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Review Article

Beyond the Breakouts: Exploring the Pathophysiology and Integrating the Clinical Insights, Phytotherapeutics, Therapeutic Advances and Future Directions for Acne Management

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ABSTRACT

Acne vulgaris is a common chronic inflammatory skin disease, characterized by increased sebum production, follicular hyperkeratinization, dysbiosis of Cutibacterium acnes and inflammation. Common therapies such as topical retinoids, benzoyl peroxide, antibiotics and hormonal therapies are widely used, but adverse effects, antibiotic resistance and recurrence remain major challenges. This review highlights the therapeutic potential of medicinal plants as adjunctive modalities in acne management such as *Glycyrrhiza glabra* (licorice), *Camellia sinensis* (green tea) etc. These ingredients contain bioactive phytoconstituents that have potential anti-inflammatory and antioxidant activity. Green tea may also help to regulate sebum, and licorice may help to reduce skin pigmentation associated with inflammation. Other medicinal plants such as *Azadirachta indica*, Aloe vera, *Curcuma longa* and *Melaleuca alternifolia* have also been discussed for their possible antimicrobial, soothing and anti-inflammatory effects. In addition, the review describes new methods for drug delivery such as liposomes, nano emulsions, solid lipid nanoparticles and nanostructured lipid carriers that can revolutionize drug stability, follicular delivery, skin retention and controlled release. Available clinical evidence suggests potential benefits of some herbal and conventional therapies, although strong clinical evidence of licorice and green tea use in the acne treatment is still missing. Future research should be directed toward standardization of extracts, optimization of formulations, safety evaluation, and controlled clinical trials to determine therapeutic efficacy and long-term benefits. To summarize, evidence-based herbal research along with modern drug delivery technologies may provide promising complementary approaches for improved management of acne.

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INTRODUCTION

Acne also called acne vulgaris is a long-term skin disease that happens when hair follicles get clogged with dead skin cells and oil from the skin. Acne triggers persistent inflammation in the sebaceous glands and results in various forms, such as open and closed comedone (blackheads and whiteheads), papules, pustules, nodules, and cysts (Fig. 1). There are various kinds of acne such as acne conglobate, acne excoriate, acne rosacea, pomade acne, acne fulminans, acne keloid Alises nuchae, acne chloracne, acne mechanic and acne medicamentosa. Unfortunately, these skin lesions may result in scarring and hyperpigmentation. Stress, smoking, genetic susceptibility, diet, and drugs all play a role in influencing the disease's activity. (1,2) Acne is a common skin disease that mainly affects adolescents and young adults, especially males. There are strong associations of specific factors such as bacterial colonization and inflammation to the etiologic of this disease. The main clinical signs of Acne are non-inflammatory and inflammatory lesions mainly located on the face, neck, trunk and back (3) Acne vulgaris, a widespread chronic inflammatory skin condition, impacts roughly 85% of teenagers and a significant portion of adults globally. Data on prevalence of adult acne is scanty Especially in Indian population. This study was conducted to evaluate the prevalence, clinical characteristics, etiologic and aggravating factors, and differences from adolescent acne (4)Over the past few years, natural remedies have been widely researched as safer and environmentally friendly alternatives to conventional acne treatments. The use of herbal remedies, such as those developed by Traditional Persian Medicine, to cure acne has become more popular in recent years. (5) For the purpose of developing future antiacne treatments, the current review focused on herbs that are currently in use and those that have a high potency. Four mechanisms—anti-bacterial, anti-inflammatory, antioxidant, and anti-androgen activities—are involved in these medicinal herbs' anti-acne properties.(6) Patients with mild to moderate-severity inflammatory acne, including papules and pustules, are treated with topical antibiotics along with retinoids. The primary line of treatment for people with moderate to severe inflammatory acne is oral antibiotics.(7) A recent systematic review of botanical and phytochemical treatments for acne vulgaris reviewed 23 clinical trials, of which three studied Kampo/Chinese herbal medicine (CHM) preparations. The CHM preparations showed improvement in mild to moderate acne. Limitations of these clinical trials included lack of acne grading methods, and lack of a control or placebo group.(8)

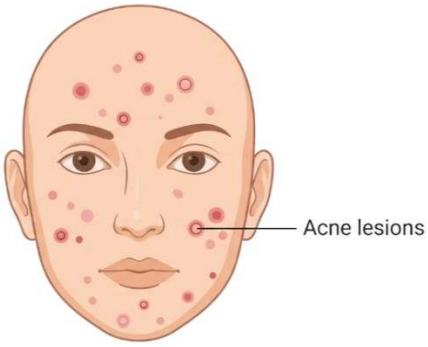


Figure 1: Acne

2. TYPES

The pilosebaceous unit is affected by common acne, also known as acne vulgaris, which manifests as inflammatory papules, pustules, nodules, and cysts on the face, back, and chest in addition to non-inflammatory open and closed comedones. The typical manifestation occurs throughout adolescence because of an increase in sebum production caused by a surge in androgens, particularly dehydroepiandrosterone (DHEAS). There are various kinds of acne such as acne conglobate, acne excoriate, acne rosacea and many more which are discussed in detailed in the Table 1 (9)

Table 1: Different Types of Acne

Type of Acne	Definition	Triggers	Clinical features	Common sites	Complications	Reference
Acne Conglobata	This severe type of cystic acne features an insidious onset of extensive inflammatory papules, pustules, nodules, interconnecting abscesses, and sinus tracts.	Hormonal changes, genetic factors and excessive sebum production	Deep nodules, cysts, pustules, abscesses, sinus tracts and grouped comedones.	Face, chest, back, shoulders and buttocks	Severe permanent scarring, pigmentation and psychological distress	(10)
Acne Excoriee	It is also called excoriated or picker's acne and is considered a psychodermatological disorder where often an adolescent female picks real or imaginary acne lesions over the face out of compulsion or stress.	Habitual picking, stress and anxiety.	Haemorrhage, crusts, erosions, excoriations, and pigmentation following inflammation.	Mostly on faces.	secondary infection, pigmentation, and permanent scarring.	(10)
Acne Rosacea	Apersistent inflammatory face condition that resembles acne but typically doesn't have comedones.	Sunlight, heat, spicy foods, alcohol, stress, temperature changes.	Facial flushing, persistent redness, papules, pustules and visible small blood vessels.	central face, cheeks, nose, chin, forehead.	Persistent redness, telangiectasia, rhinophyma, eye involvement	(11)
Pomade Acne	Greasy hair products clog the hair follicles, causing pomade acne. It often appears as acneiform and comedonal lesions scattered along the hairline and forehead.	pomades, greasy conditioners, hair oils, and styling supplies.	Small comedones and papules, often concentrated along the hairline.	Forhead, temples and hairline.	Persistent acne inflammation and pigmentation	(12)

Type of Acne	Definition	Triggers	Clinical features	Common sites	Complications	Reference
Acne Fulminans	An uncommon and very severe kind of inflammatory acne is called acne fulminans. Systemic symptoms and painful, ulcerated nodules appear out of nowhere.	Often linked to hormonal fluctuations, it can happen throughout adolescence and can cause acne to flare quickly.	Abrupt, excruciating nodules, pustules, ulcers, crusting, and systemic symptoms such joint pain or fever.	Mainly chest, back and face.	severe ulceration scars, joint/bone pain, and systemic issues	(13)
Acne Keloidalis Nuchae	A long-term inflammatory follicular disease that mostly affects the back of the neck and leaves behind keloid-like scars.	Ingrown hairs, friction, close shaving, and mechanical discomfort.	Firm papules, pustules, itching and eventually keloid-like plaques/scar.	Back of neck and occipital scalp.	Secondary infection, hair loss, and permanent scarring	(14)
Acne Mechanica	It often appears when the skin is rubbed by tight clothes, helmets, masks, or equipment.	Sporting equipment, straps, masks, helmets, tight clothes, and extended friction.	papules, pustules, and occasionally nodules in regions to pressure or friction.	Shoulders, back, chest, forehead, and regions beneath clothes or equipment.	Inflammation, pigmentation and scarring.	(15)

3. RISK FACTORS OF ACNE

A positive familial history of acne was significantly associated with increased risk for acne presentation, even after adjustment for age, gender, family monthly household income, BMI, smoking status, alcohol drinking habit and physical activity (16) Individuals with a history of acne in their mother, father or sibling had more acne than those without, with higher odds for paternal than maternal or sibling history (17). The association between BMI and acne remains unclear, with conflicting findings in adolescents and adults. However, obesity in PCOS may promote insulin resistance and hyperandrogenism, increasing free testosterone levels and contributing to acne development (18). (52-47%) of the patients were able to connect the deterioration of their lesions to the meals they ate. (41-37%) felt irritated after eating oily food, (11-10%) after eating a high-glycemic diet, and (23-20%) after eating meat (19). There are various types of risk factors (Fig.2) in acne such as family history and genetics, Age puberty, Increase sebum production, Dietary factor, Cutibacterium acnes, Follicular hyperkeratinization.

3.1 Family History and Genetics

Family history and genetics Having first-degree relatives with acne increases a person's likelihood of developing acne (20). Through influences on sebaceous gland activity, androgen-related pathways, follicular features, and inflammatory responses, genetic variables may affect an individual's vulnerability to acne. According to studies, those who have a positive family history of acne may also acquire the condition earlier and with more severity or persistence.(21)

3.2 Age and Puberty

Age and Puberty Because increased androgen activity promotes sebaceous gland development and sebum production, acne frequently starts during puberty. Comedone development and inflammatory acne lesions are encouraged by excess sebum, follicular hyperkeratinization, and alterations in the follicular microbiota.(22)

3.3 Increase Sebum Production

Increase Sebum Production One of the main causes of acne is sebum production is increased by androgenic

stimulation of sebaceous glands, resulting in a lipid-rich follicular environment that encourages inflammation, follicular blockage, and C. acnes growth.(23)

3.4 Follicular hyperkeratinization:

Follicular hyperkeratinization is crucial to the development of acne. Blackheads, whiteheads, and inflammatory acne lesions may develop because of microcomedone creation caused by excessive keratin synthesis and buildup within the hair follicle, which can obstruct the follicular opening.(24)

3.5 Cutibacterium acnes:

Cutibacterium acnes is a normal member of the skin microbiota, but its dysbiosis and increased abundance in the sebum-rich pilosebaceous follicle can contribute to acne development.(25) It can degrade components of the sebum and to activate innate immune responses leading to the release of pro-inflammatory mediators. This leads to inflammation of the hair follicles and contributes to the formation and progression of inflammatory acne lesions.(26)

3.6 Environmental & Lifestyle:

The production of sebum, oxidative stress, and skin inflammation can all be exacerbated by environmental and lifestyle variables. High temperatures, humidity, and air pollution can disrupt the skin barrier and encourage follicular obstruction.(27) Inflammatory and hormonal pathways may be impacted by psychological stress and sleep deprivation, exacerbating the severity of acne. Acne may also develop because of friction and occlusion from helmets, masks, tight clothes, and improper skincare products.(28) See at fig number 2.

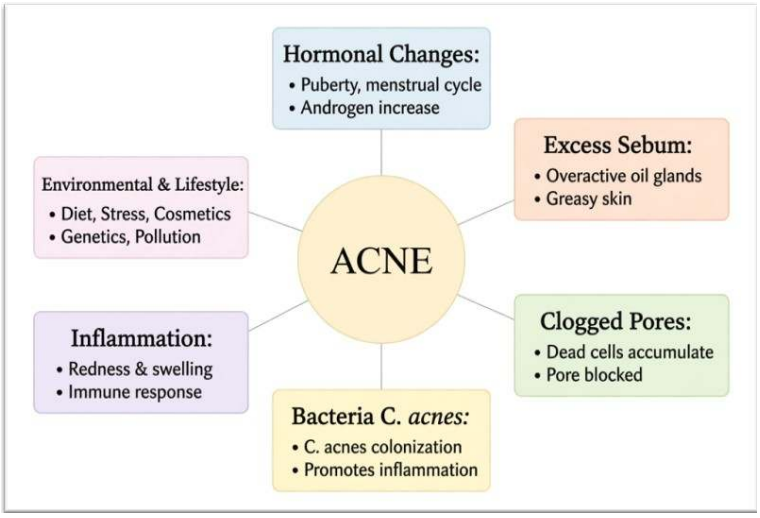


Figure 2: Risk Factors of Acne Vulgaris

4. PATHOPHYSIOLOGY OF ACNE

Acne vulgaris is a common chronic inflammatory disease of the pilosebaceous unit that is mainly characterized by comedones, papules, pustules, nodules, and sometimes cysts.(29) The pathophysiology is multifactorial, mainly involving increased sebum production, follicular hyperkeratinization, Cutibacterium acnes dysbiosis, and inflammation (30). Androgenic hormones stimulate the sebaceous glands, resulting in excess sebum production, while abnormal keratinocyte proliferation causes follicular plugging and comedone formation. The lipid-rich follicular environment facilitates C. acnes dysbiosis, which elicits immune responses and inflammatory mediators.(31). The inflammation causes the development of acne lesions and, in severe or prolonged cases, post-inflammatory pigmentation and scarring. Androgen stimulation increases sebum production and promotes follicular blockage.(32) The abnormal shedding of keratinocytes results in the development of microcomedone and comedone the lipid-rich follicle promotes dysbiosis of C. acnes and activates TLR2-mediated immune responses.

4.1 Increased Sebum Production

Sebaceous glands are stimulated and sebum production is increased by androgenic hormones, specifically testosterone and dihydrotestosterone (DHT). In the pilosebaceous unit, excess sebum builds up and causes

follicular occlusion, which aids in the development of microcomedone.(33) Additionally, sebum offers a lipid-rich environment that fosters Cutibacterium acnes proliferation and modified activity. Sebum lipid oxidation can also produce oxidative stress and pro-inflammatory molecules, which intensify inflammatory reactions. Thus, follicular obstruction, microbial dysbiosis, oxidative stress, and inflammation are the ways that excessive sebum production causes acne. (34)

4.2 C. acnes Dysbiosis

Cutibacterium acnes is a normal part of the skin microbiota but changes in its abundance and strain composition within the pilosebaceous unit are associated with acne development. Increased microbial activity can lead to the release of lipases and other bacterial factors that change the lipids in sebum, resulting in the formation of inflammatory mediators. (35) These bacterial components can activate innate immune pathways such as Toll-like receptor 2 (TLR2) and induce the release of cytokines like IL-1β, IL-6 and TNF-α. This inflammatory response contributes to follicular inflammation and the progression from comedonal lesions to inflammatory acne lesions (36)

4.3 Inflammation

Microbial components of Cutibacterium acnes and altered sebum in acne activate TLR2/TLR4 on keratinocytes, sebocytes and immune cells, leading to activation of NF-κB and MAPK signaling. This leads to the release of pro-inflammatory mediators such as IL-1β, IL-6, IL-8 and TNF-α, attracting immune cells to the pilosebaceous unit.(37) C. acnes can also activate the NLRP3 inflammasome which also leads to increased production of IL-1β. Destruction of the follicular wall and formation of papules, pustules, nodules and severe inflammatory acne lesions are caused by chronic inflammation.(38)

4.4 Acne Lesion Formation

Acne lesions begin with an excessive sebum production and an abnormal keratinization of the follicles, resulting in the obstruction of the follicle and the formation of microcomedones and comedones. The build-up of sebum and changes in the follicular microbiota, particularly Cutibacterium acnes, promote local immune activation and inflammation. (39) The inflammatory response leads to papules and pustules, and deeper, longer-lasting inflammation can lead to nodules and cystic lesions. Hence, the development of acne lesions is a progression of the combined effects of excess sebum, follicular obstruction, microbial dysbiosis, and inflammation.(40) See at fig number 3.

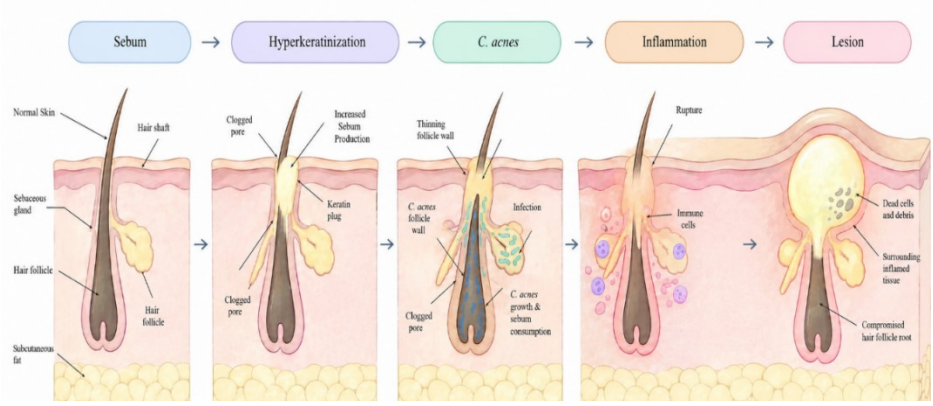


Figure 3: Pathophysiology of Acne

5. Diagnosis

Diagnosis of acne is mainly clinical and based on the skin examination and detailed history. The diagnosis is usually clinical based on the characteristic morphology, number and distribution of acne lesions. (41) Common lesions include open and closed comedones, papules, pustules, nodules, and cysts. Comedones represent noninflammatory lesions, whereas papules, pustules, nodules, and cysts are associated with different levels of inflammation. Acne affects areas of the skin that have a high concentration of pilosebaceous units, especially the face, chest, shoulders and upper back.(42) During clinical evaluation, the physician assesses the type and extent of lesions, disease duration, progression, prior treatment, family history, and aggravating factors. The configuration of the lesions is of great importance in diagnosis.(43) Open comedones or blackheads occur when the follicle is blocked and the contents of the follicle are exposed to air. Closed comedones are small whitish or skin-coloured elevations. Inflammation in the obstructed pilosebaceous unit gives rise to inflammatory lesions.(44) Papules and pustules are usually superficial inflammatory lesions while nodules and cystic lesions represent deeper and more severe inflammation. The clinical examination should also include the presence of post inflammatory erythema, post inflammatory hyperpigmentation and acne scarring, as these findings provide information about disease severity and chronicity (45) . Assessment of acne severity is an important part of diagnosis because it helps in selection of treatment and evaluation of therapeutic response. Various clinical grading systems have been proposed including Pillsbury classification, Cook's grading system, Leeds acne grading system, Global Acne Grading System (GAGS) and Investigator's Global Assessment (IGA). (46) Such systems consider lesion count, lesion type, inflammation, anatomical distribution, and the presence of nodules or scarring. Several grading methods are available, but no single system has been universally accepted for all clinical and research settings. (47) The differential diagnosis of acne is discussed below:

5.1 Clinical Assessment

A clinical examination of the skin is the primary method used to diagnose acne. The doctor examines the afflicted regions and assesses the distribution, quantity, and shape of lesions. Examining the back, shoulders, chest, and face is typical.(48)

5.2 Identification of Lesions

Open and closed comedones, papules, pustules, nodules, and cysts are among the several forms of acne lesions that are seen during diagnosis. Additionally, the existence of both inflammatory and non-inflammatory lesions is evaluated. This aids in identifying the acne's clinical kind.(49)

5.3 Evaluation of Severity

The quantity, kind, and size of lesions are used to determine the severity of acne. Acne can be categorized as mild, moderate, or severe. Extensive inflammation, nodules, cysts, and a higher chance of scarring can all be signs of severe acne.(50)

5.4 Drug and Medical History

To determine potential contributing variables, a thorough medical and drug history is acquired. Certain medications, cosmetics, and skin care items have the

potential to cause or exacerbate acneiform outbreaks. Additionally considered are prior acne treatments and their results.(51)

5.5 Hormonal Assessment

When acne is accompanied by symptoms of a hormonal imbalance, a hormonal examination may be taken into consideration.(52) The need for further testing may be indicated by symptoms like irregular menstruation, abundant facial hair, or other indications of androgen excess. When clinically necessary, conditions like polycystic ovary syndrome (PCOS) may also be evaluated.(53)

6. Conventional Treatments

The aim of acne therapy is to reduce sebum production, follicular hyperkeratinization, C. acnes proliferation and inflammation.(54) Treatment depends on the severity and type of acne and may include topical retinoids, benzoyl peroxide, antibiotics and keratolytic agents.(55) For moderate to severe acne, oral antibiotics, hormonal therapy or isotretinoin may be needed under medical supervision. Intralesional corticosteroids can give prompt relief in large painful inflammatory nodules.(56) The detail treatment therapy for acne management has been discussed in the Table 2

Table 2: Conventional Treatments for Acne Vulgaris

S.no	Category	Examples	Mechanism of Actions	Side effects	Reference
1.	Topical Retinoids	Tretinoin, Tazarotene.	Topical retinoids bind to nuclear retinoic acid receptors (RARs) to regulate gene transcription and normalize follicular keratinization. They inhibit the formation of microcomedones increase the clearance of comedones, and decrease follicular plugging. Which helping to reduce inflammatory acne lesions and preventing new comedones from forming.	Dryness, erythema, burning/stinging, peeling, itching, irritation, skin discomfort.	(57,58)
2.	Benzoyl peroxide	2.5-10% benzoyl peroxide.	Benzoyl peroxide (BPO) produces reactive oxygen species (ROS) that oxidize bacterial proteins and has bactericidal activity against Cutibacterium acnes. It has anti-inflammatory effects on acne and prevents follicular obstruction due to its mild keratolytic and comedolytic activity.	Increased skin sensitivity and temporary worsening of irritation, especially during initial treatment.	(59)

S.no	Category	Examples	Mechanism of Actions	Side effects	Reference
3.	Topical Antibiotics	Clindamycin, Erythromycin.	Topical antibiotics such as clindamycin and erythromycin bind to the 50S ribosomal subunit of Cutibacterium acnes and inhibit bacterial protein synthesis. They inhibit the growth of bacteria and reduce the production of inflammatory mediators which in turn decreases the inflammatory acne lesions.	Antibiotic resistance, particularly with clindamycin or erythromycin.	(60)
4.	Keratolytic/Comedolytic Agents	Salicylic acid and Azelaic acid.	These agents, eg, salicylic acid and azelaic acid, stimulate exfoliation and normalize follicular keratinization. They remove accumulated dead cells and reduce comedone formation, which helps unclog pores. Azelaic acid also has antimicrobial and anti-inflammatory properties for reducing acne lesions.	Dryness, peeling, redness, burning, skin irritation and increased sensitivity.	(61)
5.	Oral antibiotics	Doxycycline, Minocycline, Sarecycline.	Doxycycline and minocycline are oral antibiotics that inhibit bacterial protein synthesis through binding to the 30S ribosomal subunit of Cutibacterium acnes. They inhibit bacterial growth and reduce inflammatory mediators. This helps decrease inflammatory acne lesions, including papules and pustules.	Nausea, diarrhea, abdominal discomfort, and headache. Tetracyclines may cause photosensitivity, dizziness, and esophageal irritation.	(62)
6.	Hormonal Therapy	Combined oral contraceptives, Spironolactone.	Hormonal therapy works by decreasing androgen activity, by blocking the androgen receptor or by decreasing the production of androgen. This reduces the stimulation of sebaceous glands and the secretion of excessive sebum. Thus, it is effective in the reduction of follicular obstruction and formation of acne lesions.	Nausea, headache, breast tenderness, menstrual irregularities, and mood changes.	(63)

S.no	Category	Examples	Mechanism of Actions	Side effects	Reference
7.	Intralesional Corticosteroids	Triamcinolone acetonide.	Intralesional corticosteroids such as triamcinolone acetonide exert their effects locally via activation of glucocorticoid receptors and suppression of xinflammatory signalling. They decrease the production of pro-inflammatory cytokines and inflammatory cells which results in a rapid decrease in swelling and erythema.	Skin atrophy, hypopigmentation, and pain at the injection site.	(64)

7. Herbal Treatments

The treatment of acne with herbs (Table 3) is based on the use of medicinal plants and their active components that act on the main causes of acne. Topical formulations like gels, creams, lotions and face washes utilize herbal extracts.(65) Herbal therapies may represent a possible alternative complementary approach for acne treatment by targeting excess sebum, inflammatory processes and microbial activity, but their efficacy depends on the formulation and further clinical studies are necessary to confirm their safety and efficacy.(66) These herbs work in different ways: tea tree oil and neem may help to control microbial activity associated with acne, green tea helps to regulate excess sebum production, and licorice and turmeric may help to reduce inflammation and oxidative stress. Aloe vera helps to soothe irritated skin and help keep moisture. (67)

Table 3: Herbal Therapeutics for Acne Management

S.no	Common Name	Biological Name	Bioactive Phyto-constituents	Mechanism	Side effects	References
1.	Tea tree oil	Melaleuca alternifolia.	Terpinen-4-ol, α-Terpineol	Bacterial cell-membrane integrity is disrupted by tea tree oil, especially by its main component terpinen-4-ol, which reduces membrane function and microbiological survival. Additionally, it has anti-inflammatory properties by lowering inflammatory reactions, which helps to lessen inflammatory acne lesions, swelling, and redness.	Allergic contact dermatitis, Eye irritation, Dryness	(68)

S.no	Common Name	Biological Name	Bioactive Phyto-constituents	Mechanism	Side effects	Refer-ences
2.	Green tea	*Camellia sinensis*	Epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), epicatechin (EC), and other polyphenols and flavonoids.	By inhibiting inflammatory mediators and lowering oxidative stress, green tea, in particular its primary catechin epigallocatechin-3-gallate (EGCG), demonstrates anti-inflammatory and antioxidant properties. Additionally, it might help control the production of sebum, which would lessen the excess oiliness and inflammation linked to acne.	Allergic contact dermatitis, erythema, pruritus, xerosis, and localized burning sensations	(69)
3.	Aloe-vera	*Aloe barbadensis*	Acemannan, glucomannan, aloin, aloe-emodin, and various phenolic compounds.	By lowering inflammatory mediator activity and promoting skin hydration, aloe vera has calming and anti-inflammatory properties. Its polysaccharides, especially acemannan, support the healing of wounds and preserve the skin barrier, which may lessen irritation and aid in the healing of skin damaged by acne.	Abdominal cramps, diarrhea, electrolyte imbalance, and hypokalaemia.	**(70)**
4.	Licorice	*Glycyrrhiza glabra.*	Glycyrrhizin, glycyrrhetinic acid, glabridin, liquiritin, isoliquiritin, and licochalcone A.	By inhibiting inflammatory mediators and lowering oxidative stress, licorice, in particular its bioactive components glycyrrhizin and glabridin, demonstrates anti-inflammatory and antioxidant properties. Glabridin may also lessen post-inflammatory hyperpigmentation linked to acne by inhibiting tyrosinase activity.	localized erythema, pruritus, skin irritation, and allergic contact dermatitis in susceptible individuals	(71)
5.	Grape seed	Vitis vinifera	Proanthocyanidins, catechin, epicatechin, and gallic acid	By scavenging reactive oxygen species and regulating inflammatory reactions, grape seed proanthocyanidins demonstrate antioxidant and anti-inflammatory properties. These actions could lessen inflammation and oxidative stress in skin affected by acne.	Generally well tolerated topically, but irritation or allergic reactions may occur	(72)

S.no	Common Name	Biological Name	Bioactive Phyto-constituents	Mechanism	Side effects	References
6.	Neem	Azadirachta indica	Nimbidin, nimbolide, azadirachtin, gedunin, and nimbin.	Demonstrates anti-inflammatory and antibacterial properties through bioactive components including nimbolide and nimbidin. These components may lessen inflammation and skin irritation linked to acne by preventing microbial growth and the production of inflammatory mediators.	Allergic reactions may occur in sensitive individuals. Oral neem oil ingestion can cause serious systemic toxicity, particularly in children.	(73)
7.	Turmeric	Curcuma longa	Curcumin, desmethoxycurcumin, bisdemethoxycurcumin, ar-turmerone, α-turmerone, and β-turmerone.	Curcumin inhibits inflammatory signaling pathways including NF-κB and decreases the production of pro-inflammatory cytokines. Its antioxidant activity may help to neutralize reactive oxygen species, potentially reducing the inflammation associated with acne lesions.	Irritant or allergic contact dermatitis, erythema, pruritus, and localized burning sensations	(74)
8.	Indian Sarsaparilla	Hemidesmus indicus	Hemidesmin, 2-hydroxy-4-methoxybenzaldehyde, saponins.	Hemidesmus indicus has anti-inflammatory, antioxidant, and antimicrobial activities. It can decrease inflammation related to acne by inhibiting pro-inflammatory cytokines like IL-8 and TNF-α. It has antioxidant activity that helps to neutralize reactive oxygen species (ROS) and reduce oxidative stress. Therefore, it can be a complementary herbal agent for inflammatory acne.	Possible gastrointestinal discomfort or allergic reactions.	(75)

S.no	Common Name	Biological Name	Bioactive Phyto-constituents	Mechanism	Side effects	References
9.	Holi Basil (Tulsi)	Ocimum tenuiflorum	Eugenol, rosmarinic acid, ursolic acid, flavonoids.	Ocimum tenuiflorum (Holy Basil) has antimicrobial, anti-inflammatory and antioxidant activities. It may reduce acne-causing bacterial growth and skin inflammation. Its constituents like eugenol and ursolic acid might help in inhibiting inflammatory mediators and oxidative stress.	Skin irritation, contact allergy, or redness with topical use.	(76)
10.	Pomegranate	Punica granatum	Punicalagins, ellagic acid, anthocyanins	Punica granatum, have antibacterial, anti-inflammatory, and antioxidant properties. Its promise as a supplemental herbal remedy for acne management is supported by its bioactive components, especially punicalagin, which may inhibit germs linked to acne and lower inflammation.	Occasional skin irritation or allergic reactions.	(77)

8. Novel Drug Delivery system and Formulations Approaches

By improving the administration of anti-acne medications to the pilosebaceous unit, which includes hair follicles and sebaceous glands, Novel Drug administration Systems (NDDS) are cutting-edge pharmaceutical techniques. (78) These systems allow for regulated or prolonged medication release while enhancing drug solubility, stability, skin penetration, and local retention. They may lessen systemic medication exposure, minimize skin irritation and other side effects, and enhance patient compliance and therapeutic results in the treatment of acne.(79) Nano emulsions, liposomes, noisome, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), transferosomes, hydrogels, and micro sponges are common formulation techniques.(80) Depending on the formulation and active component, these systems may enhance medication solubility, stability, penetration, and controlled release. (81)

Major Novel and Drug Delivery System and Formulation Approaches in Acne

8.1 Liposomes: Liposomes are spherical vesicles made up of phospholipid bilayers that can encapsulate both hydrophilic and lipophilic drugs. They improve drug stability, skin penetration and local retention. They aid in the delivery of drugs to pilosebaceous units that contain hair follicles and sebaceous glands for acne treatment. They can offer controlled drug release, less skin irritation and less systemic exposure. Thus, liposomes are expected to be promising carriers for targeted topical acne therapy. (82)

8.2 Noisomes: Noisome are vesicular delivery systems for drugs composed of non-ionic surfactant and cholesterol. They encapsulate hydrophilic and lipophilic drugs and improve drug stability and skin penetration.(83) They improve targeted delivery of the drug to hair follicles and sebaceous glands in the treatment of acne. They may provide sustained drug release, improve the therapeutic efficacy and reduce the skin irritation. Thus,

niosomes are promising topical carriers for targeted therapy of acne with possibly less systemic exposure.(84)

8.3 Nanoemulsions: The significance of nano emulsions in acne therapeutics is because of their ability to improve topical delivery of poorly water-soluble anti-acne drugs and herbal phytoconstituents. The small droplet size could improve drug penetration into hair follicles and localized delivery to pilosebaceous units. (85) They can help in delivering agents with antimicrobial, anti-inflammatory and sebum-regulating properties, enabling the targeting of key factors in acne development. Nano emulsions might also enhance drug solubilization and formulation performance and might have the potential to reduce systemic exposure. However, their clinical efficacy and safety in acne still need to be further evaluated.(86)

8.4 Solid Lipid Nanoparticles (SLNs): SLNs are nanosized drug carriers made of solid lipids stabilized by surfactants. They prevent physical and chemical degradation of anti-acne drugs and herbal phytoconstituents thus enhance their stability. Their lipid matrix favors drug deposition in the skin and hair follicles, improving localized delivery to the pilosebaceous units.(87) SLNs can offer controlled and sustained drug release that could reduce skin irritation and systemic drug absorption. They are thus promising carriers for the enhancement of efficacy and tolerability of topical acne treatments. (88)

8.5 Nanostructured Lipid Carriers (NLCs): Nanostructured lipid carriers (NLCs) are nanoscale delivery systems for drugs made up of a combination of solid and liquid lipids, which are stabilized by surfactants. Their imperfect lipid matrix results in higher drug-loading capacity and less drug leakage during storage.(89) They can enhance drug stability, skin retention and controlled release and may also reduce irritation related to traditional formulations. Therefore, NLCs are promising carriers for targeted topical acne therapy.(90)

8.6 Microsponge Systems: Microsponges are porous polymeric microspheres which are designed to entrap the active pharmaceutical ingredients in their internal pores. They can slowly release anti-acne agents like benzoyl peroxide and tretinoin onto the skin providing prolonged local drug availability in treatment of acne. (91) Their porous structure may help in controlling drug release, improving formulation stability, and reducing excessive drug deposition on the skin. This may decrease irritation with controlled release to maintain therapeutic efficacy. (92)

8.7 Hydrogels and Nanogels: Hydrogels are three-dimensional, water-rich polymer networks suitable for topical drug delivery while nanogels are nanosized gel-based carriers. In acne treatment, they may improve the delivery and retention of anti-acne drugs and herbal phytoconstituents in the skin.(93) Their polymeric structure can allow for controlled release of drugs, hydration of skin, and localized delivery to pilosebaceous unit. These systems can also improve drug stability and reduce irritation compared to some conventional formulations.(94)

8.8 Transferosomes: Transferosomes are ultra deformable lipid vesicles consisting of phospholipids and edge activators (e.g. surfactants) which increase the flexibility of the membrane. The highly flexible structure of ethosomes may improve the penetration into the skin and localized delivery of anti-acne drugs and herbal phytoconstituents. They can induce the accumulation of drugs in hair follicles and pilosebaceous units, sites involved in the pathogenesis of acne. (95)

8.9 Polymeric Nanoparticles: Polymeric nanoparticles are nano-sized drug carriers that are made from natural or synthetic polymers, such as chitosan and poly (lactic-co-glycolic acid) (PLGA). They are used to protect the active pharmaceutical ingredients and the herbal phytoconstituents from degradation and to achieve controlled drug release.(96) In acne treatment they may cause increased drug retention in hair follicles and sebaceous glands, targeting pilosebaceous units involved in the development of acne. These carriers can improve local drug delivery, increase the residence time of the drug in the skin and potentially reduce skin

irritation associated with conventional formulations.(97)

8.10 Microemulsions: Microemulsions are transparent, thermodynamically stable systems of oil, water, surfactants and often co-surfactants. They enhance the solubilization of poorly water-soluble anti-acne drugs and herbal phytoconstituents.(98) Due to their small droplet size and the ingredients in the formulation, they may penetrate the skin better and deliver the drug to the acne affected areas They can improve localized drug delivery and potentially enhance therapeutic efficacy while diminishing systemic exposureTherefore, microemulsions are promising carriers for topical acne treatment.(99)

9. Clinical Evidence

Clinical evidence is scientific evidence that comes from studies done on human patients to determine the effectiveness and safety of acne treatments (Table 3). (100) These studies look at whether a treatment can reduce the number of acne lesions, control inflammation, prevent new pimples and improve skin condition. Clinical evidence may be derived from clinical trials, observational studies and systematic reviews. (101) This helps health care professionals and researchers identify which acne treatments are safe and effective for patients.(102)

Table 3: Clinical Trial Data for Acne Vulgaris

s.no	Drug Name	Objectives	Methodology	Outcomes	References
1.	Adapalene 0.1% + Benzoyl peroxide 2.5%	To evaluate efficacy and safety of combination therapy in acne vulgaris.	Single-blind, randomized controlled trial of 1,670 participants over 12 weeks.	The combination was more effective than either drug alone or vehicle in decreasing acne lesions.	(103)
2.	Adapalene 0.1% Gel	To compare adapalene with benzoyl peroxide in mild acne	Randomized, double-blind study of 60 patients. Treatment daily for 2 months with follow-up evaluation.	Both treatments reduced acne lesions with a greater reduction in total and non-inflammatory lesions seen for adapalene at later assessments.	(104)
3.	Green tea extract	To assess the effectiveness of green tea in accne	Systematic Review and Meta-Analysis of Randomized Clinical Trials of Green Tea Therapy on Acne Outcomes	The analysis showed some evidence of reduced inflammatory lesions with green tea topical, but this is pooled evidence and not from any one individual clinical trial.	(105)
4.	Spironolactone	To assess its efficacy in treating acne in adult women.	A multicentre, double-blind, placebo-controlled, randomized phase 3 trial of spironolactone vs. placebo.	Spironolactone improved acne outcomes with the treatment benefit being more evident at 24 weeks.	(106)

s.no	Drug Name	Objectives	Methodology	Outcomes	References
5.	Licorice	To evaluate the potential of licorice extract as an adjunctive treatment for acne-related inflammation.	Licorice is known to contain bioactive compounds like glabridin and glycyrrhizin. The studies on its anti-inflammatory and antioxidant activities have been mostly conducted in laboratory and experimental settings.	Experimental results indicate possible anti-inflammatory and antioxidant effects. However, acne-specific clinical evidence in human patients is not yet available.	(107)
6.	Oral minocycline	To evaluate its effectiveness in acne and compare it with another tetracycline antibiotic.	A double bind comparative clinical trials accessed minocycline and doxycycline in patient with acne.	Both antibiotics were assessed for clinical improvement; the study is an older source, and findings should be interpreted according to current antibiotic stewardship recommendations.	(108)
7.	Clascoterone 1% cream	To assess the efficacy and safety of topical androgen-receptor inhibition for facial acne.	Two randomized double-blind vehicle-controlled Phase III trials in 1,440 patients treated twice daily for 12 weeks.	Both trials demonstrated significantly higher treatment success with clascoterone than vehicle.Adverse events were generally mild.	(109)

10. Current Limitations

Acne vulgaris is a common chronic inflammatory disease of the pilosebaceous unit involving increased sebum production, follicular hyperkeratinization, microbial imbalance and inflammation.(110) Despite the availability of several treatment options, the management of acne remains a challenge because of side effects, resistance to antibiotics, relapse and differences in patient response. Some treatments may not fully prevent post-inflammatory hyperpigmentation and scarring. Herbal medicines have shown possible anti-inflammatory, antioxidant and antimicrobial properties. (111) Nevertheless, there is not enough evidence for their efficacy in clinical practice. Further, differences in phytochemical composition, extraction methods and formulation stability restrict their therapeutic reliability. Hence, well-designed clinical trials are needed to determine the efficacy, safety and long-term benefits of the herbal formulation for the management of acne.(112) The emerging limitations of acne are explained below:

10.1 Antibiotic Resistance

Long-term use of topical and systemic antibiotics can result in antimicrobial resistance, especially in Cutibacterium acnes. Resistant bacterial strains can decrease the efficacy of treatment and cause chronic inflammatory lesions. Antibiotic monotherapy is therefore usually avoided, and antibiotics are often combined with other treatments, such as benzoyl peroxide, to help reduce the development of resistance. (113)

10.2 Side effects of traditional treatments

Unwanted effects of conventional acne medications may compromise tolerability of treatment. Topical retinoids and benzoyl peroxide can cause dryness, redness, peeling, burning, and irritation.(114) Oral isotretinoin can cause dry skin and lips and requires close monitoring because of the drug's significant risks of pregnancy and other potential adverse effects. Some patients stop therapy because these reactions are uncomfortable in daily life and interfere with skin care. (115)

10.3 Limited clinical evidence for herbal therapies

Herbal medicines such as licorice (Glycyrrhiza glabra), green tea (Camellia sinensis), neem, aloe vera, and tea tree oil have been emphasized for their potential anti-inflammatory, antioxidant, antimicrobial, and soothing properties.(116) But the evidence available varies considerably between herbs and formulations. Much of the evidence is based on laboratory work, animal studies or small clinical trials, rather than large, well-controlled studies in humans. Thus, the optimal concentrations, long term safety and efficacy and ability to prevent acne recurrence are not well defined. (117)

10.4 Standardization and variation in herbal formulations

Different plant species, plant parts, extraction techniques, geographical origins, storage conditions, and concentrations of active phytoconstituents can all affect the medicinal effectiveness of herbal medicines.(118) For instance, two licorice extracts could not have the same effects because they contain different amounts of glabridin and glycyrrhizin. It is challenging to compare data across studies and prove repeatable clinical effects in the absence of standardized formulations, uniform dosing, and validated quality-control measures.(119)

10.5 Insufficient data to support dietary and lifestyle changes

For some people, acne may be influenced by specific lifestyle variables, stress, sleep, and dietary habits. However, the evidence for each of these elements varies in strength and consistency, thus diet by itself cannot be regarded as a dependable treatment for all patients.(120) The results of studies on high-glycaemic diets and certain dairy-related correlations are inconsistent. To ascertain which lifestyle changes, offer clinically significant benefits and for whom, more carefully planned research is required.(121)

10.6 Acne recurrence

After effective therapy, acne may return, especially if the underlying causes of inflammation, follicular obstruction, and excessive sebum production are still present. After quitting treatment, some patients develop new lesions, necessitating maintenance therapy. Consequently, long-term illness control is not necessarily ensured by short-term improvement.(122)

11. Future Perspective

Future work in acne management will be geared toward the development of safe, effective and specific therapies that circumvent the problems associated with conventional treatments such as skin irritation, antibiotic resistance, recurrence and variable therapeutic responses.(123) Novel approaches including nanotechnology-based delivery systems for drugs, modulation of microbiome and personalized therapy may improve drug penetration, enhance therapeutic efficacy and minimize adverse effects.(124) Herbal medicines especially Glycyrrhiza glabra and *Camellia sinensis* are also promising for research opportunities due to their potential antioxidant, anti-inflammatory, antimicrobial and sebum regulating properties.(125) Future research should focus on standardization of herbal extracts, optimization of formulations, and evaluation of safety and efficacy by well-designed clinical trials. To summarize, novel pharmaceutical delivery systems, evidence-based herbal therapies and individualized treatment approaches may lead to better management of acne and help in prevention of recurrence, scarring and post-inflammatory hyperpigmentation.(126)

There are some main Feature Prospects are as follow

Future research on acne management should explore the creation of safer, more effective and targeted treatments that can overcome the shortcomings of the current therapies.(127) More advanced drug-delivery systems offer a promising avenue for improving anti-acne therapy since they allow targeting the pilosebaceous units and enhancing topical agents' follicular penetration, dermal delivery and retention while decreasing irritation.(128) Further research should consider optimizing the design and formulation of such delivery systems, including solid lipid nanoparticles, nanostructured lipid carriers, liposomes and nano emulsions, and assessing their long-term safety and therapeutic efficacy.(129) Herbal and phytochemical-based treatments are also a viable option, considering the reported anti-inflammatory, antimicrobial, antioxidant and sebum-regulating activity of many plant extracts and compounds.(130) *Camellia sinensis and*

Glycyrrhiza glabra are particularly worth considering due to their anti-inflammatory and antioxidant properties, which may be beneficial for reducing the pro-inflammatory effects of acne and regulating keratinocyte proliferation.(131) The antimicrobial activity of phytochemicals may also be beneficial for controlling Cutibacterium acnes proliferation and the associated inflammatory response. A more comprehensive analysis of the active constituents and their mechanism of action is required to fully assess the potential of herbal and phytochemical-based treatments.(132) Microbiome-based and non-antibiotic therapies can also help manage antibiotic resistance by reducing the reliance on traditional antibiotics and promoting the resilience of the skin ecosystem. Further research is needed into the therapeutic potential of probiotics, postbiotics, bacteriophages and antimicrobial peptides, including an analysis of their safety, mechanism of action and long-term efficacy.(133) Personalized approaches can also help optimize the management of acne by selecting the most appropriate treatment methods based on individual factors, such as skin sensitivities, sebum production levels, hormonal status, lesion types and disease severity.(134) (135) The role of personal factors in the development and manifestation of acne should be further explored to improve the personalization of care and achieve better outcomes. Early intervention and proper maintenance are critical for preventing complications, such as post-inflammatory hyperpigmentation and scarring, and ensuring lasting remission.(136) Thus, further clinical studies are needed into the role of comedogenic skin care products, topical retinoids and antibiotics in the development of acne and the optimal therapeutic regimens for its maintenance-stage management.(137) Finally, randomized controlled trials with adequate sample sizes should be conducted to verify the effectiveness and safety of the novel treatment methods and further elucidate their mechanism of action.(138) Individual response variability, optimal dosage, potential adverse effects, extract standardization, manufacturing methods and cost-benefit considerations should also be considered.(139)

CONCLUSION

Acne vulgaris is a prevalent persistent inflammatory skin disease characterized by enhanced amount of sebum, hyperkeratosis follicularis, Cutibacterium acnes dysbiosis and an inflammatory response, resulting in frequent post-inflammatory hyperpigmentation, scarring and psychological damage. Clinically relevant examination and analysis of lesion presentation, and, if needed, hormonal assessment, are crucial diagnostic procedures for selecting a particular treatment approach for each individual patient. Despite the availability of numerous traditional topical and systemic treatments for moderate acne vulgaris, such as retinoids, benzoyl peroxide, antibiotics, keratolytic agents and hormonal therapy, they are frequently connected with skin irritation, emergence of antibacterial resistance and treatment relapses. Due to their recognized anti-inflammatory, antioxidant and antibacterial effects, as well as regulating properties on sebum production and follicular keratinization, herbal medicines appear to be a promising tool for acne vulgaris treatment. Specifically, the extract of *Glycyrrhiza glabra* (licorice root) and *Camellia sinensis* (green tea) have drawn considerable scientific attention due to their powerful anti-inflammatory and antibacterial properties, as well as the presence of various polyphenols and flavonoids that participate in cellular metabolism regulation and antioxidant activity. Numerous other medicinal plants, including neem, aloe vera, turmeric and tea tree oil, might demonstrate therapeutic and anti-inflammatory effects, however, their clinical benefits require further verification. A variety of innovative drug delivery systems, such as liposomes, noisome, nano emulsions, solid lipid nanoparticles and nanostructured lipid carriers, micro sponges and various other nano systems, can be used to maximize topical therapy efficacy, enhance follicular targeting, optimize drug release rate and extend drug residence time on the skin surface while minimizing irritation potential. However, their application in clinical practice requires further investigation to determine optimal fabrication technologies and establish reliable extract preparation and quality control techniques to guarantee skin compatibility and clinical efficacy. Investigation of personalized and microbiome-oriented treatment

approaches, as well as prevention of lesion recurrence and post-acne complication development, should also be the focus of future studies. From this perspective, the combination of conventional therapeutic modalities and individualized herbal medicine-based care and advanced drug delivery systems can provide the effective and safe treatment for acne vulgaris patients.

13. List Of Abbreviation

1. AV- Acne Vulgaris
2. BMI- Body Mass Index
3. BPO- Benzoyl Peroxide
4. CHM- Chinese Herbal Medicine
5. C. acnes- Cutibacterium acnes
6. DHEAS- Dehydroepiandrosterone Sulfate
7. DHT- Dihydrotestosterone
8. EC- Epicatechin
9. ECG- Epicatechin Gallate
10. EGC- Epigallocatechin
11. EGCG- Epigallocatechin-3-gallate
12. GAGS- Global Acne Grading System
13. IGA- Investigator's Global Assessment
14. IL-1β- Interleukin-1 Beta
15. MAPK- Mitogen-Activated Protein Kinase
16. IL-6- Interleukin-6
17. IL-8- Interleukin-8
18. NLC- Nanostructured Lipid Carriers
19. NDDS- Novel Drug Delivery Systems
20. NF-κB- Nuclear Factor Kappa B
21. NLRP3- NOD-like Receptor Family Pyrin Domain Containing 3
22. PCOS- Polycystic Ovary Syndrome
23. TNF-α- Tumour Necrosis Factor Alpha
24. SLNs- Solid Lipid Nanoparticles
25. TLR2- Toll-like Receptor 2
26. TLR4- Toll-like Receptor 4
27. ROS- Reactive Oxygen Species.

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