**Review Article**

**Acne Vulgaris: An Evidence-Based Review of Current and Emerging Therapies**

**ABSTRACT**

Acne vulgaris is a prevalent dermatological condition characterized by a range of non-inflammatory and inflammatory skin lesions, primarily affecting regions rich in pilosebaceous units, such as the face, neck, and back. The pathophysiology of acne involves increased sebum production, abnormal keratinization of hair follicles, and the proliferation of Cutibacterium acnes, which, along with various external factors and hormonal influences, exacerbates inflammation. Although acne is not preventable or curable, effective management strategies exist, including dietary modifications, topical treatments, and hormonal therapies. The current research underscores the significance of early intervention to mitigate physical and psychological impacts, emphasizing the need for patient education on the condition and its treatment options. This comprehensive overview aims to elucidate the multi factorial nature of acne, explore its underlying mechanisms, and highlight both conventional and natural therapeutic approaches while advocating for improved patient compliance and education in managing this common yet impactful skin disorder.

**Keywords**: Acne vulgaris, whiteheads, blackheads, skin, pimples.

**1.1 INTRODUCTION**

The Greek word "acme," which means "prime of life," is where the word acne originates. Despite being widely regarded as a harmless, self-limiting situation, acne can result in lifelong disfiguring scars or serious psychological issues (1).

The pilosebaceous unit, which consists of skin hair follicles connected to an oil gland, is the site of acne. Non-inflammatory lesions (open and closed comedones), and inflammatory lesions (papules and pustules) are among the clinical characteristics of acne with different levels of scarring. Acne is found in the areas with the largest density of pilosebaceous units, which include the face, neck, upper chest, shoulders, and back. Physical symptoms including discomfort, itching, and soreness are caused by acne, but its primary effects are on one's quality of life. It is important to remember that psychological morbidity is not a minor issue exacerbated by a number of factors, including the fact that acne affects the skin, which is a vital organ of social display; that blemishes skin is expected by society and popular culture; that acne is perceived by medical professionals as a minor, self-limiting condition; and that acne peaks during adolescence, a critical period for establishing confidence and self-worth. The emotional impact of acne may not be immediately apparent or voluntary, but even mild acne can cause significant distress; patients should be informed that online acne information, including from some support groups, varies in quality and can reflect sponsor bias; and clinicians have a role in directing patients to trustworthy resources. Because acne treatments work by preventing new lesions rather than treating existing ones, an initial response might not appear for some weeks.Most effective treatments can take months to work (2).

Sebum, which typically exits the hair follicle and drains to the surface, becomes stuck in the skin pore when the hair follicles get obstructed. This leads to the eventual attack of sebum by bacteria called Propionibacterium acnes, which causes acne and skin irritation. Numerous factors, such as genetics, hormones, sebaceous activity, bacteria, temperature, chemicals, and psychology, might contribute to acne. Although there are several contributing factors to acne, genetics is typically the main one. Three out of four children will develop acne if both parents had it. One out of every four children will get acne if one parent had it (3).Although acne cannot be avoided or cured, it can be successfully managed. Although acne rarely results in long-term health issues, it can leave skin scars (4).

Clinical assessment is usually used to make an acne diagnosis. Asking patients about their family history, symptoms, and indicators of hyperandrogenism or another endocrine disorder—such as an excess of growth hormone or cortisol—is important. It’s critical to examine the patient's skin care regimen before developing a treatment plan, including how often they wash, what cleansers they use, and hydrating agents that are applied. Acne sufferers are generally advised to avoid using scrubs, astringents, or other irritating products, to wash only twice a day, and to use mild cleansers for tender skin. When used over topical treatment, a fragrance-free moisturizer can reduce related irritation in people with sensitive skin (5). No solid proof exists that washing causes or resolves acne. Antimicrobial skin cleansers may help treat minor acne, and acidic cleansing bars are likely superior than conventional alkaline soaps. Excessive washing and scrubbing, on the other hand, dries up the skin and encourages the creation of additional oil. For patients already using alternative, possibly irritating topical therapies, antibacterial skin cleaners offer no extra benefits (6).

**1.2 SKIN**

The organ that creates the barrier between the body and the outside world is the skin. Through thermoregulatory secretory activity, it aids in maintaining internal homeostasis, creates a self-repairing barrier against chemical and physical attacks. Each of the layers that make up the human skin has a distinct structure and purpose. Understanding how different skin layers behave mechanically is crucial for clinical and cosmetic research, including the creation of personal hygiene products and the knowledge of skin conditions (7).



**Figure 1: Different layers of skin**

**1.2.1 Dermis**

The dermis is divided into two anatomical regions: the reticular and papillary. The papillary dermis is the thinner outermost portion of the dermis, making up about 10% of the 1-4 mm thick dermis. It contains a relatively small and loose distribution of collagen and elastic fibrils within a significant amount of ground substance. The papillary and reticular dermis are the two anatomical regions that make up the dermis. About 10% of the 1-4 mm thick dermis is made up of the thinner outermost layer, known as the papillary dermis (8).

**1.2.2 Hypodermis**

The innermost layer of the skin in the human body is called the hypodermis, or subcutaneous tissue. Wound healing, energy balance maintenance, body temperature management, mechanical force lubrication, and tissue connection are some of its roles (9). The hypodermis thins with age, in contrast to other fat depots. The hypodermis is a significant source of hormones, adipokines, and stem cells. It is filled with blood-derived and local immunocytes that support the skin's innate immune system. In addition to causing skin thinning and drooping, hypodermis aging seriously compromises the dermal micro environment and skin function (10).

**1.2.3 Epidermis**

The epidermis and dermis are the two layers that make up the skin. The primary cell type of the terminally developed stratified squamous epidermis is the keratinocyte. In reaction to damage, keratinocytes also release cytokines. There are three layers, or "strata," that make up the viable epidermis. Keratinocytes make up the majority of epidermal cells and move upward to the skin's surface, where they lose their viability. When keratinocytes migrate to the skin's surface, they alter their size, shape, and physical characteristics. The stratum basale, where cell division takes place, is the deepest layer. It is made up of one to three layers of tiny cubic cells. The stratum spinosum, the following layer, contains the larger and more polyhedral cells are joined by symmetrical lamination structures called desmosomes (11).

**1.3 Acne**

Acne vulgaris is a long-term inflammatory skin disorder that mainly targets the pilosebaceous units, which include the hair follicles and sebaceous (oil) glands. It occurs most frequently in teenagers and young adults, though it may continue into later stages of life. The condition is commonly characterized by the presence of comedones (both blackheads and whiteheads), papules, pustules, nodules, and cysts. These lesions typically develop on the face, chest, and back—areas with a high density of sebaceous glands (12).

**1.3.1 TYPES OF ACNE**



**Figure 2: Types of acne**

**1.3.1.1 Blackheads**: Obstructing hair shafts with dead skin cells and excess oil causes blackheads, which are non-inflammatory acne lesions. The term "open comedo" refers to a blackhead because the skin surface is left uncovered and appears dark, like brown or black. Mild acne known as blackheads typically develops on the face, arms, chest, neck, back, and shoulders (13).

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**Figure3: blackheads**

**1.3.1.2 Whiteheads:** These are tiny pimples and a non-inflammatory acne lesion that appear on the skin when bacteria, oil, and skin cells obstruct the pores that open in hair follicles. Whiteheads are known by the name closed comedowns because the white, closed bumps are closed. Although they can appear anywhere on the body, whiteheads are most common in the Tzone, which includes the chin, nose, and forearm (14).

**1.3.1.3 Papules:** Swelling, heat, redness, and discomfort are the signs of inflammation, which is the body's reaction to infection, excessive oil production, and androgen activity. A pink lump that is usually less than 5 mm in diameter and devoid of pus is how papules appear on the skin. A whitehead becomes papules. There are two varieties that are observed: an inflammatory type and a non-inflammatory type that lasts for roughly two weeks. The inflamed papule is characterized by a painful spot on the skin and a minor discomfort (15).



 **Figure 4: papules**

**1.3.1.4 Pustules:** Caused by dead skin cells and excess oil clogging the pores, pustules are inflammatory lesions and tiny lumps on the skin. Inflammatory lesions called pustules are filled with fluid or pus. the centre. Though they can appear anywhere on the body, pustules are most common on the shoulders, chest, back, face, neck, underarms, pubic area, and hairline (16).

 

Figure 5: pustules

**1.3.1.5 Nodules**: distinctly seen on the skin's surface. These are big, painful, solid pimples that are visible on the skin's surface yet are located deep within the skin (17).



Figure 6: nodules

**1.3.1.6 Cysts:** A severe form of inflammatory acne, cystic acne develops beneath the skin as a result of clogged pores brought on by the buildup of oil, dry skin cells, and bacteria. A cyst usually manifests as huge, painful, pus-filled lesions that are white or red and can occasionally leave scars. Although cystic acne can develop anywhere on the body, the face, arms, shoulders, back, chest, and neck are the area’s most commonly affected. A small number of active lesions are often limited to the face, and patients with mild acne primarily have white and blackheads, as well as open and closed comedones (18).

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**Figure 7: cysts**

**1.4 THE PATHOPHYSIOLOGY**

In the classical aetiology of acne vulgaris, a number of causative variables are thought to be important. Increased sebum excretion rates, endocrinological variables like androgens, abnormal keratinization of the follicular infundibulum, bacterial infection growth, and the resulting inflammation are the causes of chronic acne skin diseases, as was previously mentioned.

1. **Increased Sebum Production**: One of the main factors contributing to the development of acne is an increase in sebum production in the hair follicles. Sebum production and release are increased by androgen hormones, particularly testosterone and insulin growth hormone. Increased sebum production is a crucial factor that patients with acne vulgaris should take into account because there is a direct link between it and the severity and frequency of acne lesions.



**Figure 7: basic mechanism involved in the pathogenesis of acne.**

**b) Abnormalities in hyperkeratinisation of the pilosebaceous follicles:** In general, single-cell keratinocytes are frequently released into the lumen by healthy follicles before being eventually removed. Nevertheless, keratinocytes overproliferated in acne sufferers and are not expelled into the lumen, resulting in the buildup of irregular desquamated corneocytes in the pilosebaceous follicles together with lipids and monofilaments.

**c) Propionibacterium acnes (P. acnes) hyperproliferation:** Propionibacterium is another acne-causing agent that contributes significantly to the pathophysiology of inflammatory acne. The gram-positive, anaerobic, lipophilic pathogen Cutibacterium acnes, formerly known as Propionibacterium acnes, likes to colonize sebaceous follicles due to their high sebum production and superior anaerobic environment for bacterial development. Comedones and skin irritation may result from P. acne’s release of the lipase enzyme, which breaks down sebum triglycerides into glycerol and fatty acids.

**c) Hyperproliferation of Propionibacterium acnes (P. acnes):** Propionibacterium is another acne-causing agent that plays a major role in the pathophysiology of inflammatory acne. Cutibacterium acnes, formerly known as Propionibacterium acnes, is a gram-positive, anaerobic, lipophilic pathogen that prefers to colonize sebaceous follicles because of their high sebum production and ideal anaerobic environment for bacterial growth. The lipase enzyme released by P. acnes converts sebum triglycerides into glycerol and fatty acids, which can lead to comedones and skin irritation.

 **e) DNA Methylation:** Gene expression can change in response to environmental stress due to epigenetic alteration, which is the meeting point of genetics and the environment. Due to its role in the mechanisms of inflammatory, autoimmune, and malignant skin disorders, DNA methylation—one of the well-studied types of epigenetic modification—is receiving more and more interest in the dermatological community. DNA methylation has been shown to play a role in the pathogenesis and progression of inflammatory skin diseases such as hidradenitis suppurativa, atopic dermatitis, psoriasis, and other inflammatory skin disorders. Epigenetics plays a significant role in the development of acne vulgaris and may offer insights into its molecular mechanisms and potential therapeutic approaches (19).

**1.5 ETIOLOGY**

The hypersensitivity of the sebaceous glands to normal amounts of androgens in the blood leads to acne. The bacterial species Cutibacterium acnes (C acnes) and the ensuing inflammation further worsen this process.

Among the hypothesized causes of acne are:

* usage of drugs such steroids and lithium.
* exposure to too much sunshine.
* usage of occlusive clothing, including underwire, headbands, backpacks, and shoulder padding.
* face massages and cosmetics with an oil base.

repetitive mechanical damage brought on by using cleansers and detergents to scrub the afflicted skin.

* A diet high in carbohydrates or processed sweets, such as bread and chips**.**
* Changes in hormones brought on by puberty or pregnancy.
* Some drugs, like corticosteroids or birth control pills.
* Whiteheads, blackheads, tiny pimples, nodules, and cysts are all indicative of acne lesions.
* Women's fluctuating hormone levels during menstruation.
* Although acne is essentially a natural physiological phenomenon, the following common circumstances might exacerbate its symptoms.
* Poking, prodding, or barely pressing the acne lesions, which disturbs them.
* Wearing clothing, headgear, sports helmets, and other items that completely cover the face and forehead might exacerbate acne breakouts.
* Washing too much to remove acne-related debris can irritate and dry up the skin. In essence, a moderate wash is preferred.
* Avoid applying pressure on the acne completely.
* Acne in some cases may be inherited or may worsen as a result.
* In certain patients, pressure from collars, suspenders, chin straps, helmets, and similar items might exacerbate acne (20).

**1.6 DIAGNOSIS**

The history and physical examination are used to diagnose acne. Areas with the highest concentration of sebaceous glands, such as the face, neck, chest, upper arms, and back, are where lesions most frequently appear. Both visible open comedones (also known as "blackheads") and closed comedones (sometimes known as "whiteheads") may develop from the microcomedo. Inflammatory nodules, pustules, and papules may then appear (21).

**1.7 TREATMENTS**

* **Acne and Diet**
The link between nutrition and acne is becoming more and more clear. Consumption of dairy products, particularly skim milk, high glycaemic index diets, and whey protein have all been linked (22).
* **Further Topical Treatments**

Patients with inflammatory acne have demonstrated clinical effectiveness with dapsone gel. It has manageable side-effect profile and is frequently used as first-line treatment for women with acne, patients with sensitive skin, and women with darker skin tones who also have acne. Salicylic acid, a comedolytic drug that comes in a variety of forms, is frequently seen in over-the-counter acne remedies despite having very little clinical evidence. Although it is thought to be less effective than topical retinoid, it has a fair safety record and is an excellent first-line over-the-counter treatment for really mild acne (23).

* **Topical antibiotics**

Erythromycin and clindamycin are the two main topical antibiotics used to treat acne.30 These substances have anti-inflammatory and bacteriostatic qualities.11 30 32 Topical antibiotics are used when inflammatory lesions are present in mild to moderate acne. Benzoyl peroxide has bactericidal properties, which minimize bacterial resistance; topical antibiotic courses should be limited to 12 weeks whenever possible; retinoid or benzoyl peroxide therapy should always be used in conjunction with topical antibiotics; and several double blind randomized controlled trials have found that the addition of retinoid or benzoyl peroxide therapy to topical antibiotics improves treatment outcomes (24).

* **Combination treatment**For instance, retinoids and antibiotics work better together than either medication alone.13. Nevertheless, unless they are known to be compatible, the agents ought to be applied at different times. If benzoyl peroxide is administered concurrently with a retinoid, such tretinoin, it may oxidize it. Adapalene gel 0.1% plus clindamycin 1.0% treatment was shown to be more effective than clindamycin 1.0% administered alone in a 12-week randomized controlled trial that included 249 participants with mild to moderate acne. Topical antibiotics with benzoyl peroxide should be used in conjunction with topical retinoid if there are inflammatory lesions (e.g., topical antibiotic with benzoyl peroxide in the morning and retinoid at night) (25).
* **Isotretinoin**

A vitamin A derivative called isotretinoin is thought to influence every theory regarding how acne develops. Isotretinoin reduces sebum production and comedolysis by directly inhibiting sebaceous gland function. Reduced sebum production causes C. acnes to proliferate less, which in turn reduces the generation of chemotactic inflammatory modulators, which in turn reduces cutaneous inflammation. Common side effects of isotretinoin that are dose-dependent include headaches, dry eyes, xerosis, cheilitis, flare-ups of acne, and increased levels of hepatic and lipid enzymes. Previously More recent research has not validated the hypothesized links between isotretinoin and mood disorders, suicidal thoughts, or inflammatory bowel disease, and some studies have found that isotretinoin helps individuals with depressive symptoms (26).

* **Retinoids Topical**

A broad class of vitamin A compounds that alter gene expression is known as topical retinoids. Topical retinoids approved by the US Food and Drug Administration (FDA) to treat acne vulgaris, such as adapalene, tretinoin, and tazarotene, have anti-inflammatory properties and inhibit the production of comedones by controlling keratinocyte proliferation and differentiation. Since topical retinoids reduce the number of comedones and inflammatory acne lesions, they are the recommended treatment and maintenance therapy for all types of acne (27). For a long time, tretinoin has been the gold standard by which new products are evaluated. Compared to tretinoin 0.05% gel, 0.1% microsphere gel, or 0.05% cream, adapalene gel is less irritating. In an RCT, 6-9 Tazarotene 0.1% gel demonstrated 52% reduction in overall acne lesions, compared to 33% with the vehicle (28).

* **Hormonal treatments**

Regardless of the underlying hormonal imbalances, hormonal medications are an effective second-line treatment for acne in women.30 To benefit from antiandrogen therapy, one does not have to exhibit androgen excess. According to clinical observations, hormone therapy appears to be particularly effective for deep-seated nodules on the neck and lower face (29).

* **Physical treatments available**

Comedone extraction, chemical peels and microdermabrasion, intra lesion corticosteroid injection for acne cysts, high-intensity, narrowband blue light photodynamic therapy, injectable fillers, and laser resurfacing are examples of physical therapies for acne. Nevertheless, the peer-reviewed literature offers little proof in favor of these therapies (30).Chemical peels have been validated by the findings of tiny pilot studies, and there is some evidence that corticosteroid injections can be beneficial in treating big inflammatory lesions (31).

* **Some of herbal treatments:**

Although topical and oral ayurvedic medications, as well as herbal therapies like tea tree oil, appear to be well tolerated, little is known regarding their effectiveness and safety in treating acne. Although topical tea tree oil had a later onset of action than conventional topical medicines, one clinical research demonstrated its effectiveness. A systematic review of the efficacy of currently regarded supplemental or alternative acne therapies is being conducted by the Cochrane Collaboration (32).

* **Salicylic acid**Although there aren't many well-designed studies demonstrating salicylic acid's safety and effectiveness, it has been used for many years to treat acne. Compared to topical retinoids, its comedolytic effects are thought to be less strong. It is frequently applied to patients whose skin sensitivity prevents them from tolerating a topical retinoid (33)
* **Counseling:**
1. Advise patients on how to take isotretinoin correctly; advise female patients to sign the document, of which a copy is provided declares in their patient file that they will not become pregnant while undergoing treatment and for a month after that. Make them aware of the severe teratogenic effects of using isotretinoin.
2. When isotretinoin is administered, promote the sale of lip balm and sunscreen with an SPF of 50. This will moisturize parched lips and help shield the skin from the sun.
3. Patients are advised not to pick at their acne scars because doing so can cause the acne to spread. Additionally, advise patients to wash their hands after touching acne-affected areas.
4. Because topical antibacterials have a higher antibacterial penetration when used with topical isotretinoin or benzoyl peroxide, advise patients to use these medications in combination.
5. Advise the patient that basic anti-acne medication should provide a general improvement after eight to twelve weeks, and that if this doesn't work, they should consult a dermatologist or general practitioner.
6. Inform the patient that benzyl peroxide can cause skin peeling, burning, and dryness, and that they can take a day or two off from therapy before beginning it again.
Particularly for those with fair or sensitive skin, patients should begin treatment at the lowest dose possible (34).

**1.8 NATURAL TREATMENTS FOR ACNE**

**Turmeric:** specifically its active compound curcumin, has been investigated for its potential benefits in treating acne due to its anti-inflammatory, antioxidant, and antimicrobial properties.

**Mechanism of action** **of turmeric for acne treatment:**

**1. Anti-inflammatory Action**

Acne is primarily an inflammatory skin condition, and curcumin has been shown to reduce inflammation by inhibiting the activation of nuclear factor-kappa B (NF-κB), a protein complex involved in inflammatory responses. By downregulating NF-κB, turmeric reduces the production of pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6, which are known to play a central role in acne pathogenesis (35).

**2. Antimicrobial Properties**

Curcumin has demonstrated antimicrobial activity against several bacterial strains, including *Propionibacterium acnes* (P. acnes), the bacterium that is a major contributor to acne development. By inhibiting the growth of P. acnes, turmeric helps to prevent the development of acne lesions (36).

**3. Antioxidant Effects**

Curcumin acts as a potent antioxidant, scavenging free radicals and reducing oxidative stress. Oxidative stress is known to exacerbate acne by increasing inflammation and promoting the production of sebum, the oily substance that contributes to clogged pores. By neutralizing these free radicals, turmeric helps in preventing the oxidative damage associated with acne (37).

**4. Sebum Regulation**

Some studies suggest that curcumin might also help regulate sebum production by balancing the activity of certain enzymes and hormones involved in sebaceous gland function. This helps prevent the clogging of pores, which is a key factor in the formation of acne (38).

**CHEMICAL CONSTITUENT**

**1.Curcumin**

* **Type**: Polyphenolic curcuminoid
* **Role in Acne**:Strong anti-inflammatory agent: inhibits inflammatory cytokines (e.g., TNF-α, IL-1β).
* Exhibits antibacterial activity against *Propionibacterium acnes* (now *Cutibacterium acnes*), the acne-causing bacteria.
* Helps reduce oxidative stress in skin tissues.
* Regulates sebum production and promotes skin healing.

**2.Demethoxycurcumin and Bisdemethoxycurcumin**

* + **Type**: Minor curcuminoids
	+ **Role in Acne**:
		- Enhance antioxidant and anti-inflammatory effects.
		- Support curcumin’s bioactivity (39).

**3.Turmerone (especially ar-turmerone and α-turmerone)**

* + **Type**: Sesquiterpene in turmeric essential oil
	+ **Role in Acne**:
		- Exhibits antimicrobial activity.
		- Promotes skin regeneration and wound healing.

**4.Zingiberene**

* + **Type**: Sesquiterpene hydrocarbon
	+ **Role in Acne**:
		- Contributes to antibacterial and anti-inflammatory effects (40).

**5.Flavonoids and Phenolic Acids**

* + **Type**: Antioxidant compounds
	+ **Role in Acne**:
		- Neutralize free radicals that worsen acne inflammation.
		- Support skin repair (41).

**Aloe vera:** has long been used in traditional medicine for its therapeutic properties, particularly in treating skin conditions such as acne. The beneficial effects of aloe vera on acne are primarily due to its anti-inflammatory, antimicrobial, and wound-healing properties. Here's a detailed breakdown of how aloe vera works in the treatment of acne:

**1. Anti-inflammatory Properties**

Inflammation is a central component of acne formation, and aloe vera has well-documented anti-inflammatory effects. The active compounds in aloe vera, such as glucomannan and polysaccharides, help reduce the inflammation associated with acne lesions. Aloe vera inhibits the production of pro-inflammatory mediators, such as interleukins and prostaglandins, which are involved in the inflammatory response that exacerbates acne (42).

**2. Antimicrobial Action**

Aloe vera contains compounds such as anthraquinones (e.g., barbaloin and aloesin) that possess antimicrobial properties. These compounds can inhibit the growth of acne-causing bacteria, particularly *Propionibacterium acnes* (P. acnes), the bacterium responsible for much of the inflammation in acne. Aloe vera's antimicrobial effects help to prevent bacterial overgrowth on the skin and may reduce the frequency of acne breakouts (43).

**3. Antioxidant Effects**

Aloe vera has powerful antioxidant properties, mainly due to the presence of vitamins C and E, and beta-carotene. These antioxidants help to neutralize free radicals, which are compounds that cause oxidative stress. Oxidative stress can increase inflammation and worsen acne, so by reducing free radical damage, aloe vera helps in preventing acne flare-ups and promoting clearer skin (44)*.*

**4. Regulation of Sebum Production**

Excess sebum production is a key factor in acne development, as it leads to clogged pores. While aloe vera does not directly "dry out" the skin or reduce sebum production drastically, it can help balance skin hydration levels. By maintaining proper moisture levels in the skin, aloe vera reduces the risk of overcompensatory sebum production that occurs with over-drying treatments (45).

**5. Soothing and Cooling Effect**

Aloe vera is often praised for its soothing properties. The gel derived from aloe vera is cooling and can reduce the redness and irritation associated with active acne lesions. It calms the skin and promotes a healthier skin barrier, which can help prevent further breakouts (46).

**Chemical Constituents of Aloe Vera Used for Acne**

1. **Aloin (Barbaloin)**
	* **Type**: Anthraquinone glycoside
	* **Role in Acne**:
		+ Exhibits antibacterial and anti-inflammatory effects.
		+ Helps reduce swelling and redness associated with acne.
2. **Aloe-emodin**
	* **Type**: Anthraquinone compound
	* **Role in Acne**:
		+ Antibacterial against acne-causing bacteria like *Cutibacterium acnes*.
		+ Supports curbing excessive oil production (47).
3. **Acemannan**
	* **Type**: Polysaccharide
	* **Role in Acne**:
		+ Stimulates wound healing and collagen synthesis.
		+ Reduces inflammation and promotes skin regeneration.

 **4.Salicylic Acid (Naturally Present)**

* + **Type**: Beta-hydroxy acid (BHA)
	+ **Role in Acne**:
		- Exfoliates dead skin cells, unclogs pores.
		- Has mild antibacterial properties (48).

**5.Saponins**

* + **Type**: Glycosides
	+ **Role in Acne**:
		- Act as natural cleansers and antimicrobials, helping prevent bacterial infection in acne lesions.

**6.Vitamins (A, C, E, and B12)**

* + **Role in Acne**:
		- Provide antioxidant protection, support skin repair, and reduce inflammatory damage (49).

**Honey:** particularly manuka honey, has gained recognition as an effective natural treatment for acne due to its antimicrobial, anti-inflammatory, and wound-healing properties. The therapeutic effects of honey in treating acne are primarily attributed to its bioactive compounds, such as hydrogen peroxide, methylglyoxal (MGO), and flavonoids. Here’s a breakdown of the mechanism of action of honey for acne treatment.

**1. Antimicrobial Activity**

Honey is well-known for its antibacterial properties, particularly due to the production of hydrogen peroxide. When honey is applied to the skin, it releases low levels of hydrogen peroxide, which kills acne-causing bacteria such as *Propionibacterium acnes* (P. acnes). This reduction in bacterial growth helps prevent the formation of acne lesions (50).

In addition to hydrogen peroxide, manuka honey contains methylglyoxal (MGO), a compound with potent antimicrobial properties. MGO is effective against a wide range of bacteria, including those that contribute to acne, making manuka honey particularly beneficial for acne treatment (51).

**2. Anti-inflammatory Properties**

Acne is fundamentally an inflammatory condition, and inflammation is often triggered by the overproduction of sebum and the presence of bacteria. Honey contains natural flavonoids and phenolic acids that possess anti-inflammatory properties. These compounds inhibit the release of pro-inflammatory cytokines like interleukins (IL-1β, IL-6) and tumor necrosis factor-alpha (TNF-α), which are involved in the inflammation process that exacerbates acne (52).

**3. Antioxidant Effects**

Honey, especially darker varieties like manuka honey, is rich in flavonoids and phenolic compounds, which have antioxidant properties. These antioxidants help neutralize free radicals that contribute to oxidative stress, a key factor in acne development. By reducing oxidative damage, honey can help prevent skin damage, reduce acne lesions, and minimize scarring(53).

**4. Hydration and Skin Repair**

Honey is a humectant, meaning it draws moisture into the skin. This helps maintain hydration, keeping the skin from becoming too dry, which can lead to overproduction of sebum. By maintaining proper hydration, honey helps regulate skin function and prevent the clogging of pores, which is a major cause of acne (54).

**5. Skin Barrier Protection**

The antibacterial and anti-inflammatory effects of honey help protect the skin from further irritation or infection. By strengthening the skin’s natural barrier function, honey helps to reduce the risk of acne flare-ups. It also aids in calming irritated skin, which is often a concern for individuals with acne-prone skin (55).

**Chemical Constituents of Honey Used for Acne:**

1. **Hydrogen Peroxide (H₂O₂)**
	* **Source**: Produced by the enzyme glucose oxidase in honey.
	* **Role in Acne**:
		+ Acts as a **broad-spectrum antibacterial** agent.
		+ Helps kill acne-causing bacteria like Cutibacterium acnes (56).
2. **Methylglyoxal (MGO)** *(especially in Manuka honey)*
	* **Type**: Reactive aldehyde compound
	* **Role in Acne**:
		+ Has strong antimicrobial properties.
		+ Inhibits the growth of bacteria even without hydrogen peroxide (57).
3. **Flavonoids (e.g., pinocembrin, chrysin, galangin)**
	* **Type**: Polyphenolic antioxidants
	* **Role in Acne**:
		+ Reduce oxidative stress and inflammation.
		+ Support skin healing and reduce scarring (58).

**Witch hazel** (*Hamamelis virginiana*) is a medicinal plant commonly used in topical preparations for acne. Its anti-acne properties arise from its astringent, anti-inflammatory, antioxidant, and antimicrobial effects.

**Mechanism of Action of Witch Hazel for Acne:**

**1. Astringent Effect**

* Tannins in witch hazel shrink skin tissues and dry out excess oils (sebum) from the skin surface.
* This helps reduce pore size and oil buildup, which are common contributors to acne (59).

**2****. Anti-Inflammatory Action**

* Witch hazel contains flavonoids and proanthocyanidins, which inhibit the release of inflammatory mediators like prostaglandins.
* This reduces redness, swelling, and inflammation in acne lesions (60).

**3. Antioxidant Activity**

* The antioxidants in witch hazel, especially gallic acid and ellagic acid, help neutralize free radicals.
* This protects skin from oxidative stress and helps prevent acne-related skin damage (61).

**4. Mild Antimicrobial Action**

* Witch hazel has shown mild antibacterial activity against *Propionibacterium acnes* (now *Cutibacterium acnes*), which is involved in acne development (62).

**Chemical Constituents of Witch Hazel Used for Acne**

1. **Tannins (especially Hamamelitannins)**
	* **Type:** Polyphenolic compounds
	* **Role in Acne:**
		+ Act as astringents – tighten skin and shrink pores.
		+ Help remove excess oil (sebum) from skin.
		+ Possess antibacterial and anti-inflammatory properties.
2. **Gallic Acid and Ellagic Acid**
	* **Type:** Phenolic acids
	* **Role in Acne:**
		+ Exhibit antioxidant and anti-inflammatory effects.
		+ Soothe inflamed or irritated skin (63).
3. **Proanthocyanidins**
	* **Type:** Flavonoid-type polyphenols
	* **Role in Acne:**
		+ Provide antioxidant protection to the skin.
		+ Help prevent acne-induced tissue damage.
4. **Flavonoids (e.g., quercetin, kaempferol)**
	* **Type:** Plant pigments with antioxidant properties
	* **Role in Acne:**
		+ Contribute to anti-inflammatory effects.
		+ Help reduce redness and swelling (64).
5. **Volatile Oils (essential oils)**
	* **Constituents:** Eugenol, hexenol, and other terpenes
	* **Role in Acne:**
		+ Exhibit mild antimicrobial activity.
		+ Help cleanse the skin and inhibit acne-causing bacteria.
6. **Saponins**
	* **Type:** Natural glycosides
	* **Role in Acne:**
		+ Serve as natural cleansers and surfactants.
		+ Help in removing dirt and oil from skin (65).

**Neem oil:** derived from the seeds of *Azadirachta indica*, is an effective natural remedy for acne due to its antibacterial, anti-inflammatory, antioxidant, and wound-healing properties. It combats acne by killing acne-causing bacteria, reducing inflammation, preventing oxidative skin damage, and promoting the healing of pimples and scars(66).

**Mechanism of Action of Neem Oil in Acne Treatment**

Neem oil is widely used in traditional and modern skincare for treating acne due to its antibacterial, anti-inflammatory, antioxidant, and wound-healing properties.

**Mechanisms & Effects**

**1.Antibacterial**

Inhibits growth of Cutibacterium acnes and other acne-causing bacteria (67).

Biswas K. et al. (2002). Biological activities and medicinal properties of neem. Current Science, 82(11):1336–1345.

**2.Anti-inflammatory**

Reduces redness, swelling, and irritation in acne lesions (68).

**3.Antioxidant**

Protects skin cells from oxidative damage and inflammation (69).

**Chemical Constituents of Neem Oil Used for Acne**

1. **Azadirachtin**
	* **Type:** Tetranortriterpenoid (limonoid)
	* **Role in Acne**:
		+ Exhibits strong antibacterial activity against acne-causing bacteria (*Cutibacterium acnes*).
		+ Has anti-inflammatory properties that help reduce swelling and redness.
2. **Nimbin and Nimbidin**
	* **Type:** Triterpenoids
	* **Role in Acne:**
		+ Possess anti-inflammatory, antifungal, and antibacterial properties.
		+ Help reduce acne lesions and skin irritation (70).
3. **Nimbidol**
	* **Type:** Sesquiterpene alcohol
	* **Role in Acne:**
		+ Effective antimicrobial and antiseptic compound.
		+ Helps disinfect skin and prevent acne breakouts.
4. **Gedunin**
	* **Type:** Limonoid compound
	* **Role in Acne:**
		+ Provides antioxidant and anti-inflammatory effects.
		+ Aids in healing acne scars and lesions (71).
5. **Fatty Acids (Oleic, Stearic, Palmitic, Linoleic acids)**
	* **Type:** Essential fatty acids
	* **Role in Acne**:
		+ Help moisturize skin without clogging pores.
		+ Linoleic acid in particular can regulate sebum production, important in acne management.
6. **Vitamin E (Tocopherol)**
	* **Type:** Antioxidant vitamin
	* **Role in Acne:**
		+ Neutralizes free radicals and reduces oxidative stress on acne-prone skin.
		+ Promotes healing and reduces scarring (72).

**Spearmint tea:** (*Mentha spicata*) is a natural herbal remedy that has shown promising results in hormonal and inflammatory acne, especially in women. Its anti-acne effect is mainly attributed to its anti-androgenic, anti-inflammatory, and antioxidant properties (73).

**Mechanisms of Action**

**1.Anti-androgenic**

Reduces testosterone and androgen levels, thereby decreasing sebum (oil) production—a key factor in acne development (74).

**2.Anti-inflammatory**

Inhibits inflammatory pathways that contribute to acne lesions and redness (75).

**3.Antioxidant**

Neutralizes oxidative stress in the skin, helping to reduce and prevent acne flare-ups (76).

**Chemical Constituents of Spearmint Tea Used for Acne**

1. **Rosmarinic Acid**
	* **Type**: Polyphenolic antioxidant
	* **Role in Acne**:
		+ Exhibits anti-inflammatory and antioxidant activity.
		+ Helps reduce redness and swelling in acne.
		+ May inhibit pro-inflammatory mediators like COX-2 and NF-κB.
2. **Menthol**
	* **Type**: Monoterpene alcohol
	* **Role in Acne**:
		+ Provides a cooling and soothing effect on inflamed skin.
		+ Mild antibacterial and analgesic action (77).
3. **Carvone**
	* **Type**: Monoterpene ketone (major compound in spearmint oil)
	* **Role in Acne**:
		+ Antibacterial activity; helps reduce acne-causing microbes.
		+ Contributes to spearmint's aromatic and therapeutic profile.
4. **Flavonoids (e.g., Luteolin, Apigenin)**
	* **Type**: Plant antioxidants
	* **Role in Acne**:
		+ Help lower oxidative stress in the skin.
		+ Show anti-inflammatory properties, beneficial in treating acne lesions.
5. **Tannins**
	* **Type**: Polyphenols
	* **Role in Acne**:
		+ Have astringent properties that tighten pores and reduce oiliness.
		+ Mild antiseptic activity (78).
6. **Essential Oils (including Limonene, 1,8-Cineole)**
	* **Type**: Volatile compounds
	* **Role in Acne**:
		+ Exhibit antimicrobial properties.
		+ Help cleanse the skin and reduce acne-causing bacteria.
7. **Phytoestrogens**
	* **Type**: Plant-derived estrogen-like compounds
	* **Role in Acne**:
		+ Can help regulate androgen levels in the body.
		+ May reduce hormonal acne, especially in women with high androgen levels (e.g., PCOS) (79).

**Tea tree oil:** is a widely used natural remedy for acne due to its antibacterial, anti-inflammatory, antiseptic, and comedolytic properties. It works both by killing acne-causing bacteria and reducing skin inflammation (80).

**Mechanisms of Action**

**1.Antibacterial**

Kills Cutibacterium acnes (formerly Propionibacterium acnes), a key bacterium involved in acne formation (81).

**2.Anti-inflammatory**

Reduces swelling, redness, and inflammation of acne lesions (82).

**3.Comedolytic**

Helps unclog pores by dissolving excess oil and dead skin cells (83).

**Chemical Constituents of Tea Tree Oil Used for Acne**

1. **Terpinen-4-ol**
	* **Type:** Monoterpene alcohol
	* **Role in Acne:**
		+ The main active compound in tea tree oil (30–40%).
		+ Exhibits strong antibacterial activity against *Cutibacterium acnes*.
		+ Possesses anti-inflammatory properties — reduces acne redness and swelling.
		+ Enhances immune response in skin cells.
2. **α-Terpineol**
	* **Type:** Monoterpene alcohol
	* **Role in Acne:**
		+ Provides antimicrobial and antioxidant benefits.
		+ Supports skin healing and reduces infection (84).
3. **1,8-Cineole (Eucalyptol)**
	* **Type:** Monoterpene oxide
	* **Role in Acne:**
		+ Has anti-inflammatory and antiseptic properties.
		+ Present in small amounts — high levels may irritate sensitive skin.
4. **γ-Terpinene**
	* **Type:** Monoterpene hydrocarbon
	* **Role in Acne:**
		+ Contributes to antioxidant and antimicrobial effects.
		+ Works synergistically with other components.
5. **α-Pinene and β-Pinene**
	* **Type:** Monoterpenes
	* **Role in Acne:**
		+ Offer antibacterial and anti-inflammatory actions.
		+ May help reduce acne lesion size and prevent secondary infections (85).
6. **p-Cymene**
	* **Type:** Aromatic monoterpene
	* **Role in Acne:**
		+ Has mild antimicrobial activity.
		+ May contribute to the overall antimicrobial profile of tea tree oil (86).

**Calendula officinalis**: commonly known as marigold, is a medicinal plant widely used in dermatology for its anti-inflammatory, antimicrobial, wound-healing, and antioxidant properties. These actions make calendula a valuable natural remedy for managing acne.

**Mechanisms of Action**

**1.Anti-inflammatory**

Inhibits pro-inflammatory cytokines (e.g., IL-6, TNF-α), reducing redness, swelling, and irritation (87).

**2.Antimicrobial**

Inhibits growth of acne-causing bacteria like Cutibacterium acnes and Staphylococcus aureus (88).

**3.Antioxidant**

Protects skin cells from oxidative stress, which contributes to acne inflammation and scarring (89).

**Chemical Constituents of Calendula Used for Acne**

1. **Triterpenoids (e.g., Faradiol, Taraxasterol, Lupeol)**
	* **Type**: Triterpene alcohols and esters
	* **Role in Acne**:
		+ Exhibit potent anti-inflammatory properties.
		+ Reduce redness, swelling, and pain associated with acne.
		+ Promote wound healing in damaged skin.
2. **Flavonoids (e.g., Quercetin, Isorhamnetin, Kaempferol)**
	* **Type**: Polyphenolic antioxidants
	* **Role in Acne**:
		+ Possess anti-inflammatory, antioxidant, and antibacterial activities.
		+ Protect skin from oxidative stress and reduce acne-related inflammation (90).
3. **Saponins**
	* **Type**: Natural glycosides
	* **Role in Acne**:
		+ Act as natural surfactants and cleansers.
		+ Help remove oil and bacteria from the skin surface.
4. **Essential Oils (e.g., α-Cadinol, γ-Cadinene, Calamenene)**
	* **Type**: Volatile oil components
	* **Role in Acne**:
		+ Exhibit antimicrobial and anti-inflammatory properties (91).
5. **Carotenoids (e.g., Lutein, Beta-carotene, Lycopene)**
	* **Type**: Pigmented antioxidants
	* **Role in Acne**:
		+ Provide antioxidant protection against free radicals.
		+ Support skin repair and renewal.
6. **Phenolic Acids (e.g., Caffeic acid, Chlorogenic acid)**
	* **Type**: Polyphenols
	* **Role in Acne**:
		+ Contribute to antioxidant and antimicrobial effects.
		+ Help control inflammation and bacterial overgrowth (92).

**CONCLUSION**

Acne is an extremely common skin condition and, despite the immediate danger, it can have a destructive physical and psychological effect on the lives of vulnerable adolescents. Effective and secure treatment methods of acne are available, but many do not consider this as a problem that deserves to be treated. Acne treatment should be started as early as possible to avoid scarring and the most effective treatment with the least risk of side effects should be chosen (93). A significant problem is the inability of patients to take medications in a way that produce a therapeutic effect (94). Health education should ensure that patients receive accurate information about the causes of acne, as well as have realistic expectations about the duration of treatment and expected results. Better education and care provided to patients by medical staff and other professionals is important for concordance, as it will enable patients to treat themselves more effectively (95).

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