IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Understanding Acne: Deep Insights Into Pathophysiology, Molecular Targets, Challenges, And Pharmacotherapeutics

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Abstract: Over 80% of people between the ages of 11 and 30 suffer from acne, a common yet serious skin ailment. Only 42.5% of men and 50.9% of women in their twenties are completely healthy. The overuse of antibiotics has resulted in microorganisms that are more resistant to treatment. Therefore, it is vital to identify new lead molecules/bioactives and develop rational methods of transporting existing medications to the site of action (for enhanced therapeutic effect). Plants and products generated from plants have been used for medical purposes from the beginning of time. Therefore, the current research provides a summary of both plants already used to treat acne and those that show significant potential for this purpose. The concept, demography, classification, pathophysiology, economical perspectives, types, challenges, and treatment approaches of acne are highlighted.

Keywords: Acne, Pathophysiology, Challenge, Drug delivery, Treatment

1. Introduction

Comorbidity between long-term skin diseases and mental health concerns has been acknowledged for some time, particularly in the relatively new disciplines of psychodermatology and neurodermatology. Depression, anxiety, and other mental health issues have all been related to acne vulgaris, a common skin condition. Acne is marked by androgen-induced sebum hyperplasia, altered follicular keratinization, hormonal imbalance, immunological hypersensitivity, and bacterial (*Propionibacterium acnes*) colonisation of the pilosebaceous follicles **(Figure 1)**. Acne is not a life-threatening condition and does not hinder physical fitness, but it may have serious, long-lasting implications, including visible and intangible scarring on the skin and in the mind. A person's sense of self-worth is damaged, and they experience emotional anguish and social exclusion as a result [1].

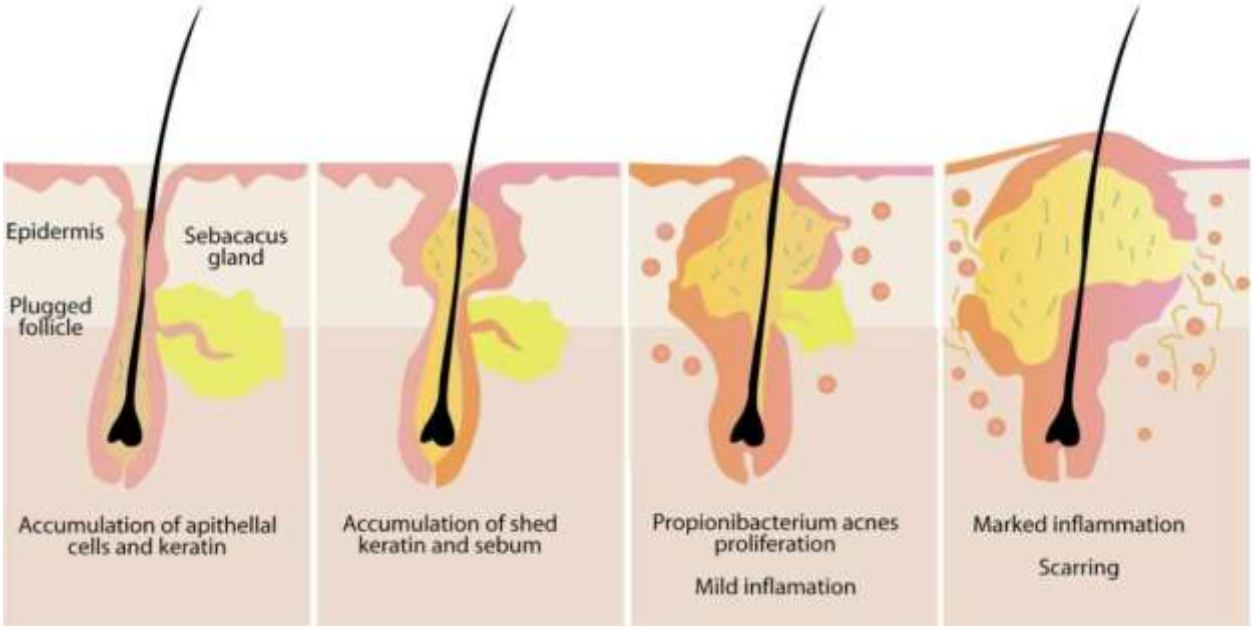

Figure 1. Formation of acne.

2. Clinical symptoms

Acne manifests clinically as seborrhea (excess oil), non-inflammatory lesions (open and closed comedones), inflammatory lesions (papules and pustules), and scarring of varied degrees owing to cyst formation. Acne is distinguished by a high density of pilosebaceous units and manifests itself on the face, neck, upper chest, shoulders, and back. Lesion types (mild papular, scarring papular, and nodular) determine whether acne is inflammatory (inflammatory acne) or non-inflammatory (purely comedonal acne) [2].

3. Classification

Depending on how bad the acne is, it may be classed as mild, moderate, or severe. Twenty comedones (both open and closed) and fifteen inflammations (both open and closed) make up mild acne. Comedones (20-100), inflammatory lesions (15-50), and total lesions (range, 30-125) are also prevalent in severe acne, as are papules and pustules. Nodules, scarring, a high number of cysts (>5), a high number of comedones (>100), a high number of inflammatory lesions (>50), and a total number of lesions (>125) are all indicative of severe acne [3].

4. Demographic data

Despite the low mortality rate associated with this illness, severe physical and psychological morbidity is often present. Eighty-five percent of teenagers and young adults (12 to 25 years old), 8 percent of adults (25 to 34 years old), and 3% of middle-aged and older adults (35 to 44 years old) have acne at some time in their life. On average, the prevalence of the illness remains at 42.5% in boys and 50.9% in females in their twenties. New study suggests that 30% of reproductive-aged women will have acne for at least 30 days. In the United States, acne affects between 40 and 50 million people annually, and many adults continue to have breakouts well into adulthood. Population studies in Germany reveal that 64% of adults aged 20-29 and 43% of people aged 30-39 suffer from acne. Another study of almost 2000 people in Germany indicated that between the ages of 40 and 49, 3% of men and 5% of women had definite moderate

acne. In a research including 309 people from southern India, the ratio of closed to open comedones was found to be 4.9 to 1. Among those diagnosed with acne vulgaris, 186 patients (60.2% of the total) had grade-1 acne, 85 (27.5%) had grade-2, and 8 (2.6%) had grade-3, and 30 (9.7%) had grade 4. According to current studies, acne is roughly 80% heritable in first-degree relatives, and it is more severe in those who have a positive family history of the condition. There is a dose-dependent association between smoking and acne severity and prevalence [4].

5. Economic perspectives

Although we don't have a firm number, we know that acne is expensive for everyone involved because of how common it is. The annual cost of treating acne and lost productivity is estimated to be $3 billion in the United States [5].

6. Pathophysiology

Acne's multi-factorial pathogenesis originates in the pilosebaceous unit, which comprises of a hair, a follicular canal bordered by epithelium, and a set of multi-lobulated sebaceous glands. Acne pathophysiology **(Figure 2)** is thought to involve a number of factors, including: follicular hyperkeratinization followed by proliferation of *Propionibacterium acnes* within the follicle; sebaceous gland hyperplasia with seborrhoea; changes in the quality of sebum lipids; inflammatory processes other than the immune response; dysregulation of the hormone microenvironment; interaction with neuropeptides; and so on [6].

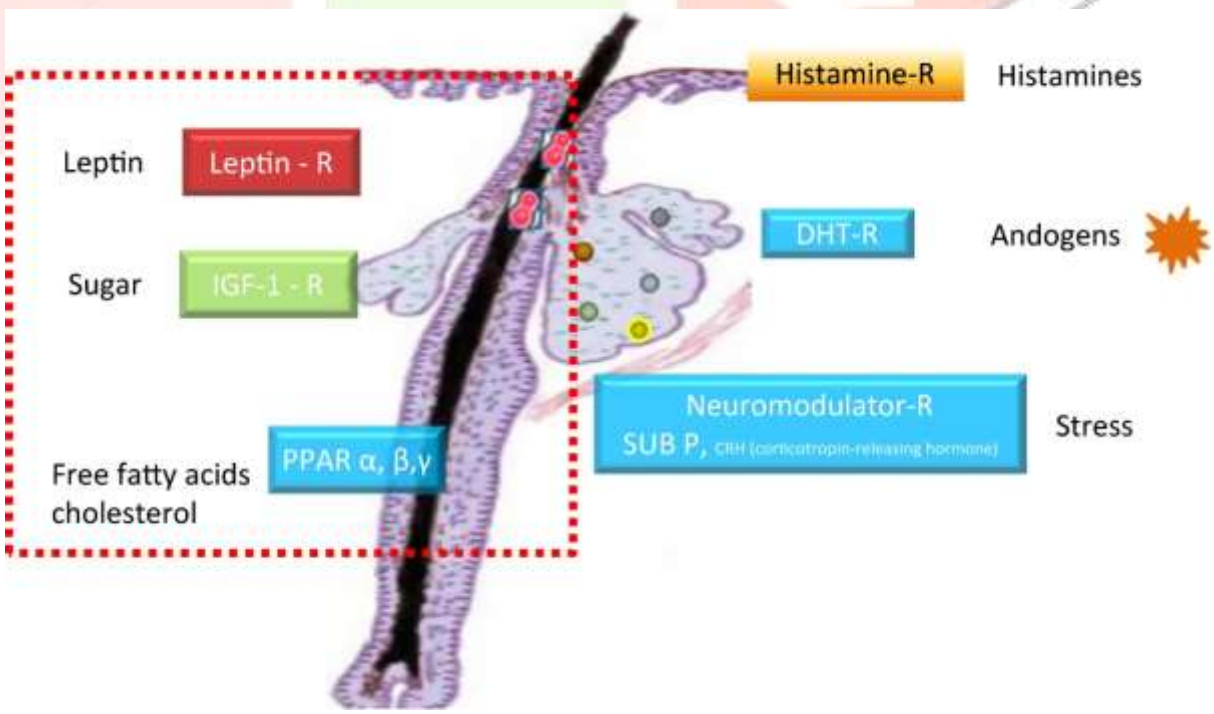

Figure 2. Pathophysiology of acne formation.

Sebum production is linked to testosterone levels in people with acne vulgaris. Acne begins with the overproduction of sebum due to the expansion of the sebaceous glands, which is triggered by androgens. Dehydroepiandrosterone (DHEAS) is converted to dihydrotestosterone (DHT) by steroid metabolising enzymes in the sebaceous glands. In addition, the scalp, chest, sebaceous glands, genitourinary tissue,

dermal papillae, and hair follicles all house 5-reductase isozymes that convert testosterone to the more potent DHT. Overproduction of sebum clogs the pilosebaceous unit and speeds up cell turnover in the follicular canal. In a second stage of pathogenesis, macrophages and inflammatory mediators with surface Toll-like receptors (TLR2) surround pilosebaceous follicles. The inflammatory response is initiated and sustained by TLR2 activation, which in turn induces keratinocyte hyperproliferation through the expression of cytokines such as interleukin-1 (IL-1), IL-8, and granulocyte macrophage-colony stimulating factor (GM-CSF). The comedo is a thin-walled cystic lesion caused by the retention of desquamated keratinocytes inside the pilosebaceous unit, which produces follicular clogging and obstruction. When keratinocytes and sebum accumulate, they irritate the skin and eventually cause the microcomedo wall to rupture [7].

A comedone is a greasy blockage that forms on the skin and is formed of keratin, oil, bacteria, and the outer layer of melanin, which may be either black or white. Cracked comedones with a dark centre (from tyrosine being oxidised to melanin) are known as "black heads" or open comedones. However, "white heads" or closed comedones arise when keratinocytes and sebum get impacted and distend the follicle, causing the follicle to remain subcutaneously as a closed follicle. Depending on the pathologic conditions, these lesions may be characterised as a papule, pustule, nodule, or cyst [8].

P. acnes is an anaerobic Gram-positive bacterium that produces propionic and acetic acid. Since comedones are rich in a lipid substrate that may be used as a food source, the follicular infundibulum is home to a large population of *P. acnes*. According to ultrastructural analyses, the peptidoglycan cell wall of *P. acnes* is between 0.4 and 0.7 μm in width and 3 and 5 μm in length, and the cytoplasm of *P. acnes* is rich in ribosomes. *P. acnes* contributes to inflammatory acne by activating complements and metabolising sebum triglycerides into fatty acids that irritate the follicular wall and surrounding dermis. Exoenzymes are produced, and neutrophils are drawn in by chemotaxis. In addition to producing inflammatory mediators including lipases, proteases, and hydrolases, *P. acnes* also produces stress proteins that lead to comedone rupture and stimulates the inflammatory response by binding to TLR-2. Hyperkeratinization, cell adhesion, follicular obstruction, and inflammation are thought to result from this because it causes follicular keratinocytes and macrophages to produce more cytokines including IL-6 and IL-8. Sequential processes promote vascular and cellular events of the inflammatory response and follicular disruption, resulting in the appearance of papules, pustules, and nodules [9].

7. Challenges to traditional acne treatment

Managing acne is a long-term process that requires tailored care. Diagnosing a patient's sickness and coming up with a treatment plan for them goes hand in hand. Choose the right drug for your acne type and severity by considering its mechanism of action in relation to its ability to address one or more of the pathogenic factors. Acne treatment is complicated in this scenario because of the wide variety of therapeutic medications accessible [10].

7.1. Antibiotic resistance

The persistent use of antibiotics in acne treatment is associated with the development of antibiotic-resistant bacteria. Multifactorial interactions between bacteria and antimicrobials contribute to the development of antibiotic resistance. That's why it's important to consider other potential answers to this problem. Anti-biotic resistance and hefty treatment costs have prompted researchers to look at other treatments for acne [11].

7.2. Issues related to dermatological pharmacotherapy

For inflammatory and infectious skin conditions like acne, dermatological pharmacotherapy often seeks dermal dispersion of active drugs. Avoiding first-pass metabolism and gastrointestinal discomfort are two advantages of topical anti-acne medications versus oral or intravenous administration. The skin's protective barrier reduces the anti-acne drugs' bioavailability by preventing them from reaching the pathologic site. Therefore, while creating topical dosage forms for acne, care must be taken to ensure that the active moiety is transported to the pilosebaceous unit of the skin. To achieve this end, it is necessary to create a delivery system that encloses the active moiety, attaches certain ligands to the active site, and is capable of circumventing any biological barriers that may stand in its way [12].

7.3. Issues related to formulations

Management of the maintenance phase requires a structure for dealing with therapeutic adjustment, which may include ideas like the absence of an efficient system for delivering anti-acne medicine. In conventional delivery methods, insufficient amounts of anti-acne medicine are delivered to the pilosebaceous unit, or the active moiety is not released. In the future, we may be able to treat acne by directly targeting the pilosebaceous unit or sebaceous gland with the active molecule, therefore eliminating the microbial flora that includes *P. acnes* and the inflammatory mediators that cause acne vulgaris. If researchers are looking to minimise problems with traditional formulations like inconsistent therapeutic efficacy and absorption, different physicochemical features of active molecules and carriers, or improper integration of active molecules and carriers in conventional vehicles, novel drug delivery systems (NDDS) may be your best bet [13].

7.4. Poor successful laboratory screening

Acne drug and delivery technique research is hampered by the absence of an animal model that can precisely mimic the human disease's complex pathophysiology [14].

8. Pharmacotherapeutics

8.1. Current therapeutic options

Effective acne treatment now requires the strategic use of currently available alternatives according to the kind and severity of acne lesions. The standard of care for acne now employs either topical treatment alone or in combination with systemic pharmaceutical therapy, depending on the severity of the condition. The current arsenal includes oral and topical retinoids, topical anti-microbials, systemic antibiotics,

keratolytics, hormonal treatment (oral contraceptives and androgen blocking medications), and combination therapy of all of the above agents [15].

Abnormal keratinocyte proliferation, hyperkeratinization, and inflammation may be reduced by comedolytic medicines such topical retinoids (vitamin A derivatives). Adapalene, a retinoid of the third generation, and modified slow-release versions are said to cause less irritation. Mild antibacterial and comedolytic activities may be found in azelaic acid, a naturally occurring dicarboxylic acid. Erythromycin and clindamycin are the two most common topical antibiotics used for acne. When antibiotic resistance is a concern, they may be helpful in inflammatory lesions. Oral anti-biotics, such as tetracyclines and macrolides, are given to patients with moderate to severe inflammatory acne, eliminating the need for topical therapies. In addition to the antibiotics listed above, trimethoprim, sulfamethoxazole, and ciprofloxacin are often used. Several studies have demonstrated that topical combination therapies are superior than monotherapy, perhaps because they target different disease pathways. It is found to have fixed-dose topical combinations like adapalene-BPO (0.1 percent/2.5 percent), clindamycin-BPO (one percent/five percent gel), erythromycin-BPO (three percent/five percent gel), erythromycin-tretinoin (4 percent/0.025 percent solution), and clindamycin-tretinoin (one percent/two and a quarter percent gel). Oral contraceptives like ethinyl estradiol combined with cyproterone acetate, levonorgestrel, norgestimate, desogestrel, drospirenone, and ethynodiol diacetate reduce serum androgen levels, boost sex hormone-binding globulin, and alleviate acne [16].

8.2. Natural products as alternative therapeutic options

Research and development efforts in the pharmaceutical and personal care industries continue to focus heavily on the quest for acne-fighting solutions. It is obvious that there will be an increase in the risk of antibiotic-resistant bacteria if antibiotics are used forever. Many factors, including the way bacteria react to antibiotics, contribute to the spread of antibiotic resistance. That's why it's important to look for and implement different answers to these problems. Antibiotic resistance and high healthcare expenses have prompted scientists to investigate medicinal plants as possible new treatments. There is mounting evidence that using medicinally potent plant actives to fight bacterial growth and the inflammatory response might be effective. Acne treatment phytotherapeutic substances may be tested on a massive scale due to the existence of 2,500,000–5,000,000. The potential of traditional herbal medicines as a source of new medications is exciting but mostly unexplored. Finding bioactive lead compounds and turning them into drugs to treat acne vulgaris has great potential for traditional therapies and natural goods. There is a concerted effort to catalogue the potential options from conventional medical systems for the treatment of acne, with the continued search for novel physiologically active botanical chemicals [17].

8.2.1. Plant Extracts

Decoction, infusion, maceration, percolation, digestion, and soxhlet extraction are only few of the common methods used to extract the useful components of medicinal plants while leaving the inert or non-active parts behind in a solvent. It may be obtained as a decoction, infusion, tincture, semisolid, or powdered extract. Here are some examples of plant extracts that have been shown to have anti-acne properties [18].

8.2.2. Essential Oils

Natural essential oil is extracted from plant parts via distillation (either with water or steam), cohobation, or the enfleurage method, all of which concentrate the hydrophobic liquid containing volatile olfactory components found in the plant. Recent research has examined the possibility of using these essential oils as a therapy for acne [19].

8.2.3. Phytomolecules

The pharmacological effects of plants are the result of a vast variety of chemical components found in plants and together referred to as phytoconstituents. Once active extract(s) have been obtained, the focus shifts to isolating and characterising the bioactive phytomolecules within the plant extract. The use of isolated phytomolecules in the treatment of acne lesions has been the focus of several recent research articles [20].

9. Mechanism of actions

9.1. Mechanistic approaches for anti-acne treatment

Human sebocytes express a plethora of receptors due to their high metabolic and physiological activity. Acne's etiology may be traced back to the binding of various ligands to these receptors, which in turn triggers a cascade of events that includes changes in cell proliferation, cytokine release, and lipid synthesis. Researchers have found putative ligands that, when binding to their receptors, trigger downstream effects including cell proliferation, cytokine production, and lipogenesis. Because different ligands (agonists) cause acne via different mechanisms, different antagonists must be used to attach to various receptors and alleviate acne. Acne therapy selection should take into account and address all of these potential entry points [21].

9.2. Reported molecular targets in anti-acne pharmacotherapeutics

- Inhibition of sebocyte proliferation, upregulation of 3-hydroxysteroid dehydrogenase, stimulation of lipogenesis and keratinocyte differentiation, and increased expression of IL-6 and IL-8 are all effects of corticotropin-releasing hormone and urocortin binding to the CRH-receptor 1 (CRH-R1) on human sebocytes.
- Among the ectopeptidases involved in sebocyte regulation are dipeptidyl peptidase-IV and aminopeptidase-N. DP-IV and APN promote cell proliferation, differentiation to the final stage, and total neutral lipid production. In addition to boosting *P. acnes* proliferation and IL-2 production, they activated T cells *ex vivo* and downregulated the expression of the immunosuppressive cytokine transforming growth factor-1.
- Fibroblast growth factor (FGF) is secreted by interleukin-1 activated fibroblasts that originate from keratinocytes and binds to FGF receptor-2, which is located in the suprabasal spinous layer of the epidermis and in sebocytes. Epithelial proliferation and differentiation are both influenced by fibroblast growth factor (FGF). Follicular hyperkeratinization and sebaceous gland hypertrophy may both arise from androgen-mediated activation of FGFR2 signalling.

- Squalene synthesis is increased in SZ95 sebocytes when histamine binds to the histamine-1 receptor. Squalene peroxide is produced as a result of lipid peroxidation. It may also interfere with sebocyte differentiation and sebogenesis, leading to inflammation and comedone formation.
- The IGF-I receptor is found on the surface of SZ95 sebocyte cells and is activated by insulin and insulin-like growth factors-1. IGF-I has a dose-dependent effect on elevating lipid accumulation in sebocytes. Androgen receptor signalling, sebocyte proliferation, and adrenal and gonadal androgen synthesis are all boosted by this compound.
- Sebocytes express melanocortin-1 and melanocortin-5 receptors (MC-1R and MC-5R), respectively, on their outer membranes, and MSH binds to these receptors. Increased MC-1R expression is seen in sebaceous glands that have been damaged by acne.
- Substance P, neuropeptides such vasoactive intestinal polypeptide (VPAC), and calcitonin gene-related peptide all bind to VPAC receptors on sebocytes in the sebaceous glands. When bound, cytokines are released, sebocytes multiply and differentiate, and lipogenesis is stimulated.
- The 5-lipoxygenation product of arachidonic acid (leukotriene B_4) is a well-known natural PPAR ligand present in the mitochondria, peroxisomes, and microsomes of sebocytes. Inhibitors of 5-lipoxygenase might be utilised to reduce lipogenesis and acne lesions since this ligand stimulates lipogenesis in human sebocytes in culture.
- The most abundant retinoid receptors in human sebocytes, retinoic acid receptors (RARs) and retinoid X receptors (RXRs), are regulated by retinoic acid (RA) and 9-cis retinoic acid, respectively.
- Sebum contains matrix metalloproteinases, which originate in keratinocytes and sebocytes and are decreased by isotretinoin along with clinical improvement. These metalloproteinases include MMP-1, MMP-13, TIMP-1, TIMP-2, proMMP-9, and MMP-13. The medication inhibited arachidonic acid, enhanced secretion, and MMP mRNA expression in HaCaT keratinocytes.
- *P. acnes* moieties activate keratinocyte TLR-2,4,6 receptors. After TLR activation, keratinocytes secrete inflammatory cytokines (TNF-α, IL-6, and IL-8).
- Cell proliferation, cell cycle regulation, lipid content, and IL-6 and IL-8 production are all time- and dose-dependently affected by vitamin-D binding to vitamin-D receptors in cultured sebocytes.
- β-Endorphin stimulates lipogenesis by binding to opiate receptors on sebaceous glands, raising the amount of fatty acids in sebocytes to a level similar to linoleic acid [22].

10. Novel Drug Delivery Strategies

Vesicular and particle delivery technologies for acne medications provide a novel way to lessen side effects without sacrificing efficacy. New drug delivery strategies that increase skin localization while lowering side effects may be useful for topical distribution of anti-acne medicines. Evidence suggests a growing dedication to developing new technologies to improve drug delivery systems that can circumvent technical hurdles by, for example, controlling drug release, increasing drug retention via targeted and reduced local drug toxicity, decreasing active agent and combination therapy doses, and making use of more

potent drugs that cannot be clinically used with conventional drug delivery. Some of the drug delivery vehicles recently explored for use against acne vulgaris include nanoparticles, liposomes, niosomes, solid lipid nanoparticles, nanoemulsions, and nanosuspensions. Their potential to enhance the topical administration of anti-acne medicines has been shown *in vitro*. Recent study has detailed the production of chitosan and tretinoin-containing solid lipid nanoparticles, which show excellent encapsulation efficiency, superior physical stability, and minimal cytotoxicity in keratinocytes. In addition, it possesses anti-bacterial activity against *P. acnes*, which increases the therapeutic efficacy of tretinoin in the treatment of acne. However, further study is needed to facilitate the widespread creation of novel medication delivery techniques at more affordable costs. Last but not least, further studies are required to verify the efficacy of these strategies in enhancing acne topical treatment [23].

11. Conclusion

The biggest challenge with existing medications for treating acne is that they have raised anti-biotic resistance and skin damage. The authors advocate for the use of natural remedies rather than synthetic drugs for acne. Acne treatment efficacy may be enhanced by focusing on molecular targets that influence many critical pathogenesis factors. This highlights the continued need for experts in the sector, since the efficacy of plant-based treatments against *P. acnes* warrants further investigation through the development of improved drug delivery systems. Depending on the cytokines expressed in acne lesions, an anti-inflammatory strategy targeting the key cytokines involved may be the best option. Initiators of sebocyte differentiation and contributors to sebum hyperproduction and hyperkeratinization, androgens, and related enzymes, can be easily mimicked in small animal models as a target for novel moieties.

Conflict of interest

No conflict of interest is declared.

Funding

No agency provided any funds

Acknowledgement

None acknowledged.

Ethical statement

No ethical statement is required.

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