acne treatment is choosing the right medication based on the type and severity of the condition and its ability to address one or more pathogenic factors through its mechanism of action. Even though there are many therapeutic agents available, treating acne presents a number of challenges in this context.

2.1. Antibiotic Resistance The use of antibiotics continue to be important in treating acne, but there is a chance that resistant bacteria will develop. The particulars of the bacterial-antibiotic relationship play a role in the multifactorial rise in antibiotic resistance. As such, there are good reasons to look for different ways to address this issue. Medicinal plants have been investigated as alternative acne treatments in an effort to combat antibiotic resistance as well as the high cost of treatment.

2.2. To Surmount the Glitches Allied with Conventional Formulations of Antiacne Drugs. A plan of action for approaching treatment modification is necessary for the follow-up phase of management. This framework may include concepts like the lack of an effective system for delivering anti-acne medications. Anti-aging medications included in traditional systems may not release the active component, causing subtherapeutic levels, or they may not be able to reach the pilosebaceous unit at the appropriate concentration. The underlying microbial flora of P. acnes and the inflammatory mediators that cause acne vulgaris can be eliminated by using cutting-edge methods that target the active molecule directly to the pilosebaceous unit or sebaceous gland. To reduce the issues with traditional formulations, such as variations in drug efficacy and absorption, physicochemical properties of the active molecules, and other issues, novel drug delivery systems (NDDS) may be preferred.

2.3. Non-Availability of Appropriate Animal Model. the existence of an appropriate animal model that can accurately replicate the various pathophysiologic features of acne is a significant obstacle in the development of a suitable medication and delivery system for the condition.

3. Current Management Approaches

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Appropriate application of currently available treatment options, based on the kind and severity of acne lesions, is currently a crucial element of effective acne therapy. Depending on the severity of acne, topical treatment may be used as a monotherapy or in conjunction with systemic medication therapy in mainstream acne management. Topical and oral retinoids, topical antimicrobials, systemic antibiotics, keratolytics, and hormonal therapy—which included oral contraceptives and androgen blocking agents—as well as combination therapy involving all of the aforementioned agents—make up the majority of the current toolkit.

Topical retinoids, which are derived from vitamin A, are comedolytic agents that lessen inflammation, hyperkeratinization, and aberrant keratinocyte mitosis. Adapalene, a third-generation retinoid, and modified slow-release formulations are said to cause less irritation. Azelaic acid is a dicarboxylic acid that occurs naturally and has mild comedolytic and antibacterial properties. The two topical antibiotics most frequently used for acne are erythromycin and clindamycin. They are helpful in cases of inflamed lesions where antibiotic resistance is a significant issue. Topical therapies are not practical when treating moderate-to-severe inflammatory acne because oral antibiotics, specifically tetracyclines and macrolides, are prescribed. Beyond from the antibiotics previously mentioned, trimethoprim, ciprofloxacin, and sulfamethoxazole are also utilized. Because topical combination therapies can target multiple pathogenic mechanisms, they have been shown in multiple trials to be more effective than monotherapy. Adapalene-BPO (0.1%, 2.5%), clindamycin-BPO (1%, 5% gel), erythromycin-BPO (3%, 5% gel), erythromycin-tretinoin (4%, 0.025 %) solution, and clindamycin-tretinoin (1.2 %, 0.025 %) gel are among the fixed dose topical combination products that are available. Regardless of the type of progestin or estrogen concentration, oral contraceptives, such as ethinyl estradiol in combination with cyproterone acetate, levonorgestrel, norgestimate, desogestrel, drospirenone, and ethynodioldiacetate, inhibit serum androgen levels, increase sex hormone binding globulin, and improve acne [33, 34].

4. Plants with the Potential to Treat Acne

The pharmaceutical and personal care industries continue to invest heavily in research and development efforts aimed at finding solutions to address acne [35]. It goes without saying that there is a chance that bacteria will develop resistance to antibiotics if they are used consistently. The particulars of the bacterial-antibiotic relationship play a multifaceted role in the development of antibiotic resistance [36]. Additionally, there are therefore excellent explanations to look for alternative medications to tackle and overcome these issues. Medicinal plants have been researched as potential alternative treatments for diseases in an effort to fight antibiotic resistance as well as the high cost of treatment. Alternatively, a number of studies have suggested that medicinally potent plant actives could be used to inhibit the bacterial growth and inflammatory response. The presence of 250,000–500,000 plant species presents a significant opportunity for the screening of phytotherapeutic agents that may be applied to the treatment of acne. For the development of new medications, traditional herbal medicines offer an intriguing and mainly unexplored source. There is a lot of hope in traditional medicine and natural products for the discovery of bioactive lead compounds and their subsequent development into acne-treatment medications [37].

4.1. Plant Extracts.

Plant extracts are sought after for therapeutic purposes; the medicinally active parts of medicinal plants are isolated from the inactive or inert components by standard extraction techniques such as decoction, swelling, infusion, digestion, percolation, and soxhlet extraction, using specific solvents. These can be found as semisolid, powdered, infusion, tincture, and decoction extracts. The following section has covered a few of the potent plant extracts that have anti-acne qualities.

Echinacea purpurea thereby stopping *P. acnes* from proliferating and reversing the inflammation caused by the bacteria, the extract had an anti-acne effect. By applying cytokine antibody arrays, it also restored elevated cytokine levels, such as IL-6 and IL-8 (CXCL8), in cell culture models of human epithelial cells in the bronchi and skin fibroblasts [38]. *Garcinia mangostana* is widely recognized for its significant ability to treat acne. An HPLC analysis revealed that the pericarp dichloromethane extract had the strongest antibacterial effect against P. acnes and S. epidermidis, with the highest concentration of α-mangosteen. According to [40], the MBC values for P. acnes and S. epidermidis were 0.156 mg/mL and 0.039 mg/mL, respectively, while the MIC values were the same. According to [39], the extracts were effective in scavenging free radicals and suppressed the production of proinflammatory cytokines. They also decreased the production of TNF-α as measured by ELISA. Furthermore, according to the broth dilution method, *Sennaalata* (0.625–2.5 mg/mL MIC*), Eupatorium odoratum*

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(0.625 mg/mL MIC), and *Barlerialupulina* (1.25–2.5 mg/mL MIC) also demonstrated potent inhibitory effects against P. acnes.

Furthermore, with a minimum inhibitory concentration (MIC) of 0.01–0.5 mg/mL, *Camellia sinensis* polysaccharide demonstrated potent inhibitory activities against hemagglutination mediated by pathogens *H. pylori*, *P. acnes*, and *S. aureus*. Results suggested that C. sinensis had a selective antiadhesive effect on P. acnes pathogens exclusively, based on the pathogens' adhesion to host cell lines [41]. Additionally, using a sebumeter, it was discovered that 3% of green tea extract emulsion decreased the amount of sebum produced on the skin of healthy human volunteers [42]. Due to the presence of alkaloids, flavonoids, glycosides, and terpenoids, the methanolic extract of *C. sinensis* exhibited the highest antibacterial activity (MIC 1.25 mg/mL) against *S. aureus*, *S. epidermis*, and *P. acnes* when compared to extracts of *Glycyrrhiza glabra* and *Calendula officinalis* by agar disc diffusion method [43]. This suggests that these phytoconstituents are responsible for the antiacne activity.

Furthermore, a rind extract from, *Punica granatum* that contained 13% ellagic acid demonstrated a strong bacteriostatic effect *P. acne (MIC 15.6 μg/mL), S. aureus, and S. epidermidis (MIC 7.8–15.6 μg/mL).* Additionally, it suppresses the release of b-hexosaminidase from antigen-stimulated rat basophilic leukemia cells, indicating its antiallergic qualities, and the production of nitric oxide by murine macrophages such as RAW 264.7 cells [44]. Strong leaf extracts of *Psidium guajava* and *Juglans regia* demonstrated an in vitro inhibitory effect on P. acnes and other microorganisms isolated from the disk diffusion method-based acne lesions of thirty-eight patients [45]. In keratinocytes, *Selaginella involvens* extract had a dose-dependent inhibitory effect on nitric oxide production, iNOS/IL-1β expression, and cytokines (IL-1α and IL-8) [46]. Testing *Terminalia arjuna* bark extract against *P. acnes* and *S. epidermidis* revealed that the flavonoid fraction (MIC 0.315 mg/mL) and its 2% cream formulation was more effective [47].

White tea, witch hazel, and rose extracts and formulations have been shown to safeguard fibroblast cells from hydrogen peroxide-induced damage by significantly reducing the amount of IL-8 that fibroblast cells produce. Furthermore, significant anticollagenase, antielastase, and antioxidant activities were also demonstrated by white tea and rose [48]. P. acnes was found to be inhibited by methanolic extracts of Rosa damascene, Eucommia *ulmoides*, and Ilex *paraguariensis*, with corresponding MICs of 2, 0.5, and 1 mg/mL. Furthermore, at a concentration of 0.1 mg/mL, the latter two inhibited the release of proinflammatory cytokines, including tumour TNF-α, IL-8, and IL-1β, by human monocytic THP-1 cells that had been treated with heat [49]. A study found that extracts from *Rubia cordifolia, Curcuma longa, Hemidesmus indicus,* and *Azadirachta* indica significantly suppressed reactive oxygen species from proinflammatory cytokine-induced monocytes and polymorphonuclear leukocytes [50]. The antiacne activity of *Coscinium fenestratum* extract was demonstrated by MIC values of 0.049 mg/mL against *P. acnes* and *S. epidermidis*, as well as MBC values of 0.049 and 0.165 mg/mL, respectively. In a similar vein, P. acnes was significantly inhibited by *Tephrosia purpurea*, *Euphorbia hirta*, *Curcubito pepo*, and *Eclipta alba* [51]. Acne can be effectively treated with the leaves and seeds of *Borago officinalis*, *Linum bienne*, and *Ruta graveolens*, as well as the aerial parts of *Malva sylvestris* and *Rubus ulmifolius* [52, 53].

MIC values for *Morus alba* root extract against *P. acnes* and *S. epidermidis* were 15.6 g/mL and 3.1 μg/mL, respectively. Moreover, extracts from *Poncirus trifoliate*, *Albizzia julibrissin*, and *Phellodendron amurense* demonstrated exceptionally low MIC values against both pathogens [54]. Similarly, it is known that *Podocarpus nagi*, which contains flavonols, and Anacardium pulsatilla, which contains polyphenols, are effective against P. acnes [55]. Another well-known plant is *Angelica anomala*, which, at MIC values of 15.6 μg/mL and 126 μg/mL, respectively, demonstrated strong inhibitory effects against P. acnes and S. epidermidis. Along with reducing the amount of IL8 and TNF-α that P. acnes induced to be secreted in THP-1 cells, *Mollugo pentaphylla*, *Matteuccia orientalis*, and *Orixa japonica* also inhibited the growth of both pathogens [56]. Plants with antibacterial (MIC 0.13 mg/mL; MBC 0.25 mg/mL), lipase inhibitory, and antioxidative qualities, such as *Caesalpinia sappan* and *Intsiapalembanica*, were found to be effective acne treatments [57].

Elephantorrhiza elephantina, Ekebergia capensis, Eucalyptus camaldulensis, and *Harpephyllum caffrum* organic extracts showed significant activity against P. acnes, with MIC values ranging from 0.05 to 1.00 mg/mL [58].

4.2. Essential Oils

In addition to the fleurage method, water distillation, steam distillation, and cohabitation are used to extract natural essential oil, a concentrated hydrophobic liquid containing

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JCHR (2024) 14(3), 1895-1906 | ISSN:2251-6727

volatile aroma compounds, from plant organs. These essential oils' extensive potential for managing acne has recently come under investition**.**

Both 5% *Melaleuca alternifolia* (tea tree oil) and 5% benzoyl peroxide lotion significantly decreased the number of inflamed and noninflamed lesions with significantly fewer side effects from tea tree oil, according to a single-blind, randomized clinical trial involving 124 patients with mild to moderate acne [59]. Terpinen-4-o1, α-terpineol, and α-pinene have all been shown to be effective against *S. aureus*, *S. epidermidis*, and *P. acnes* in tea tree oil [60]. Tea tree oil was found to be very effective in treating acne based on the total number of acne lesions and the acne severity index in a study involving sixty patients with mild to moderate acne [61]. Comparably, *Zingiber cassumunar* essential oil, also known as plai oil, demonstrates antimicrobial activity against a variety of bacteria (MC 0.62% against *P. acnes*), dermatophytes, and yeasts, indicating its potential use in the treatment of acne [62].

Furthermore, against bacteria that cause acne, *Thymus quinquecostatus* essential oil maintains strong antibacterial, antioxidant, antielastase, and anti-inflammatory properties. It may be useful in treating acne because it also causes minimal cytotoxicity in human cell lines [63]. Additionally, the bioactive ingredients in rosemary essential oil, such as 1,8-cineole, α-pinene, camphor, and camphene, are likely responsible for its antibacterial activity against *P. acnes* (MIC 0.56 mg/mL). Atomic force microscopy and phase images verified that rosemary essential oil adhered to the bacterial cell surface at lower concentrations, causing severe damage to the bacterial bodies as the concentration increased [64]. Additionally, because *of γ-terpinene* and *α-pinene*, volatile oils from *Eucalyptus globulus* (MIC and MBC 9.38 mg/mL) and Psidium guajava leaves (MIC 9.38 mg/mL, MBC 37.50 mg/mL) showed antimicrobial activity against P. acnes as assessed by agar diffusion and microdilution methods [65]. According to the results of the in vivo rat sebaceous gland model, eucalyptus oil controls the spread of acne by reducing the size of sebaceous glands, which in turn reduces sebum production .

Another well-known *Ocimum gratissimum* oil preparation in a *cetomacrogol* blend base demonstrated its efficacy in the treatment of acne by reducing lesions faster than benzoyl peroxide 10% lotion, while also being well tolerated [66]. Research has shown that *Ocimum* oil's antiacne qualities are boosted by aloe vera gel, and that using both together is more effective than using 1% clindamycin to treat acne [67]. According to a study, the essential oils of Zingiber cassumunar, Zingiber officinale, Citrus hystrix, Ocimum sanctum, Ocimum basilicum, and Cymbopogon nardus and citratus had antioxidant, antimicrobial, and anti-inflammatory qualities. The most effective of these against *P. acnes* was *Cymbopogon nardus* oil, also known as citronella oil (MIC 0.005–0.3 μL/mL). Furthermore, every essential oil, with the exception of kaffir lime oil, showed significant free radical scavenging activity. Major ingredients that were proposed to support this activity included d-limonene in kaffir lime oil and eugenol in holy basil oil [68]. Ten essential oils were found to have antiacne properties against *P. acnes* in a different study. These oils included *Mentha spicata, Zingiber officinale, Citrus limon, Citrus paradisi, Jasminum grandiflora, Lavandula angustifolia, Matricaria chamomilla, Thymus vulgaris, Rosa damascene*, and *Cinnamomum zeylanicum*. The best antibacterial properties were found in thyme, cinnamon, and rose essential oils, with MIC values of 0.016%, 0.016%, and 0.031% v/v, respectively [69].

Using the disc diffusion method, *Ocimum sanctum* (holy basil) and sweet basil *(ocimumba silicum*) essential oils and their microemulsions were tested for their in vitro activity against P. acnes in a study of ocimum oils. The results showed that the microemulsion of sweet basil oil had higher activity than that of holy basil oil, and that the MIC values of both oils were 2.0% and 3.0% v/v. *Backhousia citriodora*, an Australian essential oil, has been demonstrated to exhibit strong antimicrobial activity against methicillin-resistant *S. aureus, E. coli, P. aeruginosa, C. albicans, A. niger, K. pneumoniae*, and *P. acnes* [70].

Acne has been treated with essential oils of *Citrus aurantium, Eucalyptus radiate, Juniperus communis, Pelargonium asperum, Pogostemon cablin*, and *Styrax benzoe* [71]. The essential oils of *Salvia desoleana, Anthemis aciphylla*, and *Sclarea* also demonstrated a weak to moderate inhibitory effect against S. aureus and S. epidermidis. It was discovered that *tamariix bovena* essential oil inhibits facial flora that could be used to treat acne [72].

4.3. Phytomolecules

The medicinal qualities of plants are attributed to a wide variety of chemical components called phytoconstituents that are medicinally active. Once an active extract has been obtained, the next step is to identify, isolate, and characterize the bioactive phytomolecule(s) in the plant extract. Numerous scientific studies published recently indicate the use of

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isolated phytomolecules to target acne lesions via a variety of mechanisms, some of which are outlined below.

The main ingredient in *Rhodomyrtus tomentosa* leaves, *rhodomyrtone*, was tested using the *broth macrodilution* method against P. acnes (MIC 0.5 μg/mL) and was found to be significantly effective, reducing 99% of the bacterial cells in just 24 hours. A cytotoxicity test conducted on human normal fibroblasts revealed extremely low cytotoxicity, supporting its application as a topical medicinal anti-acne agent [73]. Pulsatilla *koreana* roots extract contained *hydropulsaquinone* and *pulsequinone*, which showed antimicrobial activity against P. acnes with MIC values of 2.0 and 4.0 μg/mL, respectively, [74]. Additionally, from methanolic extracts of *Caesalpinia sappan wood*, *Brazilin*, *protosappanin A*, and *sappanone B* were isolated. These compounds demonstrated significant lipase inhibitory and antibacterial activity, with MIC values of 0.50 mg/mL, 1.00 mg/mL, and >2.00 mg/mL, respectively. Additionally, it was discovered that *sappanone* B significantly lacked the antioxidant activity of brazilin and protosappanin A [75]. Similar to this, Momordica charantia (wild bitter melons) ethyl acetate extract contains phytol and lutein as bioactive constituents that, when stimulated THP-1 cells by P. acnes, strongly suppressed proinflammatory cytokine and MMP9 levels, attenuated granulomatous inflammation and ear swelling, and activated PRAR a and b in the transactivation assay [76]. Additionally, *rosthornins* A–D, which were extracted from the dried leaves and ether extract of *Rabdosia rosthornii*, demonstrated antibacterial activity that was particular to P. acnes(3.17–25 μg/mL) [77].

5. Summary of Different Innovative Drug Delivery Approaches

Dermal delivery of active ingredients is desirable in dermatological pharmacotherapy for the treatment of infectious and inflammatory skin disorders such as acne. Compared to oral or intravenous administration, topical application of anti-acne agents offers several advantages, including the avoidance of first-pass metabolism and the elimination of gastrointestinal irritation. Because skin acts as a good barrier against foreign penetration, antiacne agents have a harder time getting to the pathologic site, which lowers their bioavailability. As a result, topical dosage forms for acne treatment should be made in a way that makes it easier for the active ingredient to reach the skin's pilosebaceous unit, the target site. To achieve this, a cleverly constructed delivery system containing the active component should be created, adding particular ligands to target the active site and overcoming the biological barriers.

The encapsulation of anti-acne medications in vesicular and particulate delivery systems is a novel approach to reduce associated side effects while maintaining the medication's effectiveness. Improving the topical delivery of anti-acne agents can be greatly aided by innovative drug delivery techniques through improving their dermal localization while simultaneously lessening their adverse effects. There appears to be a growing commitment to developing new technologies for delivery systems optimization. These technologies may help overcome technical challenges by influencing drug release, improving drug retention by reducing local drug toxicity and targeting, lowering the dose of active agents and combination therapy, and utilizing more potent drugs that cannot be clinically used through conventional drug delivery. Recently, a variety of drug delivery vehicles, including solid lipid nanoparticles, liposomes, niosomes, nanoemulsions, and nanosuspensions, have been investigated as potential treatments for acne vulgaris. In fact, in vitro experiments have clearly demonstrated their ability to improve the topical delivery of antiacne agents [78, 79].

A recent study prepared and characterized solid lipid nanoparticles with chitosan containing tretinoin; the nanoparticles demonstrated high encapsulation efficiency, high physical stability, and absence of cytotoxicity in keratinocytes. The study revealed that tretinoin was more effective in treating acne when applied topically because it demonstrated antibacterial activity against P. acnes [80].

6. Conclusion

While topical, systemic retinoid, antibiotic, and keratolytic drug therapies are available for treating acne, the main obstacle is the increasing worries about antibiotic resistance and dermal toxicities associated with current drug regimens. The authors recommend using natural remedies instead of these manufactured medications to treat acne. The naturally derived medications from active plant extracts, essential oils, and phytomolecules that are covered in the review are included in these emerging natural therapies. But there are certain problems associated with natural therapies. For instance, when thinking about plant extracts, it's important to define the safety and quality of the extracts. Standardization using cutting-edge analytical techniques (HPLC, HPTLC, GC, and LC-MS/MS) can solve these issues. Despite their high levels of bioactivity in vitro, essential oils and phytomolecules show little to no action in vivo because of their instability, irritability, low lipid solubility, or incorrect molecular size, which leads to poor absorption and bioavailability. These obstacles could be solved by encapsulating the active component in a novel carrier that

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lowers the likelihood of the active component coming into direct contact with the environment and the skin's surface. This would make the product less irritating, which is an advantage of controlled release. Furthermore, because creating novel carriers requires less frequent administration and toxicity intervention, the overall cost is less than that of creating conventional carriers with similar activity. Another significant obstacle is the absence of an animal model that would accurately replicate the histologic and immunophenotypic features of acne. An anti-inflammatory model that focuses on the main cytokines involved may be a better choice, depending on the expressed cytokines in the acne lesions. As the initiator of sebocyte differentiation that contributes to sebum hyperproduction and hyperkeratinization, androgens (DHEAS, testosterone, and DHT) and other related enzymes (5-α reductase, anticoligenase, and elastase) are easily mimicked in small animal models as a target for novel moieties. Future animal targets may include comedolytic and antioxidant activities in the rabbit model. Additionally, to maximize the therapeutic result, molecular targets that modulate a number of important pathological factors associated with acne can be targeted. . Hence, currently we can say that still a lot of expertise and experience are needed in this area as plant drugs have massive potential against *P. acnes* which should be explored through some value added drug delivery systems.

7. Acknowledgement

The authors express their sincere gratitude to the departmental authority and the CV Raman Research Wing of JBIT College of Pharmacy and Research Wing Keshri Chand Subharti Institute of Pharmacy for their invaluable support in carrying out this study. The writers also sincerely thank the anonymous referee for their constructive criticism and insightful revision suggestions.

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