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Reviewing the Emerging Significance of Herbal Extracts in the Effective Treatment of Acne Vulgaris

Short running title: Herbal anti-acne extracts and phytomolecules

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ABSTRACT
Acne is a common but dangerous skin disorder that affects over 80% of adolescents and young adults between the ages of 11 and 30. In their twenties, 42.5 percent of males and 50.9 percent of women are still sick. Due to the reckless use of anti-biotics, bacterial resistance has reached dangerous levels. As a result, the need of the hour is to find novel lead molecules / bioactives and to transport current drugs to the site of action in a more logical manner (for greater therapeutic impact). Since the dawn of time, plants and plant-derived products have played an important role in health care. As a result, the current analysis summarizes plants that are presently used to treat acne as well as those that have a lot of promise. Most active plant extracts, such as P. granatum, M. alba, A. anomala, and M. aquifolium; aromatic oils of C. obovoides, C. natsudaidai, C. japonica, and C. nardus; and phytomolecules such rhodomyrtone, pulsaquinone, hydropulsaquinone, honokiol, magnolol, xanthohumol lupulones, chebulagic acid and rhinacanthin-C against P. acnes. In addition, novel medication delivery techniques for significant botanical leads in the treatment of acne were highlighted.

Keywords: Acne, Extract, Herbal, Phytochemicals, Drug delivery, Treatment

I. INTRODUCTION

1.1. Background

In the developing fields of psychodermatology and neurodermatology, the comorbidity of chronic skin problems with mental health issues has long been recognised. Acne vulgaris is a prevalent dermatological disorder that has been linked to depression, anxiety, and other psychological complications. Acne is a multifactorial chronic inflammatory illness of the pilosebaceous follicles that is characterised by androgen-induced sebum hyperplasia, altered follicular keratinization, hormonal imbalance, immunological hypersensitivity, and bacterial (Propionibacterium acnes) colonisation. Although acne does not have the urgency of a life-threatening disease and does not impede general fitness, it has long-term consequences that may be significant, leaving cutaneous and emotional scars that last a lifetime. It affects a person's confidence, inflicting physical, social, and psychological harm, as well as lowering self-esteem and generating emotional pain [1].

Seborrhoea (excess grease), non-inflammatory lesions (open and closed comedones), inflammatory lesions (papules and pustules), and varying degrees of scarring due to cyst development are all clinical symptoms of acne. Acne is seen on the face, neck, upper chest, shoulders, and back, and is characterised by the maximum density of pilosebaceous units. Acne may be characterised as non-inflammatory (purely comedonal acne) or inflammatory (inflammatory acne) depending on the kind of lesion (mild papular, scarring papular, and nodular). Acne may be classified as mild, moderate, or severe depending on its severity. Mild acne consists of 20 open and closed comedones, 15 inflammatory lesions, and a total of 30 lesions. Similarly, papules and pustules are common in severe acne, as are comedones (20-100), inflammatory lesions (15-50), and total lesions in the range of 30-125. Severe acne is defined by severe lesions, such as nodules and scarring, as well as cysts (>5), a high total comedone count (>100), a high overall inflammatory count (>50), and a high total number of lesions (>125) [2].

1.2. Epidemiology

Although there is almost no death with this condition, there is typically significant physical

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and psychological morbidity. According to statistics, roughly 85 percent of young adults aged 12–25 years old, approximately 8% of people aged 25–34 years old, and 3% of adults aged 35–44 years old suffer from acne at some point in their lives. In their twenties, on average, 42.5 percent of males and 50.9 percent of women still have the condition. Acne may last for up to 30 days in 30% of women throughout their reproductive phase, according to new research. Acne affects 40 to 50 million individuals in the United States each year, and a considerable proportion of adults suffer from it even into their adolescent years. According to population research in Germany, 64 percent of people aged 20 to 29 and 43 percent of those aged 30 to 39 have noticeable acne. Another research of more than 2000 persons in Germany found that 3% of men and 5% of women had definite moderate acne at the age of 40 to 49 years old. Closed comedones varied from open comedones by a proportion of 4.9:1 in a study of 309 participants in southern India. Grade-1 acne vulgaris affected 186 patients (60.2%), whereas grades 2, 3, and 4 affected 85 (27.5%), 8 (2.6%), and 30 (9.7%) of patients, respectively. Acne is about 80% heritable in first-degree relatives and is more severe in individuals with a favourable family history, according to recent research. Acne is more common and severe among smokers, according to a dose-dependent relationship. The cost of acne to society was not fully defined, but its prevalence reinforced the high expenses, imposing a significant financial burden on the community. According to a recent analysis from the United States, the cost of acne treatment and lost productivity is projected to be $3 billion each year [3,4].

1.3. Acne Pathophysiology

The pilosebaceous unit, which consists of multi-lobulated sebaceous glands, an epithelium-lined follicular canal, and a hair, is where the multi-factorial pathogenesis of acne begins. Sebaceous gland hyperplasia with seborrhoea, alteration in the quality of sebum lipids, inflammatory processes other than immune response, dysregulation of the hormone microenvironment, interaction with neuropeptides, and follicular hyperkeratinization followed by proliferation of Propionibacterium acnes within the follicle are all thought to play a role in acne pathophysiology [5].

In acne vulgaris, there is a known relationship between testosterone levels and sebum production. The initial cause of the development of acne is androgen-induced sebaceous gland enlargement, which leads to excessive sebum production. Steroid metabolising enzymes in the sebaceous glands convert dehydroepiandrosterone (DHEAS) to dihydrotestosterone (DHT). Furthermore, testosterone is converted to the more active DHT by two kinds of 5-α-reductase isozymes, type-1 and type-2, which are found in the scalp, chest, sebaceous glands, genitourinary tissue, and dermal papillae, as well as hair follicles. Excess sebum production obstructs the pilosebaceous unit and promotes follicular canal cell turnover. Furthermore, pilosebaceous follicles are surrounded by macrophages and inflammatory mediators that express Toll-like receptors (TLR2) on their surface in the second component of pathogenesis. TLR2 activation causes nuclear factor triggering, which leads to the expression of cytokines like interleukin-1 (IL-1), IL-8, and granulocyte macrophage-colony stimulating factor (GM-CSF), which initiates and propagates the inflammatory response, which further induces keratinocyte hyperproliferation. The retention of desquamated keratinocytes inside the pilosebaceous unit causes follicular plugging and blockage, which leads to the obliteration of the follicle's normal architecture and the creation of the comedo, a thin-walled cystic lesion. The microcomedo wall ultimately ruptures when keratinocytes and sebum build, causing irritation [6].

A developing comedone is a greasy clog made up of keratin, oil, germs, and the surface layer of melanin that may be black or white in appearance. "Black heads" or open comedones are comedones that break through the skin surface and have a core black look (owing to the oxidation of tyrosine to melanin by tyrosinase). Impaction and distension of the follicle caused by incorrectly desquamated keratinocytes and sebum, on the other hand, results in the formation of "white heads" or closed comedones that persist under the skin surface as closed follicles. These lesions might be classified as a papule, pustule, nodule, or cyst, depending on the severity of the pathologic circumstances [7].

Propionic and acetic acid are produced by Propionibacterium acnes, an anaerobic Gram-positive bacterium. Because comedones are packed with a lipid substrate as a nutrition source, a considerable number of P. acnes are found in the follicular infundibulum, making it an attractive location for anaerobes. P. acnes has a ribosome-rich cytoplasm and a rather thick peptidoglycan cell

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wall, measuring 0.4 to 0.7 m in width and 3 to 5 m in length, according to ultrastructural observations. By activating complements and metabolising sebaceous triglycerides into fatty acids that irritate the follicular wall and adjacent dermis, P. acnes plays a role in the development of inflammatory acne. It also creates exoenzymes and attracts neutrophils by chemotaxis. P. acnes generates lipases, proteases, and hydrolases, all of which contribute to inflammation and tissue damage; it also expresses stress proteins, which cause comedone rupture; and it activates the inflammatory response by binding to TLR-2. This is hypothesised to trigger hyperkeratinization, cell adhesion, follicular blockage, and inflammation by stimulating the production of cytokines such as IL-6 and IL-8 by follicular keratinocytes and IL-8 and IL-12 in macrophages. Acneiform lesions appear as papules, pustules, and nodules as a result of the sequential processes that induce vascular and cellular events of the inflammatory response and follicular disruption [8].

1.4. Acne Treatment Molecular Targets

Because human sebocytes are physiologically and metabolically active cells, they express a large number of receptors. Many ligands bind to these receptors and cause a variety of reactions, including changes in cell proliferation, cytokine production, and lipid synthesis, all of which are implicated in acne etiology, either directly or indirectly. Following a study of the literature, potential ligands have been identified that, when bound to their respective receptors, cause cell proliferation, cytokine expression, and lipogenesis. Each ligand (agonist) has its unique method of action in generating acne, necessitating the use of a particular antagonist to bind to these receptors and heal acne. All of these routes should be addressed and recognised prior to therapy selection when it comes to acne treatment and control [9].

- Neuropeptides such as vasoactive intestinal polypeptide (VPAC), neuropeptide Y, and calcitonin gene-related peptide, as well as Substance P, bind to VPAC receptors found on sebaceous glands' sebocytes. Binding results in the production of cytokines, sebocyte proliferation/differentiation, and lipogenesis upregulation.
- PRAR ligands include leukotriene B4, a well-known natural PPAR ligand found in mitochondria, peroxisomes, and microsomes of sebocytes (5-lipoxygenation product generated from arachidonic acid). 5-lipoxygenase inhibitors might be used to minimise lipogenesis and acne lesions since this ligand is known to increase lipogenesis in cultured human sebocytes.
- In SZ95 sebocytes, histamine binds to the histamine-1 receptor and stimulates squalene production. Lipid peroxidation occurs as a consequence, and squalene peroxide is formed as a byproduct. It also causes inflammatory reactions and comedogenesis, as well as interfering with sebocyte differentiation and sebogenesis at times.
- Insulin and insulin-like growth factors-1 activate the IGF-I receptor, which is expressed on the surface of SZ95 sebocyte cells. In sebocytes, IGF-I increases lipid accumulation in a dose-dependent manner. It is also known to promote 5-reductase, androgen production in the adrenal and gonadal glands, as well as androgen receptor signalling and sebocyte proliferation.
- Fibroblast growth factor (FGF) is released by keratinocyte-derived interleukin-1 activated fibroblasts and binds to FGF receptor 2β, which is found in the epidermis' suprabasal spinous layer and sebocytes. FGF is an important regulator of epithelial proliferation and differentiation. Simultaneously, androgen-mediated upregulation of FGFR2β signalling may occur, resulting in follicular hyperkeratinization and sebaceous gland hypertrophy.
- Corticotropin-releasing hormone and urocortin bind to the CRH-receptor 1 (CRH-R1) on human sebocytes, inhibiting sebocyte proliferation, upregulating 3-hydroxysteroid dehydrogenase, stimulating lipogenesis and keratinocyte differentiation, and increasing local inflammation by expressing IL-6 and IL-8.
- β-Endorphin binds to opiate receptors on sebaceous glands, stimulating lipogenesis and particularly increasing the quantity of fatty acids in sebocytes to a level comparable to linoleic acid.
- Melanocyte stimulating hormone binds to the melanocortin-1 and melanocortin-5 receptors (MC-1R and MC-5R) on sebocytes' cellular surfaces. In SZ95 sebocytes, MC-1R controls inflammation, and its expression is higher in acne-affected sebaceous glands.
- Retinoic acid (RA) and 9-cis retinoic acid are ligands for retinoic acid receptors (RAR and)

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and retinoid X receptors (RXR), which are the most common retinoid receptors in human sebocytes and govern cell proliferation and differentiation.

- Vitamin binds to vitamin D receptors and modulates cell proliferation, cell cycle regulation, lipid content, and IL-6 and IL-8 release in cultured sebocytes in a time and dosage-dependent manner.
- TLR-2,4,6 receptors on keratinocytes are stimulated by P. acnes moieties. Keratinocytes produce inflammatory cytokines (TNF-α, IL-6, and IL-8) after TLR activation.
- Sebum includes matrix metalloproteinases that arise in keratinocytes and sebocytes, including MMP-1, MMP-13, TIMP-1, TIMP-2, proMMP-9, and MMP-13, the latter two of which reduced with isotretinoin along with clinical improvement. In HaCaT keratinocytes, the drug blocked arachidonic acid, increased secretion, and MMP mRNA expression.
- Dipeptidyl peptidase-IV and aminopeptidase-N are ectopeptidases that attach to certain receptors and have a role in sebocyte control. Proliferation, terminal differentiation, and total neutral lipid synthesis are all boosted by DP-IV and APN. Furthermore, they activated T cells ex vivo and inhibited the expression of the immunosuppressive cytokine transforming growth factor-1 by promoting P. acnes proliferation and IL-2 production [10-12].

Acne lesions may be caused by changes in lipogenesis, sebum production, hyperkeratinization, sebocyte proliferation/differentiation, and cytokine expression. Only until the particular mechanism involved in the etiology is recognised can acne be effectively managed. Because these systems have a direct or indirect role in acne etiology, the following targets might be included when evaluating the anti-acne potential of notable active moieties in the near future [13].

II. CHALLENGES IN ACNE TREATMENT

Acne treatment is a long-term procedure that must be tailored to each individual patient. The treatment of an illness begins with the diagnosis of the condition and the development of an appropriate therapeutic approach. The selection of correct medicine based on its mechanism of action in relation to its capacity to address one or more of the pathogenic variables are the key problem connected with its treatment selection based on the type and severity of acne. In this setting, despite the various therapeutic drugs available, treating acne poses a number of obstacles [14].

2.1. Anti-biotic Resistance

Anti-biotics' continued use in acne therapy is accompanied by the threat of resistant bacteria arising. Anti-biotic resistance is caused by a variety of factors, including the unique nature of bacteria's contact with anti-biotics. As a result, there are sufficient reasons to look for alternate solutions to this issue. Alternative remedies for acne have been researched as a way to combat anti-biotic resistance as well as high treatment costs [15].

2.2. Overcome the Issues Associated with Traditional Anti-acne Drug Formulations

The management of the follow-up phase necessitates a framework for addressing therapy modification, which may include notions such as the lack of an effective mechanism for anti-acne medication delivery. Anti-acne medications used in traditional systems either don't reach the pilosebaceous unit at the right concentration or don't release the active moiety, resulting in subtherapeutic levels. The issue may be handled using future techniques that target the active molecule directly to the pilosebaceous unit or sebaceous gland, eradicating the underlying microbial flora of P. acnes as well as inflammatory mediators that cause acne vulgaris. Novel drug delivery systems (NDDS) may be preferred to reduce flaws in traditional formulations such as variations in therapeutic effectiveness and absorption, physicochemical features of active molecules and carriers, or incorrect integration of active molecules and carriers in conventional vehicles [16].

2.3. Inability to Find a Suitable Animal Model

The lack of a suitable animal model that can accurately replicate numerous pathophysiologic aspects in humans is a key obstacle in the development of effective medication and delivery method for acne [17].

III. CURRENT MANAGEMENT APPROACHES

The sensible use of existing treatment options, based on the kind and severity of acne lesions, is today a crucial component of effective acne therapy. Depending on the severity of acne, mainstream acne care uses topical treatment as a

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monotherapy or in conjunction with systemic medication therapy. Topical and oral retinoids, topical anti-microbials, systemic anti-biotics, keratolytics, and hormonal treatment, which included oral contraceptives and androgen blocking drugs, as well as combination therapy of all of the aforementioned agents, make up the present armamentarium [18].

Comedolytic drugs, such as topical retinoids (vitamin A derivatives), diminish aberrant keratinocyte mitosis, hyperkeratinization, and inflammation. It is claimed that modified slow-release formulations and third-generation retinoid adapalene are less irritating. Azelaic acid is a dicarboxylic acid that occurs naturally and has mild anti-bacterial and comedolytic properties. The most widely used topical anti-biotics for acne are erythromycin and clindamycin. They are beneficial in inflammatory lesions where anti-biotic resistance is a big issue. In moderate to severe inflammatory acne, oral anti-biotics, such as tetracyclines and macrolides, are administered, obviating the need for topical treatments. Trimethoprim, sulfamethoxazole, and ciprofloxacin are used in addition to the anti-biotics described above. Topical combination treatments have been shown to be more effective than monotherapy in several studies because they may address various disease pathways. Adapalene-BPO (0.1 percent / 2.5 percent), clindamycin-BPO (1 percent / 5 percent gel), erythromycin-BPO (3 percent / 5 percent gel), erythromycin-tretinoin (4 percent / 0.025 percent solution), and clindamycin-tretinoin (1.2 percent / 0.025 percent gel) are some of the fixed-dose topical combination products 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 ethynodiol diacetate inhibit serum androgen levels, increase sex hormone-binding globulin, and improve acne [19,20].

IV. PLANTS HAVING ANTI-ACNE POTENTIAL

The hunt for acne-fighting methods is still a significant research and development project in the pharmaceutical and personal care sectors. The use of anti-biotics indefinitely increases the danger of developing anti-biotic-resistant bacteria, which is self-evident. Anti-biotic resistance is caused by a variety of factors, including the nature of bacteria's interactions with anti-biotics. As a result, there are ample reasons to seek out and find alternate solutions to these issues. Medicinal plants have been researched as potential remedies for ailments to combat anti-biotic resistance and excessive treatment costs. Numerous studies have shown that employing medicinally powerful plant actives to combat bacteria growth and the inflammatory response might be a viable option. The presence of 2,50,000-5,00,000 plant species provides a huge opportunity for testing phytotherapeutic compounds that may be used to treat acne. Traditional herbal remedies are a fascinating and mostly untapped source of novel medication research. Traditional treatments and natural items have a lot of promise for finding bioactive lead molecules and developing them into medications to treat acne vulgaris. With an ongoing quest for new physiologically active botanical compounds, an effort is also being made to list the prospective possibilities from traditional medical systems for the treatment of acne [21].

4.1. Plant Extracts

Standard extraction processes such as decoction, maceration, infusion, digesting, percolation, and soxhlet extraction are used to separate medicinally active sections of medicinal plants from inactive or inert components using selected solvents. Decoctions, infusions, tinctures, semisolids, and powdered extracts are all available. The following are some of the active plant extracts having anti-acne effects [22].

The anti-acne activity of Echinacea purpurea extract was achieved by reducing the growth of P. acnes and reversing the bacterial-induced inflammation. It also used cytokine antibody arrays to normalise increased cytokine levels in cell culture models of human bronchial epithelial cells and skin fibroblasts, including IL-6 and IL-8 (CXCL8). The dichloromethane extract of the pericarp displayed the strongest anti-bacterial action against both P. acnes and S. epidermidis with the largest level of α-mangosteen as determined by HPLC against both P. acnes and S. epidermidis. P. acnes and S. epidermidis had the same MIC (0.039 mg/mL), but different MBC values (0.039 and 0.156 mg/mL, respectively). TNF-α production was lowered by ELISA, and the extracts were efficient in scavenging free radicals and suppressing the production of pro-inflammatory cytokines. Senna alata (0.625–2.5 mg/mL MIC), Eupatorium odoratum (0.625 mg/mL MIC), and Barleria lupulina (1.25–2.5 mg/mL MIC) were similarly shown to have high inhibitory

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effects against P. acnes when tested using the broth dilution technique [23].

Furthermore, Camellia sinensis polysaccharide inhibited hemagglutination mediated by pathogens H. pylori, P. acnes, and S. aureus with MICs ranging from 0.01 mg/mL to 0.5 mg/mL. The findings suggested that C. sinensis had a selective anti-adhesive impact solely against P. acnes infections when it came to attachment of these pathogens to host cell lines. Furthermore, using a sebumeter, 3 percent green tea extract emulsion was shown to minimise skin sebum production in healthy human volunteers. When compared to extracts of Glycyrrhiza glabra and Calendula officinalis by agar disc diffusion method (due to the presence of alkaloids, flavonoids, glycosides, and terpenoids), methanolic extract of C. sinensis possessed the highest anti-bacterial activity against S. aureus, S. epidermis, and P. acnes (MIC 1.25 mg/mL), recommending them as responsible phytoconstituents [24].

P. acnes (MIC 15.6 µg/mL), S. aureus, and S. epidermidis (MIC 7.8–15.6 µg/mL) were also resistant to Punica granatum rind extract containing 13 percent ellagic acid. It also suppresses the formation of nitric oxide by murine macrophages such as RAW 264.7 cells and the release of β-hexosaminidase from antigen-stimulated rat basophilic leukemia cells, indicating that it has anti-allergic characteristics. By using the disc diffusion technique, potent extracts of Psidium guajava and Juglans regia leaf extracts demonstrated an in vitro inhibitory impact on P. acnes and other organisms isolated from acne lesions of 38 individuals. In keratinocytes, Selaginella involvens extract suppressed nitric oxide generation, iNOS / IL-1 expression, and cytokines (IL-1 and IL-8) while also having an anti-oxidant effect. Flavonoid and tannin fractions of Terminalia arjuna bark extract were evaluated against P. acnes and S. epidermidis, with the flavonoid fraction (MIC 0.315 mg/mL) and its 2% cream formulation proving to be more efficacious [25].

White tea, witch hazel, and rose extracts and formulations have a protective effect on fibroblast cells, resulting in a considerable reduction in the quantity of IL-8 released by fibroblast cells in response to hydrogen peroxide-induced damage. In addition, white tea and rose have significant anti-collagenase, anti-elastase, and anti-oxidant properties. Rosa damascene, Eucommia ulmoides, and Ilex paraguariensis methanolic extracts were observed to inhibit the growth of P. acnes with MICs of 2 mg/mL, 0.5 mg/mL, and 1 mg/mL, respectively. Furthermore, when human monocytic THP-1 cells were pretreated with heat-killed P. acnes at a dose of 0.1 mg/mL, the latter two inhibited the release of pro-inflammatory cytokines such as tumour TNF-α, IL-8, and IL-1. Extracts of Rubia cordifolia, Curcuma longa, Hemidesmus indicus, and Azadirachta indica suppressed reactive oxygen species in polymorphonuclear leukocytes and pro-inflammatory cytokine-induced monocytes in research. The anti-acne activity of Coscinium fenestratum extract was shown by MIC values of 0.049 mg/mL against P. acnes and S. epidermidis, as well as MBC values of 0.049 mg/mL and 0.165 mg/mL, respectively. Tephrosia purpurea, Euphorbia hirta, Curcubito pepo, and Eclipta alba all demonstrated potent anti-bacterial properties against P. acnes. Borago officinalis, Linum bienne, and Ruta graveolens leaves and seeds, as well as aerial portions of Malva sylvestris and Rubus ulmifolius, have all been shown to successfully cure acne [26].

MIC values for Morus alba root extract against P. acnes and S. epidermidis were 15.6 µg/mL and 3.1 µg/mL, respectively. MIC values against both infections were likewise extremely low in extracts from Phellodendron amurense, Albizzia julibrissin, and Poncirus trifoliate. Similarly, polyphenol-rich Anacardium pulsatilla and flavonol-rich Podocarpus nagi have been shown to be effective against P. acnes. Angelica anomala is another well-known plant that has substantial inhibitory effects against P. acnes and S. epidermidis, with MIC values of 15.6 µg/mL and 126 µg/mL, respectively. Both pathogens were suppressed by Mollugo pentaphylla, Matteuccia orientalis, and Orixa japonica, as well as a decrease in P. acnes-induced release of IL-8 and TNF-α in THP-1 cells. Based on their anti-bacterial (MIC 0.13 mg/mL; MBC 0.25 mg/mL), lipase inhibitory, and anti-oxidative capabilities, Caesalpinia sappan and Intsia palembanica were identified as powerful anti-acne herbs [27].

With MIC values ranging from 0.05 to 1.00 mg/mL, organic extracts of Elephantorrhiza elephantina, Ekebergia capensis, Eucalyptus camaldulensis, and Harpephyllum caffrum showed promising action against P. acnes. Ethanolic extracts of Ammnia baccifera, Hibiscus syriacus, Quercus infectoria, Berberis aristata, Couroupita guianensis, and Symplocos racemosa showed anti-acne potential in another investigation, however, Symplocos racemosa was shown to be the most

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effective with a MIC value of 0.044 mg/mL. Acne is treated using Pisum sativum seeds, which contain proteins, lecithins, and carbs, and Trifolium pretence, which contains isoflavones [28].

The plant Vitex agnus-castus has been demonstrated to help with premenstrual acne. The anti-acne potential of Usnea barbata, Solanum dulcamara, and Saccharomyces cerevisiae is due to their anti-oxidative and anti-bacterial activities. Different Eucalyptus species, such as E. globulus, E. maculata, and E. viminalis, have strong anti-acne action in a methanol-dichloromethane extract. In vitro, MIC values for Oregon grape crude root extracts and its alkaloids berberine and jatrorrhizine against P. acnes ranged from 5 to 50 µg/mL. When a gel formulation containing 0.1 percent anthraquinone-rich fraction from the roots of R. cordifolia was compared to a normal clindamycin gel using the cup plate diffusion technique, it showed strong effectiveness against P. acnes, S. epidermidis, and M. furfur. In another investigation, the extract's MIC value against P. acnes was determined to be 600 µg/mL using the broth dilution technique, resulting in a considerable zone of inhibition [29].

Because of its anti-bacterial and antioxidant qualities, terpenoids from Gossypium barbadens have anti-acne potential. P. acnes was shown to be inhibited by Eucommia ulmoides with a MIC of 0.5 mg/mL and the release of pro-inflammatory cytokines was reduced. Phyllanthus emblica's radical scavenging activity, Aralia continentalis' COX-2 and NO expression inhibiting activity, Clerodendrum indicum's inhibitory effect on lipid peroxidation, and Clerodendron trichotomum's suppression of PGE_2 production allow them to be used against inflammatory acne. Also efficacious for inhibiting lipid peroxidation were extracts from Aglaia roxburghiana fruits, Euonymus pendulus bark, Emblica officinalis fruits, and Raphanus sativus. Lygodium japonicum extracted by pressure aided water extraction showed anti-oxidant and anti-bacterial activity against Listeria monocytogenes, Salmonella typhimurium, and Propionibacterium acnes, with MICs of 2.59 mg/mL, 3.33 mg/mL, and 7.37 mg/mL, respectively [30].

4.2. Essential Oils

Water distillation, steam distillation, and cohobation, as well as the enfleurage process, are used to extract the natural essential oil, a concentrated hydrophobic liquid containing volatile scent components, from plant organs. These essential oils have recently been studied for their potential use in acne treatment [31].

In a single-blind, randomised clinical trial involving 124 patients with mild to moderate acne, researchers found that both 5 percent Melaleuca alternifolia (tea tree oil) and 5 percent benzoyl peroxide lotion successfully reduced the number of inflamed and non-inflamed lesions, with tea tree oil having significantly fewer side effects. Terpinen-4-o1, α-terpineol, and α-pinene have been reported to be effective against S. aureus, S. epidermidis, and P. acnes in tea tree oil. Tea tree oil was shown to be extremely effective in treating acne in a study of 60 individuals with mild to severe acne in terms of total acne lesion count and acne severity index. Similarly, the essential oil of Zingiber cassumunar (Plai oil) has anti-bacterial action against a broad variety of bacteria, dermatophytes, and yeasts (MBC 0.62 percent against P. acnes), indicating that it might be used to treat acne [32].

Furthermore, Thymus quinquecostatus essential oil has anti-bacterial, anti-oxidant, anti-elastase, and anti-inflammatory properties that are effective against acne-causing microorganisms. It also causes modest cytotoxicity in human cell lines, indicating that it might be useful for acne therapy. Additionally, rosemary essential oil's anti-bacterial activity against P. acnes (MIC 0.56 mg/mL) was linked to bioactive components such 1,8-cineole, -pinene, camphor, and camphene. AFM and phase pictures indicated that rosemary essential oil bonded to the surface of bacterial cells at low concentrations, and that as the concentration increased, the bacterial bodies were badly destroyed [33].

Furthermore, owing to α-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) demonstrated anti-bacterial action against P. acnes as assessed by agar diffusion and microdilution techniques. According to an in vivo rat sebaceous gland model, eucalyptus oil reduces sebum production by shrinking sebaceous glands, hence decreasing acne spread [34].

Anti-bacterial activity of Abies koreana essential oil against medication sensitive and resistant P. acnes and S. epidermidis was outstanding. In addition, it inhibited TNF-α, IL-1, IL-6, NO, and PGE_2 release in RAW 264.7 cells, demonstrating anti-inflammatory properties. Similarly, coriander oil's anti-bacterial activity against P. acnes and S. epidermidis was tested, with MIC values of 1 percent and 1.1 percent v/v,

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respectively, determined using the agar dilution technique. Citrus obovoides and Citrus natsudaidai oils were shown to have anti-bacterial activity against P. acnes and S. epidermis (MIC 0.31 µL/mL and 2.5–10 µL/mL, respectively) as well as superoxide anion radical scavenging activity in vitro. They also inhibited P. acnes-induced IL-8 and TNF-α secretion in THP-1 cells. The essential oil of Cryptomeria japonica, which contains kaurene, enemol, β-eudesmol, and sabinene, shows significant anti-bacterial action against P. acnes and S. epidermidis (MIC 0.16–10 µL/mL) and inhibits NO, PGE2, TNF, IL-1, and IL-6 production in lipopolysaccharide-stimulated macrophages [35].

Another well-known Ocimum gratissimum oil mixture in a cetomacrogol blend base was well tolerated, more effective, and reduced acne lesions quicker than benzoyl peroxide 10% lotion, demonstrating its efficacy in acne therapy. The anti-acne activities of Ocimum oil were increased by aloe vera gel, and their combination was shown to be more effective than 1 percent clindamycin in the treatment of acne. Essential oils of Cymbopogon nardus, Cymbopogon citratus, Citrus hystrix, Ocimum sanctum, Ocimum basilicum, Zingiber cassumunar, and Zingiber officinale were shown to have anti-bacterial, anti-inflammatory, and anti-oxidant activities, according to research. Cymbopogon nardus oil (citronella oil) was shown to be the most effective against P. acnes (MIC 0.005–0.3 µL/mL). Furthermore, all essential oils, with the exception of kaffir lime oil, displayed significant free radical scavenging action. It has been proposed that significant components such as eugenol in holy basil oil and D-limonene in kaffir lime oil contribute to this function. Mentha spicata, Zingiber officinale, Citrus limon, Citrus paradisi, Jasminum grandiflora, Lavandula angustifolia, Matricaria chamomilla, Thymus vulgaris, Rosa damascene, and Cinnamomum zeylanicum were shown to have anti-acne activities against P. acnes in a separate investigation. The bactericidal activity of thyme, cinnamon, and rose essential oils were shown to be the best, with MICs of 0.016 percent, 0.016 percent, and 0.031 percent v/v, respectively [36].

Ocimum basilicum (sweet basil) and Ocimum sanctum (holy basil) essential oils, as well as their microemulsions, were screened for in vitro activity against P. acnes using the disc diffusion method, revealing that the MIC values of sweet basil and holy basil oils were 2.0 percent v/v and 3.0 percent v/v, respectively, and that the microemulsion of sweet basil oil had higher activity than that of holy basil oil. Backhousia citriodora, an Australian essential oil, has been demonstrated to have anti-bacterial action against S. aureus, E. coli, P. aeruginosa, Candida albicans, methicillin-resistant S. aureus, A. niger, K. pneumoniae, and Propionibacterium acnes.

Acne has been treated using essential oils of Citrus aurantium, Eucalyptus radiata, Juniperus communis, Pelargonium asperum, Pogostemon cablin, and Styrax benzoe. Furthermore, essential oils of Anthemis aciphylla, Salvia desoleana, and Salvia sclarea inhibited S. aureus and S. epidermidis in a mild to moderate manner. Essential oil of Tamarix bovena was discovered to suppress face microorganisms, which might be useful in acne therapy [37].

Helianthus annuus and Cucurbita pepo seed oils, as well as flax or linseed oil, which are high in linoleic and linolenic acids, were used to cure acne. Aside from the natural oils listed above, Prunus armeniaca, Argania spinosa, Persea gratissima, Adansonia digitata, Ribes nigrum, Vaccinium macrocarpon, Zea mays, Oenothera biennis, Vitis vinifera, Corylus americana, Schinziophyton rautanenii, Moringa oleifera, Elaeis guineensis, Papaver, etc. These results suggest that essential oils play an important role in acne treatment regimens that are tailored to the individual [38].

4.3. Phytomolecules

Plants have a wide spectrum of medicinally active chemical components, known as phytoconstituents, which are responsible for their pharmacological effects. The discovery, separation, and characterisation of plant extract bioactive phytomolecules are the primary goal after obtaining an active extract(s). Many recent scientific papers highlight the use of isolated phytomolecules in the treatment of acne lesions through a variety of processes, which are discussed below [39-43].

4.3.1. Rhodomyrtus tomentos

Rhodomyrtone, the active ingredient in Rhodomyrtus tomentosa leaves, was tested against P. acnes (MIC 0.5 µg/mL) using the broth macrodilution technique and found to be very efficient, killing 99 percent of the bacteria in under 24 hrs. A cytotoxicity test on human normal fibroblasts revealed extremely minimal cytotoxicity, indicating that it might be used as a topical anti-acne drug.

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4.3.2. Pulsatilla koreana

Pulsatilla koreana extract-derived pulsaquinone and hydropulsaquinone showed anti-bacterial action against P. acnes, with MIC values of 2.0 μg/mL and 4.0 μg/mL, respectively.

4.3.3. Caesalpinia sappan

Furthermore, the lipase inhibitory and anti-bacterial activity of Brazilin, protosappanin A, and sappanone B, which were isolated from methanolic extracts of Caesalpinia sappan wood, was substantial, with MIC values of 0.50 mg/mL, 1.00 mg/mL, and >2.00 mg/mL, respectively. Brazilin and protosappanin A were shown to have much stronger anti-oxidant activity than sappanone B.

4.3.4. Momordica charantia

Similarly, the phytol and lutein bioactive constituents in the ethyl acetate extract of Momordica charantia (wild bitter melons) suppressed pro-inflammatory cytokine and MMP-9 levels in P. acnes stimulated THP-1 cells, reduced ear swelling and granulomatous inflammation, and activated PRAR-α and PPAR-β in a transactivation assay.

4.3.5. Rabdosia rosthornii

Further ent-kaurene diterpenoids, rosthornins A–D, discovered from Rabdosia rosthornii's dry leaves ether extract, showed anti-bacterial action against P. acnes (3.17–25 μg/mL).

4.3.6. Rhizoma coptidis

Berberine, the active ingredient of Rhizoma coptidis, has been shown to have anti-inflammatory properties by inhibiting lipoxygenases and inhibiting COX-2 and API. Its extract inhibited the transcriptional production of numerous pro-inflammatory cytokines and cell surface components implicated in inflammatory reactions, demonstrating its anti-inflammatory efficacy.

4.3.7. Impatiens balsamina

Flavonoids such as kaempferol and quercetin, derived from Impatiens balsamina and used in conjunction with clindamycin and erythromycin, were shown to be effective against anti-biotic-resistant P. acnes, with MIC values of 32 μg/mL and 64 μg/mL, respectively.

4.3.8. Magnolia spp

Similarly, using the disc diffusion technique, honokiol and magnolol were extracted from Magnolia spp. showed significant anti-bacterial activity against P. acnes and P. granulosum, with MICs of 3-4 μg/mL and 9 μg/mL, respectively. Furthermore, their killing curve study revealed that P. acnes were swiftly killed at a rate of 10^5 organisms/mL within 10 mins of treatment. They also inhibited the release of IL-8 and TNF-α in THP-1 cells, showing that they had anti-inflammatory properties.

4.3.9. Prumnopitys andina

2β-acetoxyferruginol, a novel abietane diterpene isolated from the stem bark of Prumnopitys andina, was reported to have anti-bacterial activity against P. acnes at a concentration of 4 μg/mL.

4.3.10. Kaempferia pandurata

Panduratin A, a natural chalcone molecule discovered from Kaempferia pandurata, exhibits notable anti-staphylococcal action in vitro.

4.3.11. Mahonia aquifolium

The anti-bacterial efficacy of Mahonia aquifolium stem bark crude extract and its protoberberine alkaloids, berberine, and jatrorrhizine against twenty strains of coagulase-negative staphylococci and P. acnes (MIC 5–50 μg/mL) isolated from acne patients' skin lesions.

4.3.12. Epimedium brevicornum and Polygonum cuspidatum

When applied in sub-inhibitory quantities, Epimedium brevicornum and Polygonum cuspidatum extracts, as well as their active components icariin, resveratrol, and salidroside, were shown to have substantial anti-biofilm efficacy against P. acnes.

4.3.13. Hupulus lumulus

P. acnes (MIC 0.1–3 μg/mL), S. epidermidis, S. aureus, K. rhizophila, and S. pyogenes were all inhibited by naturally produced components xanthohumol and lupulones from Hupulus lumulus. In addition to humulones, these substances showed moderate to high anti-collagenase inhibitory activity. Xanthohumol also had the greatest total and singlet oxygen radical absorption capacities, indicating its anti-oxidative potential. S. aureus, MRSA, B. cereus, E. faecalis, A. acidoterrestris, P. acnes, and T. mentagrophytes were significantly suppressed by the flavonoids

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2′,6′-dihydroxy-3′-methyl-4′-methoxy-dihydrochalcone, eucalyptin, and 8-desmethyl-eucalyptin, which were isolated from E. maculat, α-aescin, digitonin, kaempferol, and catechin, among other saponins and flavonoids, demonstrated substantial lipase inhibitory effect with minimal toxicity, validating their efficacy against acne.

4.3.14. Psoralea corylifolia

Bakuchiol, a compound derived from the edible seeds of Psoralea corylifolia, possesses anti-bacterial, anti-collagenase, COX-2, COX-1, and production of inducible nitric oxide synthase genes inhibiting action. It efficiently quenches superoxide, hydroxy, peroxy, peroxynitrile radicals, and singlet oxygen non-radicals, as well as preventing lipid peroxidation, thanks to its wide range anti-oxidant action. According to a pilot clinical research, 1 percent bakuchiol reduced acne by around 57 percent, while 2 percent salicylic acid only decreased acne by about 48 percent, but when taken together, they reduced acne lesions and inflammation by up to 70%.

4.3.15. Angelica dahurica

The fruits and roots of A. dahurica, which include imperatorin, phellopterin, xantoroxin, byakangelcol, oxypeucedanin, neobyakangelcol, and coumarin, were shown to significantly reduce neutrophil chemotaxis.

4.3.16. Coptis chinensis

Similarly, Coptis chinensis root and stem, which contain significant levels of berberine, have a potent anti-lipogenic action; also, G. glabra, which contains glycyrrhizine, triterpene glycoside, glabric acid, flavanones, and isoflavones, has potent anti-bacterial activity against P. acnes.

4.3.17. Scutellaria baicalensis

In a subchronic cutaneous inflammatory model of tetradecanoylphorbol-13-acetate caused ear edema, wogonin (5,7-dihydroxy-8-methoxyflavone) derived from the methanolic extract of Scutellaria baicalensis potently reduced mRNA levels of COX-2, TNF-α, and PGE_2. Intercellular adhesion molecule-1 and IL-1β were similarly altered, albeit to a lesser amount.

4.3.18. Evodia rutaecarpa

Rutaecarpine, a quinazolinocarboline alkaloid, evodiamine, dehydroevodiamine, and triterpenoid evodin, all obtained from the unripe fruit extract of Evodia rutaecarpa, reduced ultraviolet A-induced ROS production in human skin cells, leading to increased expression of MMP-2 and MMP-9. It also suppressed H_2O_2-induced increases in MMP-2 and MMP-9 expression, as well as COX-2 and phospholipase A_2. Human HaCaT keratinocyte cells pretreated with heat-killed P. acnes produced considerably less IL-8 and TNF-α when given matrine, baicalin, ursolic acid, sodium danshensu, hesperidin, and andrographolide.

4.3.19. Terminalia chebula and Embelia ribes

Lipase inhibition was seen in extracts from Terminalia chebula and Embelia ribes, with a MIC of 12.5 μg/mL against P. acnes. Chebulagic acid was shown to be the main component for anti-lipase action. Isolappaol C, lappaol C, lappaol D, lappaol F, and diarctigenin were among the chemicals identified from the methanolic extract of Arctium lappa seeds, and the latter two effectively reduced NO generation in LPS-stimulated RAW264.7 cells.

4.3.20. Phyllanthus embelica

Geraniin, a compound derived from Phyllanthus embelica, shown high anti-oxidant activity in DPPH and lipid peroxidation experiments, as well as NO scavenging activity.

4.3.21. Anthemis nobilis and Matricaria recutita

Because of their physiologically active flavonoids, notably apigenin, β-bisabolol, and chamazulene, Anthemis nobilis and Matricaria recutita have been used to treat skin irritation.

4.3.22. Rhinacanthus nasutus

Rhinacanthin-C (82.59 percent) isolated from Rhinacanthus nasutus extract was shown to exhibit significant bactericidal action against S. mutans and P. acnes, with MIC values of 2–8 μg/mL.

4.3.23. Rosmarinus officinalis

In recent research, rosmarinic acid, a phenolic component from Rosmarinus officinalis, was shown to have inhibitory capability against P. acnes and S. aureus, with MIC values of 62.5 μg/mL and 31.25 μg/mL, respectively.

4.3.24. Intsia palembanica

Fustin, ampelopsin, and 4′-dehydroxyrobidanol were found to be the most active compounds in inhibiting the lipase activity of P. acnes using the 2,3-dimercapto-1-propanol

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tributyrate (BALB) method, with IC_{50} values of 13.7 μM, 36.1 μM, and 40.0 μM, respectively, in a study of ten flavonoids isolated from Intsia palembanica. The primary polyphenol in green tea, epigallocatechin-3-gallate, was discovered to decrease sebum via altering the AMPK-SREBP-1 signalling pathway and inflammation by suppressing the NF-κB and AP-1 pathways. These results were backed up by an 8-week randomised, split-face clinical study, which indicated that the molecule greatly reduced acne and was well tolerated.

2.3.25. Artocarpus

Acne manifests itself on the afflicted skin surface as dark patches (hyperpigmentation) and scars, which are caused by the overexpression and accumulation of melanin, which is controlled by the enzyme tyrosinase. Artocarpus integer root extract was shown to have tyrosinase inhibition potential (90.57 percent) as well as anti-bacterial activity against S. aureus, S. epidermidis, P. acnes, and T. mentagophytes in a research. Artocarpin and cudraflavone C, which was extracted from the aforesaid plant extract, had significant anti-bacterial activity against S. aureus, S. epidermidis, and P. acnes, with MICs of 2 μg/mL, 4 μg/mL, and 2 μg/mL, respectively, whilst artocarpanone had anti-tyrosinase potential.

The value of plant-derived therapy alternatives against acne vulgaris is shown by the foregoing discussion of the spectrum of natural treatments in the form of plant extracts, essential oils, and other isolated phytomolecules. These results also suggest that they have wide anti-P. acnes activity, either directly or indirectly, through pathways comparable to those of synthetic compounds, such as anti-inflammatory, anti-oxidative, anti-collagenase, anti-elastase, and anti-bacterial actions with fewer adverse effects [44].

V. OVERVIEW OF VARIOUS NOVEL DRUG DELIVERY STRATEGIES

Dermal distribution of active substances is desired in dermatological pharmacotherapy for the treatment of skin inflammatory and infectious diseases such as acne. Topical anti-acne medicines provide a number of benefits over oral or intravenous delivery, including avoiding first-pass metabolism and avoiding gastrointestinal discomfort. Because skin acts as a barrier to external penetration, it restricts anti-acne medicines' entrance to the pathologic site, lowering their bioavailability. As a result, topical dosage forms for acne should be developed in such a way that the active moiety is delivered to the target location, which is the pilosebaceous unit of the skin. With this goal in mind, an intelligently designed delivery system encasing the active moiety and attaching particular ligands to target the active site while overcoming biological obstacles should be devised.

Anti-acne medicines encapsulated in vesicular and particle delivery systems provide a new solution for reducing adverse effects while maintaining effectiveness. Anti-acne drugs may be better delivered topically using new drug delivery techniques that improve skin localisation while reducing adverse effects. Research is pointing to a growing commitment to developing new technologies to improve delivery systems that can overcome technical challenges by influencing drug release, improving drug retention through targeting and reducing local drug toxicity, lowering active agent and combination therapy doses, and harnessing more potent drugs that can't be clinically used through traditional drug delivery. Nanoparticles, liposomes, niosomes, solid lipid nanoparticles, nanoemulsions, and nanosuspensions are some of the drug delivery vehicles that have recently been investigated to combat acne vulgaris. In fact, in vitro investigations have shown their capacity to improve the topical administration of anti-acne drugs. Solid lipid nanoparticles containing chitosan and tretinoin were synthesised and described in a recent work, and they demonstrated great encapsulation efficiency, good physical stability, and no cytotoxicity in keratinocytes. It also has anti-bacterial action against P. acnes, boosting tretinoin's therapeutic efficiency in the treatment of acne on the skin. However, further research is required to enable the large-scale development of innovative drug delivery methods at reduced prices. Finally, further research is needed to confirm the effectiveness of these tactics in improving acne topical therapy [45].

VI. CONCLUSION

Although there are several therapeutic options for the treatment of acne (topical, systemic retinoid, anti-biotics, and keratolytics), the main difficulty is increased anti-biotic resistance and skin toxicity with current drugs. Natural therapies, rather than synthetic medications, are favoured by the writers as an acne treatment. The review discusses naturally generated pharmaceuticals

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derived from active plant extracts, essential oils, and phytomolecules. There are, however, certain concerns associated with natural remedies, such as defining the quality and safety of plant extracts when evaluating them. Advanced analytical methods (HPLC, HPTLC, GC, and LC-MS/MS) may be used to alleviate these issues through standardisation. Because of their volatility, irritant, low lipid solubility, or inappropriate molecular size, essential oils and phytomolecules have poor absorption and bioavailability in vivo, while having great bioactivity in vitro. These drawbacks might be solved by encapsulating the active moiety in a new carrier that reduces the active moiety's direct interaction with the environment and skin surface, resulting in a less irritating product (an advantage attributed to controlled release). Furthermore, since it needs less frequent injection and toxicity management, the total cost of developing new carriers is cheaper than that of traditional carriers with equivalent activity. Another key obstacle is the absence of an animal model that completely mimics the histologic and immunophenotypic aspects of acne, which is a human-only illness. An anti-inflammatory approach with a focus on the main cytokines implicated may be the preferable alternative depending on the expressed cytokines in acne lesions. Androgens (DHEAS, testosterone, and DHT) and related enzymes (5- reductase, anti-coligenase, and elastase), which are the initiators of sebocyte differentiation and contribute to sebum hyperproduction and hyperkeratinization, can be easily mimicked in small animal models as a target for novel moieties. Future animal objectives might include comedolytic and anti-oxidant properties in rabbits. Additionally, molecular targets that affect a number of major acne pathogenic variables may be targeted to improve the therapy's success. As a result, we can now claim that a lot of skill and experience is still required in this field, as plant medications offer a lot of promise against P. acnes, which should be studied using some value-added drug delivery vehicles.

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