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A Comprehensive Investigation: Exploring Conventional Medications and Ayurvedic Solutions for Managing Acne Vulnerabilities

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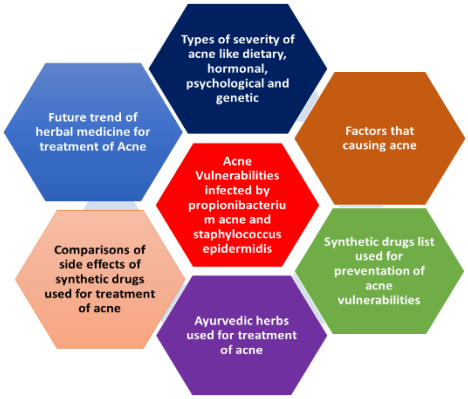
Acne vulgaris, herbal medicine, Inflammations, Propionibacterium acnes

Abstract

Over the preceding decades, there has been a discernible surge in the exploration of medicinal plants and phytochemicals as potential agents for the treatment of skin ailments, with a particular focus on addressing the challenges posed by acne vulgaris. Acne vulgaris, characterized as a persistent immune-mediated ailment of the pilosebaceous unit, predominantly manifests itself in teenagers and young adults, presenting a considerable burden on affected individuals. The therapeutic approach to acne vulgaris centers around mitigating the four primary components that contribute to its pathogenesis: increased sebum production, hyperkeratinization, proliferation of Cutibacterium acnes, and the presence of inflammation. Conventional treatments for acne vulgaris include the application of topical retinoids, benzoyl peroxide, antibiotics, and, in more severe cases, oral isotretinoin. However, the landscape of acne treatment is evolving, with a growing recognition of the potential benefits of herbal medicine as a supplementary and alternative therapeutic avenue. This emerging paradigm acknowledges the holistic and synergistic properties inherent in medicinal herbs and phytochemicals, providing a nuanced and potentially more sustainable approach to managing acne vulgaris. Against this backdrop, the primary objective of the present study is to delve into the efficacy and safety profiles of medicinal herbs and phytochemicals in the treatment of acne vulgaris. By examining the intricate interplay between these natural compounds and the underlying pathogenic mechanisms of acne, this research seeks to contribute valuable insights into the evolving landscape of dermatological therapeutics, paving the way for a more diversified and personalized approach to acne management.

Pictorial Abstract:



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Introductions

Acne vulgaris (AV) is a common chronic skin condition characterized by the obstruction and/or inflammation of pilosebaceous units, which consist of hair follicles and their accompanying sebaceous glands. It ranks among the most frequent human diseases [1]. Acne vulgaris affects over 85% of teenagers and young adults, particularly men, making it one of the most prevalent dermatological conditions. Despite being less common in adulthood, recent epidemiological data indicate an increasing incidence, reaching around 40%, with females constituting the majority [2] The main clinical symptoms of acne involve non-inflammatory and inflammatory lesions, primarily affecting the face, neck, trunk, and back [3]. While acne is typically a benign and self-limiting disorder, its most severe forms can result in scarring and skin discoloration [4].Acne pathogenesis is a complex process that involves four primary pathophysiological factors sebaceous gland hyperplasia and hyper production, sebaceous duct hyper keratinization, bacterial colonization and proliferation, primarily by Cutibacterium acnes, and inflammatory response[5].

The illness is thought to be mostly caused by the hormonal changes associated with puberty, especially the rise in androgen levels[6]. The type I 5 α -reductase enzyme converts androgens in the sebaceous glands to dihydrotestosterone, a stronger androgen that promotes lipogenesis as well as the growth and differentiation of sebocytes[7]. Linoleic acid levels fall with increased sebum production, and the absence of this substance in sebum is what allows free fatty acids produced from triglycerides to get through the follicular barrier[8,9].

Acne is classified into three types: mild, moderate, and severe. Mild acne is often limited to the face and is distinguished by the presence of non-inflammatory closed and open comedones as well as a lack of inflammatory lesions[10]. Moderate acne is distinguished by an increase in the number of inflammatory papules and pustules on the face, as well as the presence of mild truncal illness. Finally, when nodules and cysts are present, acne is called severe. Facial lesions are frequently associated with broad truncal diseaser in these situations[11,12,13].

Acne is caused by the accumulation of sebum and dead skin cells within the sebaceous follicle, which destroys the follicular wall and causes skin irritation[14]. Endogenous variables include sebum production and hormonal changes, whereas changes in the activity of the skin microbiota are the most important contributors to acne etiology[15]. P. acnes, S. epidermidis, S. aureus, Klebsiella pneumonia, Streptococcus, Enterobacter, and other microbial flora isolated from acne patients appear to contribute to acne etiology[16].

Epidemiology

The Global Burden of Disease (GBD) study, a comprehensive analysis of health conditions worldwide, unveiled a startling revelation: nearly 85% of young adults aged 12 to 25 are affected by acne vulgaris (AV). This finding underscores the pervasive nature of this dermatological condition, highlighting its significant impact on a vast demographic. Moreover, extensive research conducted across diverse regions, including the UK, France, and the USA, consistently reaffirms acne's status as one of the top three most common skin problems among the general population[17]. This widespread occurrence is further underscored by estimates suggesting that acne affects a staggering 650 million individuals globally, positioning it as the seventh most prevalent disease worldwide.[18]

Despite its prevalence, the trajectory of acne remains largely unpredictable, with individuals often experiencing fluctuations in its severity over time. While some may find relief as they age, others may witness worsening symptoms, complicating prognostic efforts. This uncertainty surrounding its course adds another layer of complexity to the management of acne, necessitating personalized approaches tailored to each patient's unique circumstances.

Beyond its physical manifestations, acne exacts a profound toll on mental health, contributing to a spectrum of psychological issues including diminished self-esteem, persistent sadness, and heightened anxiety. Furthermore, the enduring scars left in its wake can serve as constant reminders of the challenges endured, further exacerbating its impact on overall quality of life.

Remarkably, the burden of acne extends beyond its immediate effects, with research indicating a significant association between acne and depression[19,20]. In a notable epidemiological study by Yentzer et al., it was

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revealed that 8.8% of acne patients also reported experiencing depression, with women disproportionately affected compared to men. Intriguingly, the severity of acne did not appear to correlate with the prevalence of depression, highlighting the complex interplay between dermatological and psychological factors in shaping the overall burden of this condition.

In summary, acne vulgaris represents not only a prevalent dermatological concern but also a substantial public health challenge characterized by its far-reaching impact on both physical and mental well-being. Efforts to address this multifaceted condition must encompass comprehensive approaches that not only target its physical manifestations but also address the psychological sequelae it engenders, thereby improving the overall quality of life for those affected. [21,22,23]

Types of acne

Acne, a dermatological condition, is commonly stratified into mild, moderate, and severe manifestations. Mild acne primarily manifests on facial regions and is typified by non-inflammatory closed and open comedones, with a limited presence of inflammatory lesions. As the severity escalates to the moderate stage, one observes a heightened prevalence of inflammatory papules and pustules on the face, occasionally extending to involve the trunk. The classification of acne as severe is warranted when conspicuous nodules and cysts are present, often accompanied by a widespread distribution on the trunk in addition to facial involvement **table 1** [24].

The spectrum of acne encompasses diverse forms, including but not limited to acne conglobata, acne excoriee, acne rosacea, acne cosmetica, pomade acne, acne fulminans, acne keloidalis nuchae, acne chloracne, acne mechanica, and acne medicamentosa, among others [25]. However, it is noteworthy that acne vulgaris predominates, constituting 99% of reported acne cases. This prevalent type can be discerned primarily based on the nature of the lesion and its underlying causative factors. For example, acne cosmetica is elicited by the use of cosmetics, acne mechanica manifests in individuals who habitually rest their faces on their hands or experience pressure from helmets, acne medicamentosa arises due to the application of topical medications, and pomade acne is induced by the use of talcum powder [26]

Table I: Grading severity of acne.[24]

Grade	Severity	Clinical findings
I	Mild	Open and closed comedones with few inflammatory papules and pustules
II	Moderate	Papules and pustules, mainly on face
III	Moderately Severe	Numerous papules and pustules, and occasional inflamed nodules, also on chest and back
IV	Severe	Many large, painful nodules and pustules

Pharmacology

Sebaceous glands in acne formation

Particularly in teenage boys, the onset and prevalence of acne demonstrate a positive correlation with the functioning of sebaceous glands, a phenomenon that becomes more conspicuous during the transitional phases of puberty and adolescence. This correlation is attributed to androgenic influences that stimulate an increased production of sebum [27]. The skin's inherent barrier function, crucially maintained by the secretion of sebum, relies on a complex combination of lipids, including squalene, wax, cholesterol in both free and ester forms, and triglycerides [28,29].

However, the intricacies of sebaceous gland function are susceptible to hormonal impacts, leading to noteworthy changes in the composition of sebum. A prominent alteration involves a noticeable reduction in the amount of linoleic acid. This transformative shift in sebum composition has consequential effects on the skin barrier, compromising its integrity. As a result of this compromise, the natural colonization of skin flora is encouraged [30]. In essence, the hormonal fluctuations during puberty and adolescence not only trigger an

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upsurge in sebum production but also instigate compositional changes that compromise the skin barrier, fostering an environment conducive to the colonization of natural skin flora.

Propionibacterium acnes in acne formation

Water soluble lipids, primarily the face triglycerides in sebum, which are abnormalities in sebaceous gland function, are inflammatory-enhancing substances that encourage the metabolism of the normal flora, including Propionibacterium. Acne [31]. Propionibacterium. acne stimulates CD4+ expression in keratinocytes and sebocytes, toll-like receptors (TLRs), neutrophil activity, and has a mitogenic effect on T cells through the use of heat-shock proteins (HSPs)[32]. This anaerobe is colonized, and as a result, cytokines and other pro-inflammatory substances are produced, such as interleukins (IL), tumour necrosis factors (TNF), interferon (IFN) gamma, and granulocyte macrophage colony-stimulating factor (GM-CSF) [33]. Along with the production of microcomedones and follicular keratinocytes, interleukins induction also causes the attraction of lymphocytes, neutrophils, and macrophages. The bacterium activates TLRs to cause these effects [34].

The proliferation of P. acne is further aided by abnormal keratinization and a lack of linoleic acid in the follicle, which in turn encourages sebocytes to produce proinflammatory cytokines and chemokines, resulting in persistent inflammatory lesions [35].

Causes of Acne

The presence of sebum and dead skin cells within the sebaceous follicle increases the microbial load, leading to the disruption of the follicular wall and resulting in skin inflammation known as acne. Endogenous factors such as sebum production and hormonal changes play a role, with alterations in the activity of the skin microflora being a major contributor to acne pathogenesis. Microbial flora commonly isolated from acne patients, likely implicated in acne development, include P. acnes, S. epidermidis, S. aureus, Klebsiella pneumonia, Streptococcus, Enterobacter, and others **table -II [36].**

There is a consensus that acne originates from multiple factors. The four primary pathogenic contributors to acne, as mentioned earlier, are:

- Elevated sebum production stimulated by androgens
- Abnormal desquamation of follicular epithelium leading to hyper keratinization and sebaceous follicle obstruction
- Proliferation of Propionibacterium acnes
- Inflammation[37]

According to the Global Burden of Disease (GBD) study, acne vulgaris (AV) affects approximately 85% of young adults aged 12–25 years. Acne consistently ranks among the top three most prevalent skin conditions in the general population, as indicated by extensive studies in the UK, France, and the USA. Globally, an estimated 650 million people are impacted by acne, making it the eighth most common disease worldwide [38]. While there is a common belief that acne vulgaris tends to naturally diminish or decrease over time as individuals age, there is currently no definitive method to predict how long it would take for acne to start decreasing or disappear Acne gives rise to considerable morbidity, marked by residual scarring and psychological distress, including issues like poor self-image, depression, and anxiety. These factors collectively contribute to a negative impact on overall quality of life. In an epidemiologic study conducted by Yentzer et al., it was found that 8.8% of patients with acne reported experiencing depression[39]. Interestingly, women suffered from depression twice as often as men (10.6% vs. 5.3%), but this prevalence was unrelated to the severity of acne [40]. One of the reasons of acne is hormonal activity, such as menstrual cycles and puberty. The sebaceous gland, which is situated around a hair follicle, enlarges, and produces more sebum during puberty as a result of the rise in androgens, the male sex hormones [41,42,43]. Sebaceous glands are impacted when their activity spikes above and beyond what is considered normal. When the hair follicles become blocked, P. acnes will attack the trapped sebum beneath the skin's surface. Sebaceous glands create more sebum, an oily material that can contribute to acne, in hotter climates [44]. Acne may also be brought on by chemical causes such as facial wash and exposure to specific chemical compounds, particularly those associated with harmful exposure to dioxin. Stress is a psychological element that can lead to acne by hyper activating sebaceous glands [45].

Table II: Functions of the virulence factors contributing to the pathogenic life cycle of Propionibacterium acnes and Staphylococcus epidermidis, playing a direct role in the development of acne [36]**.**

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Microorganism	Virulence factor/gene involved in pathogenesis of acne	Functions
Propionibacteriumacnes.	Christie, Atkins, Munch-Peterson Factor.	Immunoglobulin binding, pore-forming toxins.
	Triacyl glycerol lipase (gehA).	Hydrolyse sebum triglycerides.
	Haemolysin-tly.	Damage to blood cells.
	Sialidases.	Host tissue degradation.
	Porphyrins.	Damage to skin tissue.
	Endoglycoceramidases.	Disrupts cell surface Components.
	Hyaluronate lyase.	Cleaves extracellular matrix of connective tissue.
	Dermatan sulphate adhesion.	Putative adhesion.
Staphylococcus epidermidis.	Poly γ–DL-glutamic acid.	Osmoprotection for the Organism.
	Polysaccharide intercellular Adhesion.	Adhesion to the skin surface.
	Poly N-succinyl glucosamide.	Adhesion to the skin surface.
	Autolysin (Atl E).	Initial attachment factor.
	Autolysin (Aae).	Bacteriolytic & adhesive Property.
	Biofilm associated protein.	Biofilm formation.
	Accumulation associated protein.	Adhesin in skin colonization.
	Bacteriocins.	Colonization inhibition.
	Fatty acid modifying enzyme.	Inactivates bactericidal fatty acids by esterifying them to Cholesterol.
	Surface protein (fbe or sdrG)	Bacterial adherence to Fibrinogen.

Infectious

The intricate relationship between acne vulgaris and microbial factors involves the notable presence of Propionibacterium acnes and Staphylococcus aureus. Despite advancements in research, the exact roles these microorganisms play in the development of acne remain elusive. Within the realm of P. acnes, there exist sub-strains that exert influence not only on normal skin but also contribute to the persistence of long-term acne problems [46]. A concerning trend has been observed in recent times, indicating an increasing resistance of P. acnes to widely employed medications.

These microbial strains exhibit a remarkable ability to influence and adapt to various conditions associated with acne pathogenesis, including abnormal oil production, skin irritation, and inadequate sloughing of acne pores. The dynamic nature of these microorganisms in responding to environmental changes underscores the complexity of acne development [46]. Notably, the challenge of medication resistance poses a significant hurdle in the effective management of acne.

Intriguingly, beyond bacterial involvement, emerging research has shed light on another contributing factor - Demodex infection. This parasitic mite has been demonstrated to have a connection with the onset and exacerbation of acne [47]. The interplay between these microbial agents and Demodex infestation adds layers to our understanding of the multifaceted nature of acne, emphasizing the need for comprehensive approaches in its diagnosis and treatment.

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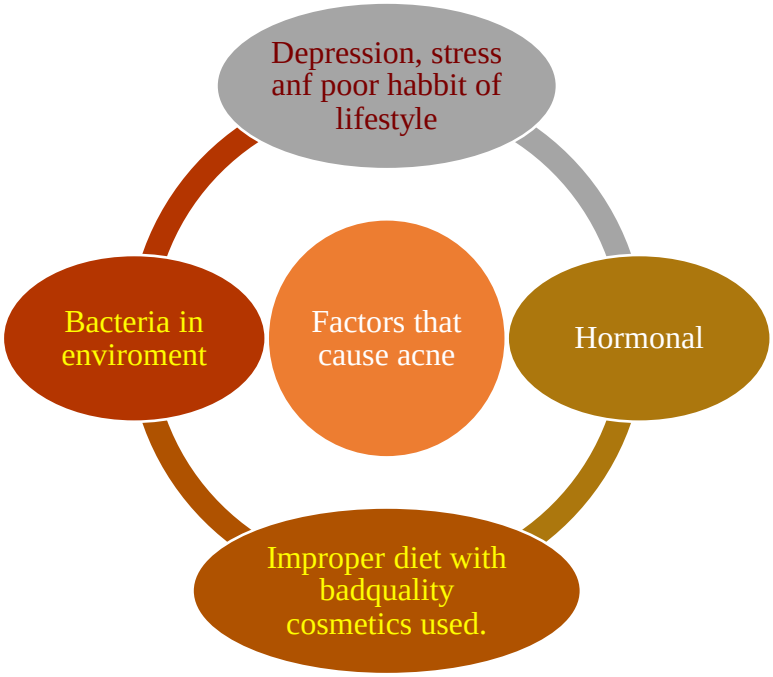

Fig.01- Factors that causing acne.[48]

Genetic

The inclination toward developing acne in certain individuals is believed to have a genetic underpinning. Substantiating this hypothesis, research examining the prevalence of acne among first-degree relatives and twin studies has provided significant support. These investigations suggest that there is a hereditary component contributing to the likelihood of acne development.

In exploring the genetic landscape of acne, numerous genes have been implicated in this dermatological condition. Polymorphisms in specific genes, such as IL-1, TNF-, and CYP1A1, among others, have been identified as potential factors associated with the predisposition to acne [49,50].

This complex interplay between genetic factors and acne susceptibility underscores the importance of genetic predisposition in understanding the development of acne. The identification of specific genes and genetic variations associated with acne not only contributes to our comprehension of its etiology but also opens avenues for targeted interventions and personalized approaches in acne management. The evolving field of genetics in dermatology continues to shed light on the intricate mechanisms underlying various skin conditions, paving the way for more precise and effective therapeutic strategies.

Hormonal

The development of acne vulgaris is intricately linked to hormonal fluctuations, notably those associated with key life stages such as puberty and menstruation [51]. During these periods, there is an increase in certain sex hormones, particularly androgens, which prompts the follicular glands to produce more sebum. This heightened sebum production is not limited to puberty; it is also observed during pregnancy and with the use of anabolic steroids, showcasing the profound influence of hormonal changes on acne development.

Several hormones play pivotal roles in the pathogenesis of acne vulgaris. Among these, insulin-like growth factor 1, as well as testosterone, dehydroepiandrosterone, and dihydrotestosterone, have been identified as significant contributors to the increased sebum production and subsequent development of acne [51].

In the context of adult females experiencing acne vulgaris, it is crucial to consider potential underlying medical conditions. Conditions such as Cushing syndrome, polycystic ovarian syndrome (PCOS), or hirsutism may manifest with acne as a symptom [52,53]. This insight underscores the complexity of acne etiology in adulthood and emphasizes the importance of considering broader health factors in understanding and managing acne presentations.

This comprehensive perspective on hormonal influences in acne development highlights the multifaceted nature of this common skin condition. Understanding the

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intricate interplay between hormones and acne not only informs the mechanisms behind its onset but also aids in tailoring effective therapeutic approaches, particularly in cases where underlying medical conditions may contribute to the manifestation of acne symptoms.

Dietary

While the connection between diet and acne lacks definitive and universally accepted evidence, emerging research sheds light on certain dietary patterns that may influence the severity of acne vulgaris. Notably, a high glycemic diet has been implicated in exacerbating acne symptoms, suggesting a potential link between the consumption of foods with a high glycemic index and the worsening of acne.

Moreover, certain food items, including milk, chocolates, and salt, have been suggested to be positively correlated with an increase in the severity of acne vulgaris. The role of chocolates in this context remains a subject of debate, given the variations in sugar content and the presence or absence of milk in different chocolate formulations.

Beyond dietary factors, the complex relationship between obesity and acne has been recognized. This adds a layer of complexity to the understanding of lifestyle influences on skin health, suggesting that body weight and adiposity may play a role in the manifestation of acne symptoms [54,55].

While acknowledging the current limitations in conclusive data, this nuanced exploration underscores the importance of considering lifestyle and dietary factors in acne management. It emphasizes the need for personalized approaches that account for individual variations in response to different dietary components, paving the way for more targeted and effective strategies in addressing acne and promoting overall skin health. As research progresses, a more comprehensive understanding of the intricate links between diet, lifestyle, and acne is crucial for refining recommendations and interventions in the realm of dermatological care[55].

Psychological

Scientific investigations have explored the intricate relationship between stress and acne, revealing a noteworthy association between heightened stress levels and increased severity of acne symptoms. Stress is not only implicated as a contributing factor but has also been identified as a potential trigger for the exacerbation of acne flare-ups. The underlying mechanisms through which stress may impact the skin, such as hormonal fluctuations and immune system modulation, have been subjects of exploration in these studies.

However, it is essential to acknowledge the nuanced landscape of research findings, as conflicting perspectives emerge from several studies. Some research challenges the established link between stress and the manifestation of acne vulgaris, raising questions about the complexity of this interaction and the varied responses individuals may exhibit. This underscores the need for a comprehensive understanding of the diverse factors influencing acne, encompassing both physiological and psychological elements.

As the scientific community continues to unravel the intricacies of stress and its potential impact on acne, the evolving narrative emphasizes the importance of personalized approaches in dermatological care. Recognizing the interplay between stress and acne as a multifaceted phenomenon allows for more tailored interventions, acknowledging individual differences and refining strategies for effective acne management[56].

Ingredients in topical acne treatments

Retinoic acid

Due to their suppressive effects on the functionality of sebaceous glands, keratolytic agents, including cis-retinoic acid, retinol, and retinol ester, are frequently utilized in dermatology to restore normal keratinization processes [57]. These compounds, derived from vitamin A, play a crucial role in inhibiting the production of interleukins (IL) and interferons (IFN), while also reducing the expression of Toll-like receptors (TLR). This dual action contributes to the regulation of immune responses and inflammation associated with skin conditions.

Furthermore, the inhibitory effects extend to the migration of immune cells, such as macrophages, CD4+ and CD8+ T lymphocytes. This blockade of cell migration is a notable aspect of the therapeutic impact of these keratolytic drugs.

Tretinoin, alternatively known as trans-retinoic acid, is another significant comedolytic agent in dermatological practice. Its mechanism involves the normalization of follicular epithelium desquamation by disconnecting the follicle. This particular action aids in the management of conditions involving abnormal cell turnover in the hair follicles.

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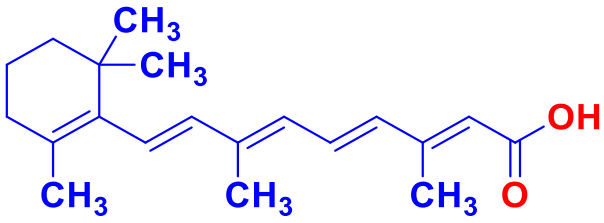
It is essential to note, however, that the use of anti-inflammatory retinoids, including the mentioned compounds, can lead to dose-dependent cutaneous irritation. This aspect underscores the importance of careful dosage considerations in clinical applications [58,59].



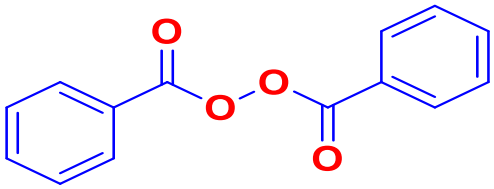
Retinoic acid

Benzoyl peroxide

Benzoyl peroxide has been incorporated into various formulations, predominantly in the form of gels, as a potent antimicrobial agent with a high affinity that effectively inhibits the growth of P. acnes and S. aureus. This is achieved through the production of reactive oxygen species (ROS) within the sebaceous follicle, exerting inhibitory effects on microorganisms. Additionally, benzoyl peroxide contributes to a reduction in free fatty acids, further enhancing its efficacy.

The multifaceted action of benzoyl peroxide results in an improvement in both inflammatory and non-inflammatory lesions, ultimately leading to the prevention of microcomedones formation [60]. The nuanced impact on these various aspects of acne pathology highlights the broad-spectrum effectiveness of benzoyl peroxide in acne management.

A comparative study was conducted to assess the efficacy of the combination of erythromycin with benzoyl peroxide versus the combination of erythromycin with tretinoin. The former formulation demonstrated significantly enhanced outcomes in the management of acne vulgaris [61]. This comparison underscores the clinical relevance of benzoyl peroxide in combination therapies, emphasizing its potential as a pivotal component in optimizing acne treatment regimens.



Benzoyl peroxide

Azelaic acid

Azelaic acids, hailing from natural sources, emerge as a versatile solution in the realm of dermatology, offering a spectrum of benefits for managing acne and related skin conditions. One of its key attributes lies in its comedolytic action, which plays a crucial role in preventing the formation of comedones, a hallmark of acne lesions. Beyond that, azelaic acids exhibit robust antibacterial capabilities, particularly against P. acnes, a major player in acne pathogenesis. This dual action of comedolytic and antibacterial activity underscores its significance in addressing multiple facets of acne development.

Moreover, azelaic acids contribute to the normalization of keratinization, a pivotal process in maintaining the integrity of the skin barrier. This normalization process aids in preventing the accumulation of keratinocytes within hair follicles, reducing the likelihood of pore blockage and subsequent acne lesion formation.

The anti-inflammatory effects of azelaic acids on neutrophil function add another layer to their therapeutic profile. By mitigating inflammation, these acids contribute to the overall amelioration of inflammatory aspects associated with acne, further supporting their role in comprehensive acne management.

Intriguingly, azelaic acids also exhibit skin-lightening properties, potentially beneficial for addressing post-inflammatory hyperpigmentation often observed in individuals with acne-prone skin.

Combining azelaic acid with other anti-acne medications, particularly synergistically with benzoyl peroxide, has been demonstrated to enhance efficacy compared to using azelaic acid alone. This combination approach showcases the potential for a more comprehensive and potent treatment strategy in addressing acne.

Remarkably, the safety profile of azelaic acid stands out, characterized by lower irritancy and phototoxicity. This aspect not only enhances patient tolerance but also

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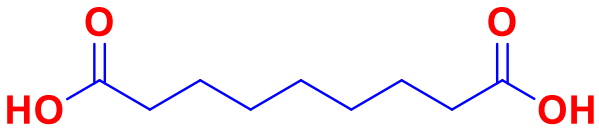
broadens the range of individuals who can benefit from its therapeutic effects.

Noteworthy is the absence of reported azelaic acid resistance in P. acnes, a significant advantage in the landscape of antibiotic resistance concerns. This lack of resistance further solidifies azelaic acid's position as a reliable and sustainable component in the arsenal against acne and related skin conditions [62].



Azelaic acid

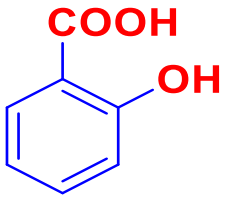
Salicylic acid

Salicylic acid has been a cornerstone in the dermatological arsenal, strategically employed to dissolve follicular blockages in various formulations, including notable instances such as alcoholic cleaning solutions. Renowned for its dual action as a moderate keratolytic and anti-inflammatory agent, salicylic acid plays a pivotal role in inhibiting prostaglandin (PG) formation, thereby contributing to the overall management of acne.

In direct comparison to benzoyl peroxide, formulations integrating salicylic acid have exhibited remarkable efficacy. This superiority implies that salicylic acid, with its distinct properties, can offer a potent alternative or complement to existing treatments in addressing acne-related concerns. Furthermore, when juxtaposed with retinoids, salicylic acid stands out as a gentler substance, highlighting its potential for those seeking a milder yet effective approach to skincare [63].

Recognizing the divergent mechanisms of action, the prospect of combining salicylic acid with benzoyl peroxide emerges as a promising avenue for improving therapy outcomes. This synergistic approach capitalizes on the complementary strengths of each component, allowing for a more comprehensive and nuanced approach to tackling various aspects of acne pathology simultaneously.

Beyond its role in addressing follicular blockages, salicylic acid has proven its versatility in dermatological procedures. Utilized in skin peeling procedures and as a cleansing agent, salicylic acid has demonstrated a capacity to significantly reduce comedones. This multifaceted application underscores its potential not only as a targeted treatment but also as a valuable asset in broader skincare practices, contributing to the overall health and appearance of the skin [64]



Salicylic acid

Medicinal Plants with Anti-Acne Activity

Herbal medicinal plants indeed show promise in addressing acne concerns with potential advantages over non-herbal formulations, as they often sidestep significant side effects such as skin dryness, rashes, wrinkling, erythema, pruritis, and the development of resistance.[65] Additionally, herbal remedies can provide a natural essence to the skin. Various plants exhibit antimicrobial, inflammation-modulating, anti-comedogenic, antioxidant, and hormone-balancing properties, making them beneficial for treating acne.[66,67] Their diverse bioactive compounds contribute to a holistic approach in managing acne, promoting skin health in a more balanced and harmonious manner, **Table IV**. Various medicinal herbs with anti-inflammatory and antibacterial properties are employed in the treatment of acne and other infectious disorders [68,69,70]. Commonly used plants for this purpose include *Matricaria recutita*, *Calendula officinalis*, and *Triticum aestivum*. Astringents and plant-based compounds such as tannins are topically applied in the form of creams or aqueous infusions after skin cleansing or steam baths. *Hamamelis virginiana* is frequently utilized for acne treatment due to its tannin content and high level of topical safety [71]. Additional plants with beneficial properties include white oak (*Quercus alba*) bark, walnut (*Juglans regia*) leaf, *Agrimonia eupatoria*, *Syzygium cuminum*, *Ledum latifolium*, *Alchemilla mollis*, *Lavandula angustifolia*, *Verbascum thapsus*, *Krameria triandra*, *Rheum palmatum*, *Hypericum perforatum*, and *Rumex crispus* ,*Vitex agnuscastus* is recommended for acne before menstruation, and the German Commission E has endorsed the topical use of *Solanum dulcamara* and the edible use of *Saccharomyces cerevisiae* for their antibacterial effects as acne remedies [72,73,74]. A randomized double-blind clinical trial with 60 patients who had mild-moderate acne found that topical use of

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50% *Aloe vera* gel with tretinoin cream was well tolerated during eight weeks and was significantly more effective than tretinoin and vehicle. Lemna minor has been applied topically to treat acne in China [75,76].

Twenty individuals with mild to moderate acne who applied green tea (*Camellia sinensis*) lotion topically for six weeks found it to be more helpful than pretreatment. Green tea's flavonoids and tannins may have an anti-acne impact since flavonoids appear to have an antibacterial effect and tannins appear to have an anti-inflammatory effect. The root of Mahonia is used in Western traditional medicine [77,78].

Achyranthes aspera

The historical applications of this medicinal plant have been diverse, encompassing the treatment of various conditions, including boils, scabies, and acne vulgaris, among others. Beyond its traditional uses, recent research has shed light on the potent therapeutic potential embedded in the plant's leaves.

Extracts derived from these leaves, with a keen focus on distinct fractions such as saponin, alkaloid, and non-alkaloid components, reveal a fascinating spectrum of biological activity. Notably, these extracts exhibit a substantial inhibitory effect on the activation of the Epstein-Barr virus early antigen in Raji cells, indicating a potential antiviral property.

Delving into the specifics, the non-alkaloid fraction, rich in non-polar compounds, emerges as a particularly promising aspect of this herbal remedy. This fraction demonstrates an outstanding inhibitory activity, reaching an impressive 96.9%, while still maintaining a noteworthy 60% cell viability. This nuanced information not only underscores the potency of the non-alkaloid fraction but also prompts further exploration into the specific compounds responsible for these inhibitory effects.

In summary, the traditional uses of this medicinal plant are complemented by contemporary insights that highlight its potential in combating viral activation. The intricate interplay of various fractions adds layers to our understanding of the plant's pharmacological properties, paving the way for potential advancements in herbal medicine and antiviral research [79,80].

Allium cepa

Individuals with seborrheic keratosis, a common skin condition characterized by non-cancerous growths, have experienced notable improvements in scar appearance through the application of a specialized gel containing onion extract. The effectiveness of this treatment is evident in the significant enhancements observed in terms of redness reduction, increased softness, and improved overall texture of the scar at the site of excision. This positive transformation becomes increasingly apparent at four, six, and ten weeks following the consistent use of the gel.

Delving into the botanical aspects, *Allium cepa* (A. cepa) and *Allium sativum* (A. sativum), commonly known as onion and garlic, respectively, have been subject to scientific scrutiny for their therapeutic properties. In a distinct study, these plant extracts showcased remarkable antibacterial and antifungal effects against various pathogens, including Malassezia furfur, Candida albicans, and diverse Candida species. Furthermore, their efficacy extended to combating several strains of dermatophytes, which are fungi responsible for causing skin infections, along with microorganisms associated with Acne vulgaris.

The multifaceted benefits observed in scar improvement and antimicrobial activity underscore the potential of onion extract, specifically *A. cepa* and *A. sativum*, in dermatological applications. These findings contribute to a growing body of knowledge regarding natural remedies and their therapeutic roles in addressing skin conditions and promoting optimal skin health [81,82]

Azadirachta indica

Within a comprehensive study exploring the efficacy of an anti-acne formulation comprised of herbal extracts, a particularly promising ethanol extract was identified. This extract contained key components, namely *Azadirachta indica*, *Glycyrrhiza glabra*, *Andrographis paniculata*, *Ocimum sanctum*, and green tea. The collective synergy of these herbal elements exhibited a notable capacity to inhibit the development of acne, suggesting a potential breakthrough in natural acne management strategies.

Furthermore, the investigation extended beyond acne-related benefits to unveil a distinct positive outcome associated with an aqueous extract derived from the leaves of *Azadirachta indica*. This specific extract demonstrated a noteworthy ability to prevent the development of murine skin cancer. Such preventive properties mark a significant contribution to the understanding of herbal extracts not only in addressing common skin concerns like acne but also in potential applications for broader skin health and cancer prevention.

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These findings highlight the multifaceted nature of herbal extracts, showcasing their potential as valuable components in formulations targeting various skin conditions. The identification of preventive effects against skin cancer adds an extra layer of significance to the exploration of natural remedies in dermatological research [83,84,85]

Rosmarinus officinalis

Rosmarinus officinalis, commonly known as rosemary, stands as a widely cultivated household plant with a global presence, contributing to various aspects of daily life. Its versatility extends to applications in cosmetics, culinary seasoning, and beverages, making it a staple in households worldwide. Within the botanical composition of Rosmarinus officinalis, the presence of Rosmarinic acid is particularly noteworthy, adding to the plant's diverse array of beneficial components.

The recognition of the potential consequences of chronic exposure to UV radiation, including the development of photocancers and accelerated aging (photoaging), underscores the need for protective measures. In this context, the antioxidant activity inherent in the aqueous extract of Rosmarinus officinalis becomes especially valuable. This extract emerges as a potent safeguard against photodamage induced by UV radiation, offering a natural and holistic approach to mitigate the effects of prolonged sun exposure [86,87].

Delving into the realm of skincare, *Rosmarinus officinalis* oil exhibits promising properties in combating acne, specifically addressing the bacteria P. acnes, a common culprit in acne development. A study evaluating the antibacterial effects of the essential oil from *Rosmarinus officinalis* on P. acnes showcased compelling results. The treatment demonstrated a significant impact not only on the size but also on the morphology of the bacteria, suggesting its potential as a natural and effective intervention in acne management [88,89,90].

These multifaceted attributes highlight the significance of *Rosmarinus officinalis* not only as a culinary and aromatic herb but also as a botanical ally in promoting skin health and providing protection against environmental stressors, such as UV radiation and acne-inducing bacteria. The exploration of its diverse properties opens avenues for incorporating natural remedies into both skincare and general well-being practices [86,87,88,89,90].

Eucalyptus globulus, E. viminalis* and *E. maculate

A comprehensive investigation into the antimicrobial properties of 29 distinct types of eucalyptus leaves provided valuable insights into their potential therapeutic applications. Specifically, extracts derived from *Eucalyptus globulus*, *E. maculata*, and *E. viminalis* were scrutinized for their inhibitory effects on six gram-positive bacteria, namely P. acnes, S. aureus, Enterococcus faecalis, *Bacillus cereus*, and Alicyclobacillus acidoterrestris, along with a fungus, Trichophyton mentagrophytes.

The findings revealed that these eucalyptus extracts demonstrated a remarkable capacity to impede the growth of the tested gram-positive bacteria and the fungal strain. However, their inhibitory activity against gram-negative bacteria was not as pronounced. Of particular note was the identification of eight-dimethyl-eucalyptin, a constituent found in E. maculate, which exhibited significant inhibitory effects against the aforementioned bacteria.

This nuanced exploration of various eucalyptus species and their specific components sheds light on the potential diversity within the antimicrobial properties of these leaves. The selective impact on gram-positive bacteria and the identification of specific active compounds, such as eight-dimethyl-eucalyptin, offer valuable insights for further research into the development of targeted antimicrobial interventions [91,92,93]

Cannabis sativus

Cannabis sativus seed oil emerges as a versatile remedy, showcasing notable effectiveness in addressing a spectrum of dermatological conditions. Its therapeutic reach extends to encompass psoriasis, eczema, dermatitis, seborrheic dermatitis, rosacea, acne, and lichen planus, making it a promising candidate for a diverse range of skin-related concerns. Furthermore, the leaf powder derived from the *Cannabis sativus* plant has proven to be highly advantageous in the treatment of cuts and sores, suggesting a broader scope of applications for this botanical remedy [94,95].

The external application of an extract from the *Cannabis sativus* plant emerges as a viable solution for alleviating the discomfort associated with itchy skin. This topical approach provides targeted relief, offering a soothing effect on irritated skin. Concurrently, the application of *cannabis sativus* seed oil contributes to skin fortification. This fortifying effect enhances the skin's resilience against various pathogens, including viruses, bacteria, and fungi. By fostering a robust skin barrier,

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the seed oil serves as a proactive measure in preventing and managing infections, presenting a holistic approach to skin health [96].

These multifaceted properties underscore the potential of *Cannabis sativus* as a comprehensive botanical remedy for diverse dermatological concerns, ranging from inflammatory conditions to wound healing and skin protection. The exploration of its varied applications opens avenues for incorporating natural solutions into skincare routines and addressing a wide array of skin-related challenges [94,95,96]

Melaleuca alternifolia

Melaleuca alternifolia, commonly known as tea tree, stands as a distinguished member of the *Melaleuca genus*, finding its roots in the diverse landscapes of Australia. Indigenous to the continent, it thrives along the north coast and adjacent regions of New South Wales [97,98,99]. This resilient plant not only graces the banks of streams but also asserts its dominance in swampy plains, showcasing adaptability and a penchant for ecological prominence [100].

The potency of tea tree oil, extracted from *Melaleuca alternifolia*, unfolds in its remarkable efficacy against a spectrum of microorganisms in vitro. This includes yeasts such as Candida albicans and a broad range of bacteria, encompassing both Gram-positive and Gram-negative strains. Notably, tea tree oil demonstrates effectiveness even against the challenging methicillin-resistant Staphylococcus aureus (MRSA) [101,102]. The mechanism underlying this antimicrobial prowess lies in the disruption of the plasma membrane barrier, orchestrated by the action of monoterpenes. This nuanced understanding of its mode of action adds depth to the appreciation of tea tree oil as a potent and natural antimicrobial agent [103,104].

Tea tree's ecological resilience and the multifaceted antimicrobial properties of its oil underscore its significance, not only in its native habitat but also in the broader context of natural remedies. The exploration of its mechanisms against microbial threats opens avenues for potential applications in skincare, wound care, and beyond, further emphasizing its role as a botanical ally in the realm of health and wellness.

Table III. Problem faced during use of Synthetic drugs for treatment of acne vulgaris:

Sl. No.	Synthetic drugs	Side effects
1.	Salicylic acid	Initially show skin burning and dry.[105]
2.	Azelaic acid	Itching, swollen, itching, redness on skin.[106]
3.	Benzoyl peroxide	Hives and rashes on the skin. [107]
4.	Retinoic acid	High pigmentation [108]

Table IV: Herbs used to treat acne vulgaris.

Sl. No.	Latin binomials medicinal plants	Common names	chemical active constituents	References
1.	*Achillea millefolium flowering top.*	Yarrow.	Trigonelline, betonicine alkaloid, coumarin.	[109]
2.	*Aloe barbadensis gel.*	Aloe vera.	Anthranol, emodin, isoemodin, aloin.	[110]
3.	*Arctium lappa root.*	Burdock.	Rutin, myricetin, pectin, qucertin.	[111]
4.	*Artemisia absinthium leaf.*	Wormwood.	Absintholide, beta-santonin and ketopepenolid-A , essential oil.	[112]
5.	*Azardirachta indica leaf.*	Neem.	Nimbidin, lauric acid, nimbin, margosinealkaloid.	[113]
6.	*Berberis vulgaris root.*	Barberry.	Berberine alkaloid	[114]
7.	*Chamaelirium luteum root.*	False unicorn.	Heloside-a, helogenin, spirostanol.	[115]
8.	*Coptis chinensis root.*	Goldthread.	Huanglianxu	[116]
9.	*Commiphora mukul resin.*	Guggul.	Myrrhanone A, guggulsterone	[117]
10.	*Embelia ribes fruit.*	Vidanga.	chlorogenic corrosive, embelin, Daraprim.	[118]
11.	*Curcuma longa rhizome.*	Turmeric.	Curcumin, dimethoxy curcuminoids, phenolic moiety.	[119]

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12.	*Emblica officinalis fruit.*	Amalaki.	Pedunculagin, Corilagin, Glutamic acid	[120]
13.	*Eucalyptus globulus leaf.*	Eucalyptus.	Phytosterol, triterpenoid, flavonoids.	[121]
14.	*Eucalyptus maculate leaf.*	Eucalyptus.	D-linalool, myrcene, citronellar.	[122]
15.	*Eucalyptus viminalis leaf.*	Eucalyptus.	Cineole, limonene	[122]
16.	*Gentiana lutea root.*	Genetian.	Isogentisin, xanthone glycosides	[123]
17.	*Hemidesmus indicus root.*	Indian sarsaparilla.	Hemidesmin, β-sitosterol, alpha-amyrin	[124]
18.	*Holarrhena antidysenterica stem.*	Kutaj.	Pholobatannin, kurchicine, b-stasterol.	[125]
19.	*Medicago sativa flowering top.*	Alfalfa.	Flavone, saponin, isoflavone	[126]
20.	*Melaleuca alternifolia leaf.*	Tea tree.	Triterpenoids , saponin, flavonoids.	[127]
21.	*Mitchella repens leaf.*	Partridge berry.	Volatile oi, sterol, flavonoids , carbohydrate.	[128]
22.	*Ocimum basilicum leaf.*	Basil.	Anethole, camphor, linalool	[129]
23.	*Piper longum fruit.*	Long pepper.	Gurjunene, piperloein B, pipernonaline	[130]
24.	*Scutellaria baicalensis root.*	Asian skullcap, scute.	Baicalin, Salvigenin, Wogonin.	[131]
25.	*Taraxacum officinale leaf and root.*	Dandelion.	Taraxacerin, Phenolic acid, sterols.	[132]
26.	*Terminalia chebula fruit.*	Chebulic myrobalan.	Chebulagic Acid, Terpinolene, β Sitosterol	[133]
27.	*Terminalia arjuna stem bark.*	Arjun.	Polyphenol, sterol, flavonoids, arjunolic acid	[134]
28.	*Aloysia citrodora.*	Vervain.	Allo-ocimene, Myrtenol, α-Copaene, Verbenyl acetate	[135]
29.	*Vitex agnus-castus fruit.*	Chaste tree, Vitex.	β-pinene, terpinolene, α-cubebene	[136]
30.	*Xanthorrhiza simplicissima root.*	Yellowroot.	Camphor, Benzofuran, Ar-curcumene	[137]
31.	*Zingiber officinale rhizome.*	Ginger.	Gingerols, Isogingerol, paradol, gingerdiol	[138]
32.	*Withania somnifera root.*	Ashwagandha.	Somniferinine, pseudo-withanine, withananine	[139]

Mechanism of action of natural remedies as well as synthetic remedies

Medicinal plants known for their efficacy against acne were sourced from literature or complementary medicine. Botanical fractions dissolved in organic solvents underwent testing for toxicity, anti-lipogenesis, anti-inflammation, and anti-microbial activities. Among these, the acidic hexane fraction of Solanum melongena (SM) displayed promising results, exhibiting selective anti-proliferative effects on SEB-1 sebocytes without causing direct cytotoxicity to other cells, while also suppressing intracellular lipid contents and demonstrating anti-inflammatory activity.Several studies have highlighted the anti-acne properties of various natural products. Gao et al. revealed the strong antibacterial activity of Aspidin BB, phloroglucinol derivatives from ferns, against P.[140] acnes. Additionally, research has shown the sebostatic, anti-proliferative, and anti-inflammatory effects of cannabidiol on human sebocytes, making it a promising therapeutic agent for acne due to its regulation of multiple physiological processes through the endocannabinoid system. Moreover, in a recent study, the application of LFCO resulted in a significant decrease of 65% and 53% in inflammatory and non-inflammatory acne lesions, respectively, by week 8, surpassing the effects of tea tree oil treatment, which only showed a decrease of 38% and 24%, respectively.[141]

Multiple synthetic agents have been developed as novel therapeutic options for treating acne. Schmidt et al. engineered Pentobra, a peptide-aminoglycoside that merges the robust ribosomal activity of aminoglycosides with the bacteria-selective membrane permeabilizing

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abilities of antimicrobial peptides.[142] Pentobra exhibited significantly enhanced antibacterial efficacy against P. acnes compared to tobramycin and demonstrated non-toxicity toward human skin cells. Electron microscopy revealed Pentobra-induced cell lysis of P. acnes accompanied by the externalization of cytoplasmic contents. Furthermore, Pentobra maintained its bactericidal effect in sebaceous microcomedones derived from donors' faces. Additionally, Pentobra suppressed P. acnes-induced chemokines, suggesting potential anti-inflammatory properties.[143] This study highlights the potential of aminoglycosides with cell-penetrating capabilities as antibiotics against slow-growing bacteria like P. acnes, offering a promising avenue for antibiotic development. Qin et al. reported that nitric oxide-releasing nanoparticles effectively eradicated P. acnes and inhibited the associated immune response. Nitric oxide, a potent biological messenger, exhibits broad-spectrum antimicrobial and immunomodulatory properties.[144] The researchers developed nanoparticles capable of sustained generation and release of nitric oxide, with an average radius of approximately 108nm. These nanoparticles demonstrated high sensitivity against P. acnes while remaining non-toxic to human cells such as HaCaT cells and peripheral blood mononuclear cells (PBMCs). The impact of these nanoparticles on the inflammasome, a cytoplasmic molecular complex involved in initiating inflammation, was investigated. Nitric oxide-releasing nanoparticles inhibited PBMC IL-1β secretion via the inflammasome pathway by suppressing caspase-1 and IL-1β gene expression, without affecting NLRP3 and ASC gene expression. [145]

Pan-In et al. reported on α-mangostin nanoparticles designed to penetrate hair follicles and deliver drugs to nearby sites, including the sebaceous glands. Mangostin, the principal component of *Garcinia mangostana* extract, possesses both anti-inflammatory and anti-P. acnes activities. The study evaluated the anti-acne and skin irritation potential of α-mangostin nanoparticles, with patients showing improvements in acne severity scores and inflammatory acne lesion counts.[146]

Conclusions

Numerous plant species exhibit compelling potential in inhibiting the proliferation of bacteria, fungi, and viruses in vitro. Furthermore, a variety of plants showcase properties known for their anti-inflammatory and anti-fat effects. Despite these promising attributes, the translation of these botanical benefits into clinical practice remains limited, particularly in addressing common skin issues such as acne. The current landscape sees chemical medications taking precedence in the treatment of acne and skin infections, although concerns about the efficacy and safety of synthetic drugs are beginning to emerge.

In light of this, certain plants explored in recent research have yielded encouraging results, introducing the possibility of integrating them into acne management strategies. These botanical alternatives can be considered either independently or as complementary measures alongside conventional therapeutic approaches, particularly in cases of mild to moderate conditions. However, a note of caution is warranted, especially when it comes to potential contact sensitization, a concern that becomes pertinent in applications involving topical or oral use.

Among the noteworthy plants demonstrating proven efficacy and safety are mountain grape roots, tea tree oil, Saccharomyces, and potentially *Ocimum basilicum*. These plant-based treatments, with their established track record, offer a promising alternative to synthetic medications for managing mild to moderate acne cases. It is crucial to emphasize that phenolic chemicals are prevalent in various plants, and assuming these compounds are solely responsible for reported anti-acne activity, further exploration into plants containing phenolic compounds is warranted for their potential anti-acne capabilities.

This nuanced understanding underscores the potential of plant-based treatments in dermatology, calling for continued research and exploration into their efficacy, safety, and applicability as alternative or complementary options in the management of skin conditions like acne.

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