



A Comprehensive Review on Polyherbal Topical Gels for Acne Therapy: Introduction, Preparation, & Evaluation Parameters.

Habib Abbas Akbarbhai^{a,b*}, Hingu Kishankumar^{a,b}, Patel Umangkumar^{a,b}, Himani Rathod^{a,b}, Patel Chirag^{a,b}

^aDepartment of Pharmaceutics, Shri Sarvajani Pharmacy College, Mehsana (GUJ.)384001, India.

^bDepartment of Pharmaceutics, Shri Sarvajani Pharmacy College, Mehsana (GUJ.)384001, India.

*Email: abbas.akbar.habib@gmail.com

DOI : <https://doi.org/10.55248/gengpi.07.0926.3022>

ABSTRACT:

Acne vulgaris is a widespread, multifactorial, chronic inflammatory skin disorder of the pilosebaceous unit, characterized by excessive sebum production, follicular hyperkeratinisation, microbial colonization by *Cutibacterium acnes*, and subsequent inflammation that exerts a profound psychosocial and clinical burden on affected populations across varying severity grades. While conventional topical and systemic therapies remain the mainstay of treatment, their long-term clinical utility is often limited by cutaneous irritation, systemic adverse effects, and escalating antimicrobial resistance. In response to these clinical challenges, polyherbal topical formulations have emerged as a promising alternative, imparting synergistic phytoconstituents to exert multi-target therapeutic effects. In response, phytomedicine has emerged as a promising alternative, leveraging protective synergy wherein diverse bioactive botanical constituents act simultaneously on multiple pathogenic pathways with reduced adverse profiles. This review comprehensively examines the anatomical and pathophysiological mechanisms underlying acne. It evaluates clinical management strategies by contrasting conventional versus advanced, and topical versus systemic interventions. Furthermore, the work details the formulation design, rheological parameters, basic gel components, and evaluation protocols (including organoleptic, physicochemical, and preliminary stability parameters) for polyherbal gel delivery systems. By synthesizing multi-herbal strategies, this review establishes a structured rationale for developing stable, patient-compliance, and effective polyherbal topical gels aimed at curing inflammatory acne while minimizing adverse effects.

Keywords: Acne Vulgaris, Pilosebaceous Unit, Protective synergy, Clinical management, Polyherbal Gel, Topical Delivery System, Phytotherapeutics.

INTRODUCTION

Acne vulgaris is a chronic inflammatory skin condition with multifactorial pathogenesis, involving abnormal keratinization, sebum overproduction, inflammation of the pilosebaceous unit, microbial colonization by *Cutibacterium acnes*, and dietary influences. Although numerous effective treatments are currently available, such as retinoids, antibiotics, and hormonal agents, they are often limited by adverse effects, antimicrobial resistance, and disruption of the skin microbiome. These limitations have intensified the search for alternative therapies that can restore microbial balance, modulate host-microbe interactions, and enhance safety & tolerability [1]. Historically, herbal remedies were utilized to cure acne through various traditional systems of medicine. In Ayurveda, neem and turmeric are used for their anti-inflammatory and antibacterial activity, purifying skin and blood. Green tea is utilized in Chinese traditional medicine for its antioxidant and anti-inflammatory properties. Topical application of green tea minimizes sebum production and inhibits bacterial growth. Liquorice root extract reduces the redness and irritation of acne and shows skin-soothing properties. In the Western system, tea tree oil and witch hazel were used for their antibacterial and astringent properties, respectively. Rose water is used for soothing the skin, and honey is used for antimicrobial and healing properties in the Unani system of medicine. These natural remedies highlight the diverse approaches to acne treatment through herbal medicine, reflecting a rich history of botanical knowledge and application [2].

A larger range of pharmacological action, reduced toxicity, and increased therapeutic efficacy can be achieved via the deliberate mixing of various medicinal plants in a single preparation, an approach known as *Polyherbalism*. Combinations of herbs have been recommended for ages to cure complicated disorders and restore physiological balance in traditional medicinal systems like Ayurveda, Siddha, and Unani, where this idea has strong roots. Combining herbs in well-defined quantities can generate greater outcomes compared to single-herb treatments. This is based on the basic idea that no single plant has all the phytochemicals necessary to address multifactorial illnesses. Synergy is a key mechanism whereby several bioactive components work together to increase therapeutic impact by acting on complementary molecular targets. In addition, there is a possibility of protective synergy, when one substance mitigates the negative effects or toxicity of another, making their combined usage safer for extended periods of time. Because skin safety and tolerance are paramount in dermatological applications, this is of the utmost importance [3].

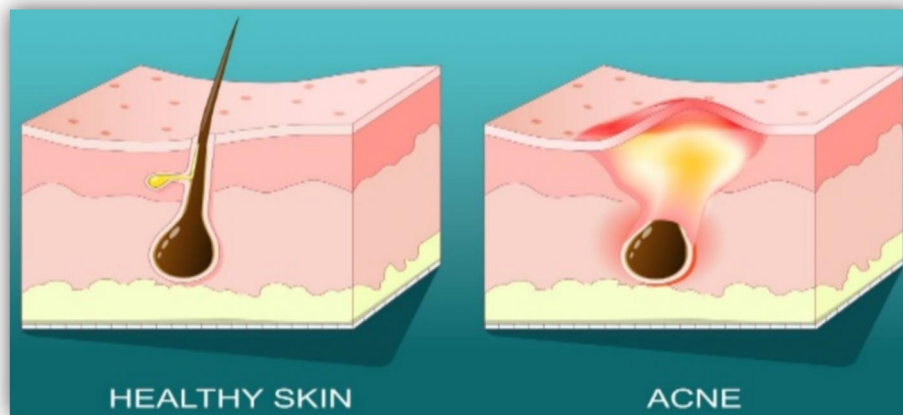


Fig 1: Comparison between Healthy Skin and Acne affected skin.

ACNE VULGARIS: AN OVERVIEW

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit, characterized by comedones, papules, pustules, nodules, and in severe cases, cysts. It predominantly affects adolescents and young adults, with global prevalence estimates ranging between 70–90% [4]. Around **20%** of neonates have an acneiform eruption but this usually resolves by **3 months**. One Danish study has shown that the average age at onset of puberty in boys has dropped from **11.92** to **11.66 years** over a **15-year** period. Friedlander et al. postulated that this younger age of puberty was the reason for the observation that younger patients between the ages of 8 and 11 were presenting with acne in their clinics [5].

1.1. Psychosocial Impact:

Although acne was once thought to be only a cosmetic problem, the disease's psychological impacts have now been scientifically confirmed. Despite the fact that acne does not cause physical harm, it can have a substantial mental impact. Severe acne is associated with increased psychological impact like depression, anxiety, poor self-image, poor self-esteem. In more severe acne and, later stages of puberty, psychiatric issues are more likely. Acne is linked to a higher risk of depression, anxiety, and suicide ideation. Adolescence is a period of substantial physical, emotional, and social growth, which can lead to mental or psychosocial problems [6]. It is found that acne patients are often stigmatized and have major professional and social difficulties, and all these leads to increased school absenteeism in adolescents and decreased professional performance at work in adults [7].

1.2. Etiology and Severity Grading of Acne:

Acne develops as a result of hypersensitivity of the sebaceous glands to normal levels of circulating androgens. This process is further exacerbated by the presence of *Cutibacterium acnes* (*C. acnes*), a bacterial species, and subsequent inflammation.

Proposed Contributory Factors for Acne Include:

- Exposure to excess sunlight.
- Genetic factors significantly influence the proportion of branched fatty acids found in sebum, with heritability estimates ranging from 50% to 90%.
- Endocrine disorders, such as polycystic ovarian syndrome, and even pregnancy. A premenstrual flare-up in acne seems to follow edema of the pilosebaceous duct. This occurs in 70% of female patients.
- Oil-based cosmetics and facial massage.
- Psychological stress is associated with increased acne severity, probably by stimulating stress hormones.
- Insulin resistance may also have a significant role in acne, as individuals with insulin resistance have increased levels of *IGF*, which is linked to increased facial sebum excretion [8].

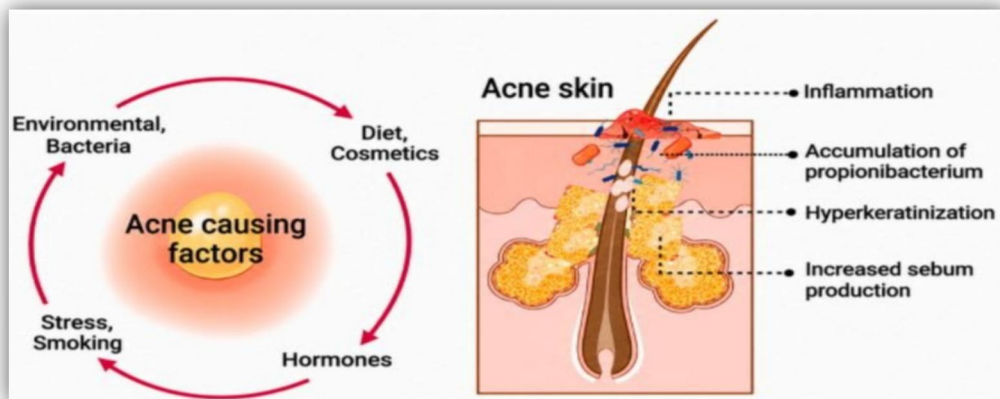


Fig 2: Representation of Acne-Inflamed Skin Tissue and Major Contributing Factors Involved in Acne Development.

Acne myths:

These factors have little effect on acne:

- *Chocolate and greasy foods:* Eating chocolate or greasy food has little to no effect on acne.
- *Hygiene:* Acne isn't caused by dirty skin. In fact, scrubbing the skin too hard or cleansing with harsh soaps or chemicals irritates the skin and can make acne worse.
- *Cosmetics:* Cosmetics don't necessarily worsen acne, especially if you use oil-free makeup that doesn't clog pores (non-comedogenics) and remove makeup regularly. Non-oily cosmetics don't interfere with the effectiveness of acne drugs [9].

Severity Grading of Acne:

United States, employs a five-point ordinal scale (zero through four) to classify acne severity as clear, almost clear, mild, moderate, or severe. This system is widely used in clinical trials and aligns with efforts to standardize acne assessment. Additionally, digital imaging techniques, including fluorescent and polarized light photography, are gaining traction for objective acne severity assessment. Beyond lesion-based grading, the guidelines advocate for incorporating quality-of-life measures, including patient satisfaction, extent of scarring, and long-term treatment outcomes, to provide a more comprehensive evaluation of acne burden [10].

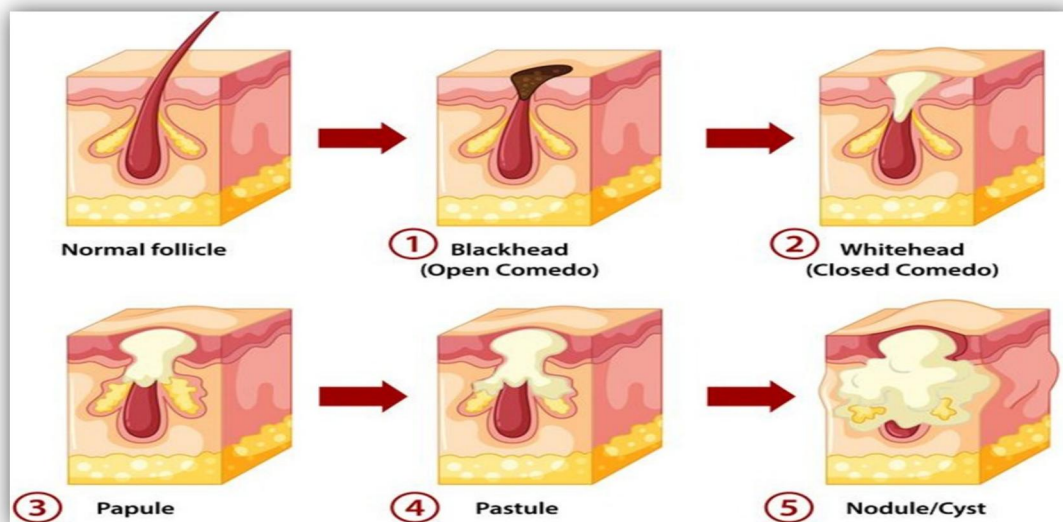


Fig 3: Stages of Acne. [①: Mild, ②&③: Moderate and ④&⑤: Severe]

Stages of Acne:

The stages can be shown as below:

- An open comedo also called blackheads.
- Pale coloured nodule like formation known as Whitehead.
- Sebum combines with desquamated cells called Papules.
- An inflammatory lesion called Pustules [11].

- Large, inflamed lesions underneath the skin's surface called Nodules, while; Large pus-filled, and painful inflammation called Cysts. (If left untreated or not treated properly, it can lead to scarring.) [12]

PATHOGENESIS OF ACNE:

Acne's multi-factorial pathogenesis originates in the pilosebaceous unit, which comprises of a hair, a follicular canal bordered by epithelium, and a set of multi-lobulated sebaceous glands. Acne pathophysiology is thought to involve a number of factors, including: follicular hyperkeratinization followed by proliferation of *Propionibacterium acnes* within the follicle; sebaceous gland hyperplasia with seborrhoea; changes in the quality of sebum lipids; inflammatory processes other than the immune response; dysregulation of the hormone microenvironment; interaction with neuropeptides; and so on [13]. The pathogenesis of acne vulgaris is multifactorial. Cytokines play an important role in the pathogenesis of acne vulgaris, together with other genetic and environmental factors. Tumor necrosis factor- α -308 gene polymorphism might be a predisposing factor for acne susceptibility with no apparent relation to its severity [14].

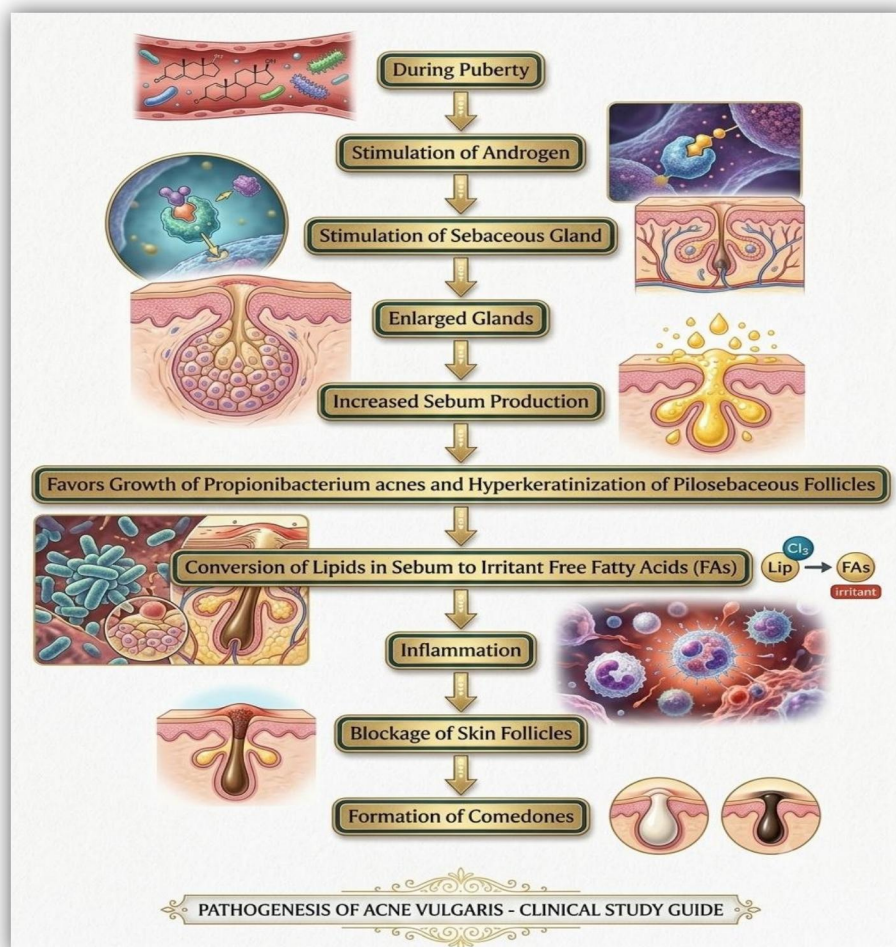


Fig 4: Pathogenesis of Acne.

1.3. Pathogenesis: Four Interlocking Processes:

Acne arises from the convergence of four tightly connected biological processes within the pilosebaceous unit:

1. Follicular hyperkeratinisation produces microcomedones through abnormal keratinocyte proliferation and desquamation, narrowing the infundibulum and obstructing outflow.
2. Sebum overproduction and altered composition, driven by androgens and metabolic signals such as IGF-1, creates a lipid-rich, anaerobic niche; sebum output correlates with acne severity.
3. Microbial factors—especially *C. acnes* colonisation—promote disease via lipases, hyaluronidases, and proteases that liberate free fatty acids, compromise the barrier, and foster comedogenesis; biofilm formation may shield bacteria from host defences and antibiotics.
4. Inflammation and innate-adaptive crosstalk amplifies and sustain lesions: IL-1 signalling, neutrophil recruitment and ROS (Reactive Oxygen

Species) generation, and leukotriene B₄-mediated cascades are implicated. Sebocytes synthesize neuropeptides, antimicrobial peptides, and antibacterial lipids, linking stress (CRH axis) and vitamin D signalling to sebaceous activity [15].

Polyherbal Gel: An Overview

A gel comprised of synthetic or natural polymer which forms three dimensional matrixes all over a hydrophilic liquid or a dispersion medium. The rigidity of gel is achieved by the gelling agent because particles interlocked and formed a network. The type of form and mature of particles which are responsible for the formation of linkages determine the composition of network and property of gel. When gel is applied on to the skin, the liquid evaporates and entrapped drug leaves in form of thin-film of gel-forming matrix which covers the skin [16].

1.4. Gels:

- A semisolid systems consisting of dispersions made up of either small inorganic particles or large organic molecules enclosing and interpenetrated by a liquid.
- A high degree of physical or chemical cross- linking may be involved.
- The increased viscosity caused by the internal friction is responsible for the semisolid state [17].



Fig 5: Gel.

1.5. It's Basic Components:

Choice of excipients depends on use of Gel i.e. oral/topical/ophthalmic etc.

Excipients may include:

1. Buffers
2. Preservatives
3. Anti-Oxidants
4. Flavors
5. Sweetening Agents
6. Stabilizers [18].

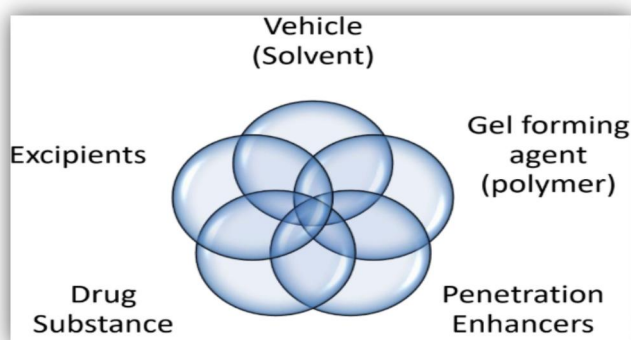


Fig 6: Components of Gel's.

1.6. Characteristics of Gel:

Gel differs from other dosage forms in that they have specific characteristics related to swelling, syneresis, ageing, stiffness, and the rheology [19].

1. **Swelling:** Selecting the appropriate gelling agent is a critical aspect of formulation because it influences the gel's hardness and plays a role in

binding viscosity between particles and the medium.

2. **Rheology:** Flocculated strong dispersion and gelling specialty arrangements are two instances of faux flexibility. Showing a reduction variation in thickness and an elevation in shear stress characterize non-Newtonian float conduct. A tighter organization of the gelling specialized eventually forms as n gels grow, upending the questionable design of inorganic trash diluted in water [20].
3. **Syneresis:** Numerous gel structures become compressed after standing. At the top layer of the gel, the interstitial fluid congregates and interacts. Along with natural hydrogels, organogels and inorganic hydrogels have also demonstrated this syneresis cycle. As the polymer cluster grows, syneresis frequently intensifies smaller.
4. **Structure:** The rigidity of a gel arises from the presence of a network formed by the interlinking of particles of the gelling agents. The nature of the particle and the stress, straightening them out and lessening the resistance to flow [21].
5. **Ageing:** Colloidal systems Usually exhibit slow spontaneous aggregation. This process is referred to as ageing [22].

1.7. Types of Gel Systems:

Gels can be classified in various ways based on their composition, the solvent used, their physical properties, and how they flow or move.

Here are the main ways to classify gels:

1. Based on colloidal phases:

A. Inorganic Gels (Two-Phase System)

- These consist of small solid particles (flocules) dispersed throughout the gel. The particles are small but not fully dissolved, and the system can be unstable if the particle size becomes too large. These gels are thixotropic, meaning they become liquid when stirred and return to a semisolid state when left undisturbed.
- Examples include gels made from aluminium hydroxide and bentonite.

B. Organic Gels (Single-Phase System)

- These consist of large organic molecules that are fully dissolved in the solvent, forming a continuous phase. Organic gels are smooth and stable due to the uniform distribution of the dissolved molecules.
- Examples include gels made from carbomer or tragacanth, often found in cosmetics or pharmaceuticals.

2. Based on the nature of the solvent:

A. Hydrogels

- Gels where water is the main solvent. They can absorb large amounts of water and are used in applications like wound dressings, contact lenses, and drug delivery systems.

B. Organogels

- Gels where the solvent is an organic liquid (e.g., oils). They are used in cosmetics, ointments, and some drug delivery systems [23].

C. Xerogels

- A xerogel is a dehydrated solid gel that undergoes indefinite shrinkage. It generally maintains high porosity (15-40%) and a large surface area.
- Example include strips of gum tragacanth, beta- cyclodextrin, dry cellulose and polystyrene, gelatin sheets and acacia tears [24]

3. Based on physical nature:

A. Elastic gels

- These gels can return to their original shape after being stretched or compressed, much like rubber. They are often used in soft tissue engineering and biomedical applications.

B. Rigid gels

- These gels are firm and do not easily change shape. They are commonly used in food products like gelatin desserts.

4. Based on Rheological Properties (Flow behaviour):

A. Thixotropic gels

- These gels become less viscous and flow when subjected to stress (e.g., shaking or stirring) but return to their original state when the stress is removed.

B. Non-Thixotropic gels

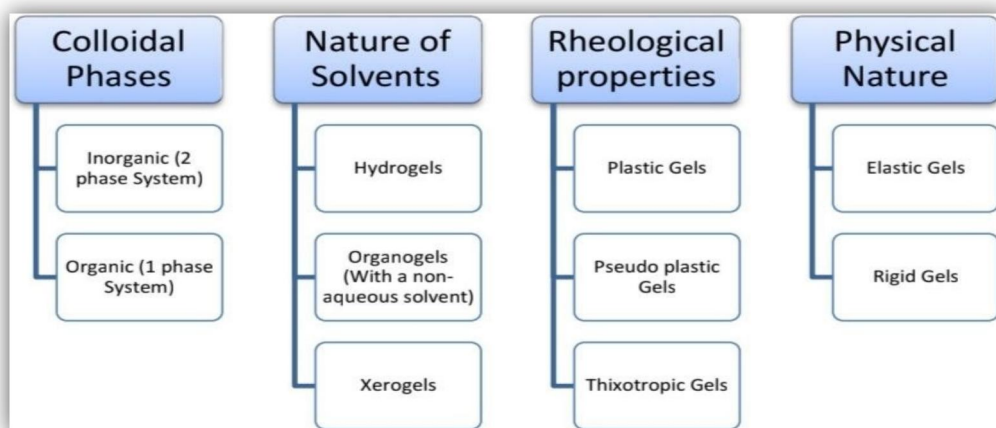
- These gels maintain their shape and consistency, even when stressed.

It includes:**a. Plastic Gels**

- Eg: Bingham bodies, flocculated suspension of Aluminum hydroxide exhibits a plastic flow and when we plot a rheogram yield value of the gels above which the elastic gel distorts and begin to flow.

b. Pseudo-Plastic Gels

- Eg: Liquid dispersion of tragacanth, sodium alginate, Na CMC etc. shows pseudo-plastic flow. That means viscosity of these gels decreases with increasing rate of shear. With increasing shear stress these disarranged molecules begin to align their long axis in the direction of flow with release of solvent from matrix [25].

**Fig 7: Types of Gel Systems.****1.8. Applications of Gels:**

- Many substances can form gels when a suitable thickener or gelling agent is added to their formula. This approach is common in the manufacture of a wide range of products, from foods to paints and adhesives.
- In fibre optic communications, a soft gel resembling hair gel in viscosity is used to fill the plastic tubes containing the fibres. The main purpose of the gel is to prevent water intrusion if the buffer tube is breached, but the gel also buffers the fibres against mechanical damage when the tube is bent around corners during installation, or flexed. Additionally, the gel acts as a processing aid when the cable is being constructed, keeping the fibres central whilst the tube material is extruded around it [26].

• Pharmaceutical Applications.

Therapeutic uses in Acne Management:

1. Microbial inhibition.
2. Anti-inflammatory action.
3. Reduction of sebum production.
4. Prevention of comedone formation.
5. Topical Drug Delivery System.
6. Drug Delivery.
7. Antimicrobial & Antiseptic use.
8. Wound Healing & Skin Repair [27].

• Cosmeceutical Applications.

1. Skin Care & Beauty Enhancement.
2. Anti-Acne & Oil Control Product.
3. Skin Brightening and Even Tone.
4. Moisturizing & Soothing Agent.
5. Natural Exfoliating Product.
6. Herbal Natural Cosmetic Product.
7. Skin Health Enhancement.
8. Proactive Skincare [28, 29].

CLINICAL MANAGEMENT STRATEGIES FOR ACNE THERAPY:

Especially due to the lack of data from outpatient care making the burden of this disease difficult to assess. A possible solution to this shortcoming is to plan and implement a computerized case sheet for each patient suffering from acne, based on a minimum data set. A physician (dermatologist himself or general practitioner) should compile this case sheet, and include the following simple, but important, information:

- Patient's age
- Sex
- Clinical form of acne (comedones, papules-pustules, nodules-cysts)
- Grade of severity (mild, moderate, severe)
- Quality of life (high, medium or low)

In this way, it could be possible to have a simple and immediate summary of the situation. Moreover, collecting these kinds of data is quick and easy and not bothersome for the patient. All this information should be introduced into a database management system, via web platform, in order to create a sort of network and provide these data to everyone whoever may need it, be it dermatologists, general practitioners, or treatment centres, etc. This could also be an efficient device to supervise the epidemiological trend of acne across different populations, different age groups of patients and its evolution throughout several years. The same device could be applied to other pathologies, of course [30].

1.9. Topical vs. Systemic Therapies:

1.9.1. Topical Therapies:

Topical antibiotics are available on prescription for the treatment of acne. They are best used twice daily. Ideally, these agents should be combined with benzoyl peroxide and/or topical retinoids. These combination agents increase the potency of the clinical response.

There are significant concerns about increased antibiotic resistance with the use of topical and oral antibiotics as monotherapy in acne. By using combination products, the risk of antibiotic resistance is markedly reduced [31].

1. Benzoyl Peroxide:

- Benzoyl peroxide (BP) has been an important component of topical therapy for acne vulgaris for more than five decades due to its ability to markedly reduce propionibacterium acnes (P.acnes) and inflammatory acne lesions and its ability to moderately reduce non-inflammatory acne lesions.
- It has mild Sebo-static and keratolytic effects without a concern for the development of drug-resistant bacteria.
- It is most effective when used in combination with other acne vulgaris therapies.
- BP is a bactericidal agent. Combining BP with a topical antibiotic in a stable formulation has been proven in clinical trials to reduce total P.acnes count by 99.7% after 1 week of therapy, eliminating both susceptible and resistant strains of P.acnes.
- However, we have recently noticed BP's benefits as monotherapy in the treatment of acne.

2. Clindamycin:

- Due to the significant increase of P.acnes strains resistant to clindamycin and erythromycin, the use of these substances alone is contra-indicated.
- Cutibacterium acnes (C. acnes) can become an exacerbating factor in acne vulgaris, where Clindamycin was found to be resistant.
- Clindamycin can be administered into the body by multiple routes. It is available topically as a foam, gel, lotion, or solution for treatment of acne vulgaris.

- The most common side effects experienced with topical use include opular, xeroderma, erythema, burning, exfoliation, or oily skin.

3. Retinoids:

- Topical retinoids are creams, lotions and gels containing medicine derived from vitamin A.
- These compounds result in proliferation and reduced keratinization of skin cells independent of their functions as a vitamin and devoid of bacterial resistance.
- Local adverse effects including erythema, dryness, itching, and stinging. Occur frequently during the early treatment phase.
- Their impact varies with the vehicle formation, Skin type, frequency and mode of application, use of moisturizers, and environmental factors such as sun exposure or temperature.
- Retinoids act to normalize desquamation by reducing Keratinocyte proliferation and promoting differentiation.
- Isotretinoin, tretinoin, and tazarotene also suppress Toll-like Receptor expression.
- Blocking these pathways reduces the release of inflammatory cytokines and nitric oxide and inhibits cellular Inflammation.

4. Dapsone:

- Topical dapsone is used for both comedonal and opular acne, though there are some concerns with G6PD deficient individuals.
- Treatment of AV with dapsone gel, 5% requires twice-Daily dosing, and some patients may not adhere to this regimen.
- Similar local tolerability compared with vehicle and had a safety and tolerability profile similar to that of twice-daily dapsone Gel, 5% in patients aged ≥ 12 years [32].

5. Azelaic Acid:

- Azelaic acid is a 9-dicarboxylic acid with efficacy on follicular keratinization and on P.acnes.
- It seems to have some inflammatory efficacy via effects on neutrophilic granulocytes.
- In clinical studies, a similar efficacy as tretinoin in comedonal acne has been demonstrated.
- The efficacy in opular-pustular acne in comparison to BPO is lower, but after 12–16 weeks similar results could be achieved.
- No bacterial resistance has yet been detected.
- Currently, azelaic acid is available in a 20% cream formulation. Clinical trials for a new formulation as a lotion have been performed which should be better tolerated in patients with more greasy skin.

6. Salicylic Acid:

- Salicylic acid has a mainly keratolytic effect.
- Additionally, it increases penetration of other substances, has a light anti-inflammatory effect and in low concentration is bacteriostatic and fungistatic by competitive inhibition of pantothenic acid which is important for micro-organisms.
- It can be supportive during maintenance therapy when used as a 1–3% alcohol solution [33].

1.9.2. Systematic Therapy:

Propionibacterium species are intrinsically resistant to metronidazole, tinidazole & ornidazole, aminoglycosides, sulphonamides, and mupirocin, while C.acnes is susceptible to many antimicrobials.

However, studies have reported that C.acnes has high rates of resistance to erythromycin and clindamycin [34].

1. Oral Isotretinoin:

- Oral isotretinoin continues to be the main stay of therapy for severe acne, because of its efficacy, ability to target all the four pathophysiologic factors, high rates of permanent remission and prevention of permanent scarring in acne.
- However, there remains ambiguity regarding the best dosage, including desired cumulative dose of isotretinoin.
- Higher dosages have led to less favourable safety/tolerability profiles.
- Isotretinoin should be considered early in the management of mild to moderate acne, with lower-dose isotretinoin (0.25-0.5 mg/kg/day for 24 weeks) offering a good balance between efficacy and dose-related side-effects.

2. HORMONAL THERAPY:

- Hormonal therapy is regarded as an excellent choice for women with acne who need oral contraception.
- Only few head-to-head comparative trials have been done comparing combined oral contraceptives (COC's) with other acne treatments.
- COC's work well in acne with oestrogen suppressing sebaceous gland activity and decreasing the formation of ovarian and adrenal androgens.
- Progestogen-only contraceptives tend to flare acne and should be avoided in women who have no contraindications to oestrogen-containing Preparations.
- In a recent review, the combinations of ethinyl oestradiol with cyproterone acetate, desogestrel or drospirenone have shown the strongest anti-acne activity and should be continued for a 6–12-month period [35].

3. Oral Antibiotics:

- Severe acne cases with inflammation, as well as moderate to severe acne unresponsive to topical treatments, and conditions such as acne fulminans and acne conglobate may require oral antibiotics.
- Tetracycline antibiotics like doxycycline and minocycline, along with Macrolide antibiotics such as erythromycin, roxithromycin, and azithromycin are commonly used for treating these types of acne.
- Tetracycline antibiotics are the preferred choice for treating acne due to their strong anti-inflammatory effects, which include inhibiting neutrophil chemotaxis and reducing proinflammatory cytokine Production. They also help reduce P.acnes levels.
- To prevent P.acnes resistance, it is not recommended to use oral antibiotics alone for acne treatment.
- They are often used in Combination with topical retinoids and benzoyl peroxide.
- Once improvement is seen, topical agents can be used to maintain the effect.
- Overuse of antibiotics may lead to resistant strains of bacteria that contribute to acne [36].

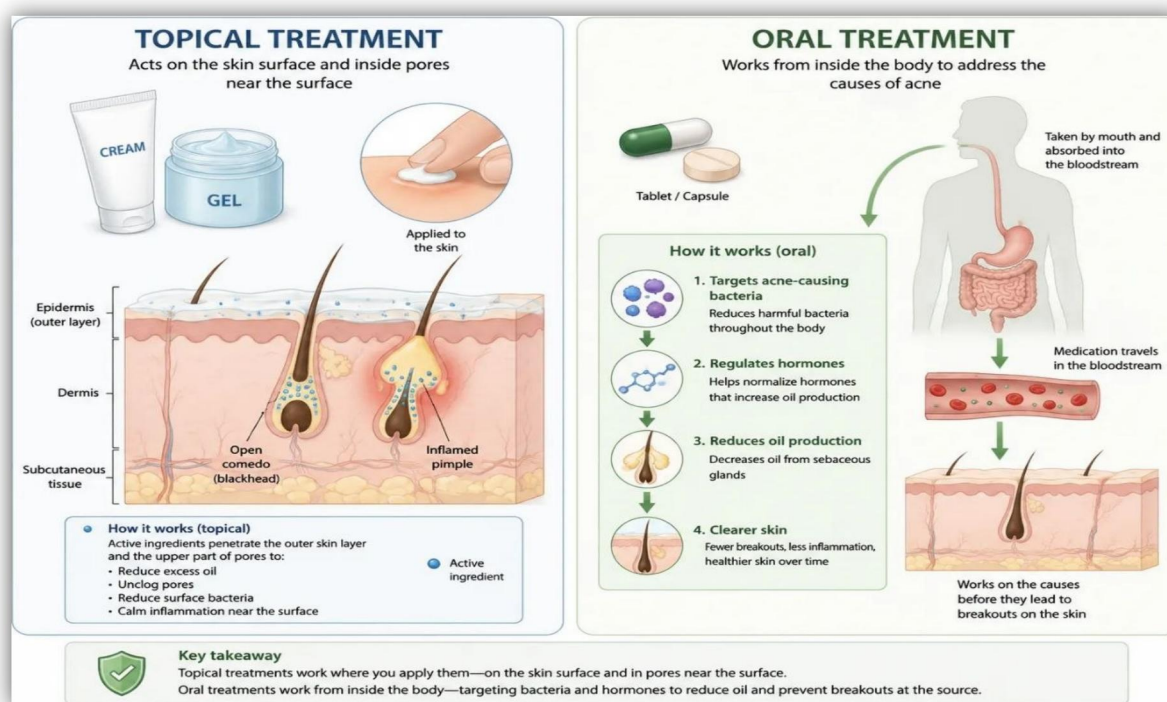


Fig 8: Illustration of Topical vs. Oral (systemic) Treatments of Acne.

1.10. Conventional vs Advanced Therapies.

1.10.1. Conventional Therapies:

Despite the wide options of topical agents, treatment failure remains a major obstacle in effective acne management. Clinical data show that 10–15% of patients fail to respond adequately to standard therapies, and most treatments, excluding isotretinoin, achieve less than 40% clearance on the Investigator's Global Assessment (IGA) scale. While isotretinoin achieves the highest success rates, its systemic toxicity limits widespread use. Poor adherence further compounds treatment outcomes, with patients either failing to initiate therapy or using it inconsistently due to side effects,

cosmetic drawbacks, or the inconvenience lipid-rich, anaerobic niche Favors C.acnes proliferation and biofilm development, further shielding bacteria from host defences [37].

There are numerous issues related to the use of the conventional drugs in treating acne, listed below:

1. Economic issue

2. Environmental issue

3. Emotional issue

4. Social issue

1. Economic issue:

- The economic issues related to the use of Conventional acne drugs for acne treatment is associated to its cost.
- As most of them are expensive, making them in-accessible for people with limited financial means.

2. Environmental issue:

- Many conventional acne medications are chemicals that can be harmful to the environment, particularly when they are washed off from the skin and enter the water supply system thereby polluting it.

3. Emotional issue:

- Acne can be a source of emotional distress and embarrassment, particularly for adolescents and young adults who are often self-conscious about their appearance.

4. Social issue:

- Many conventional acne medications have limited effectiveness.
- Instead of curing it, they cause more acne breakout.

➤ **Conventional Therapies includes:**

1. Oral contraceptives:

2. Androgen receptor blockers (cyproterone acetate, spironolactone, drospirenone, and flutamide):

3. Oral isotretinoin (a retinoid) conventional therapy for severe nodular acne:

1. Oral contraceptives:

Mechanism: Inhibit ovarian androgen production, therefore decrease sebum production.

Potential Harm: Systemic hormonal disruption, increased liver detoxification load. Not an option for men.

2. Androgen receptor blockers (cyproterone acetate, spironolactone, drospirenone, and flutamide):

Mechanism: Inhibits sebum production.

Potential Harm: Menstrual irregularities, potential hyperkalaemia, breast tenderness, fatigue, headache, fluid retention, melasma, as well as a potential association with breast cancer. {Not an option for men.}

3. Oral isotretinoin (a retinoid) conventional therapy for severe nodular acne:

Mechanism: Isotretinoin is very effective at reducing sebum secretion by at least 90% within 6 weeks. Usually prescribed for a 16-week period, after which frequently acne vulgaris does not recur. It is the only treatment that has an effect on all 4 major pathogenic factors involved in acne.

Potential Harm: A teratogen; therefore, oral contraceptives are often prescribed concurrently and regular pregnancy testing occurs throughout the treatment course [38].

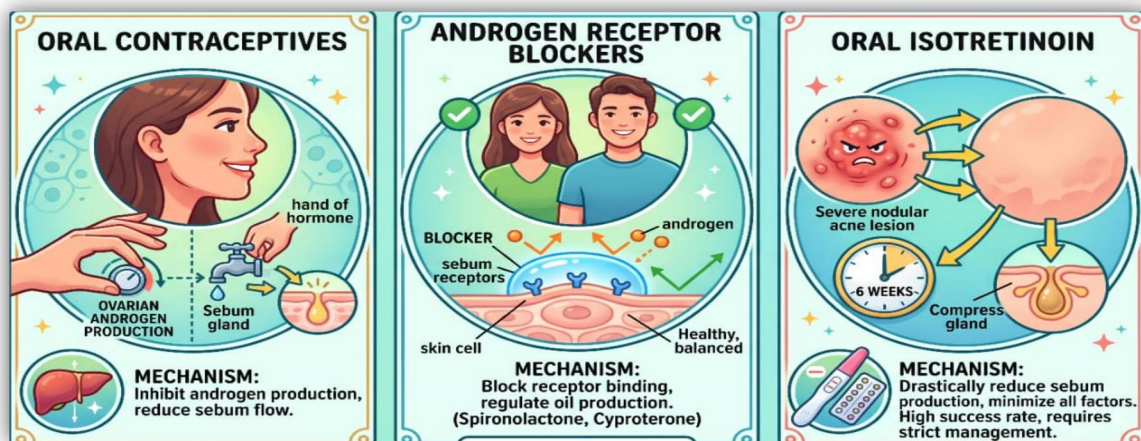


Fig 9: Different Approaches of Conventional Acne Therapies.

1.10.2. Advanced Therapies:

Advance therapy: These methods for acne treatment include various sources like broad-spectrum visible light, lasers, and photodynamic therapy.

1. Photodynamic therapy:

- **Photodynamic therapy (PDT)** is an emerging treatment for acne that involves the use of a photosensitizer in combination with a light source and oxygen [39].
- Photosensitizers are topically applied solutions that cause certain types of abnormal cells to produce light-absorbing molecules called porphyrins [40].
- **Photodynamic Therapy (PDT)** is an efficient modality for treating inflammatory acne, as it disrupts the hair follicle sebaceous gland unit and reduces the concentration of *P.acnes*.
- This therapy is particularly useful for *moderate to severe acne* cases where systemic medication has failed to produce satisfactory results or is not tolerable.
- The principle of *PDT* for acne treatment involves the application of a photosensitizer, such as topical *5-aminolevulinic acid*, to the acne lesions.
- This photosensitizer accumulates in the hair follicle sebaceous gland unit and metabolizes to produce photosensitive substances.
- This process effectively controls and improves the appearance of acne lesions by eliminating *P.acnes* and reducing sebum secretion [41].

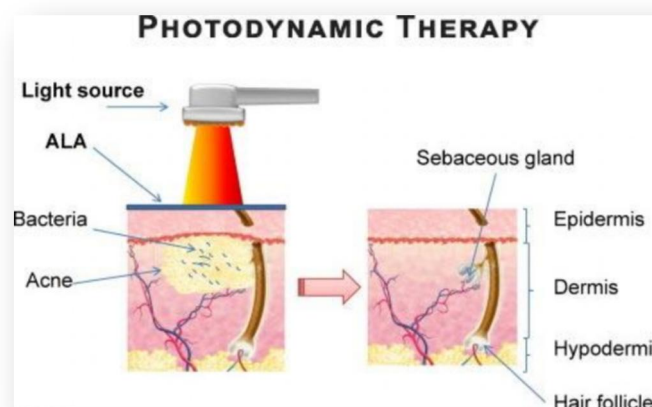


Fig 10: Photodynamic Therapy for Acne.

2. Light/Laser Exposure:

- Advanced laser and light-based treatments for acne vulgaris work mainly by targeting sebaceous glands and the bacteria *Cutibacterium.acnes* with specific wavelengths of light and laser energy.
- The use of 1726 nm lasers, such as those found in devices like Avi clear and Accure, which directly target sebaceous glands, effectively reduces

sebum production and aids in the resolution of acne lesions.

- Clinical data indicate that approximately 40% of patients with moderate to severe acne achieve clear or nearly clear skin for up to six months post-treatment, and 80–90% experience a reduction of at least 50% in inflammatory lesions [42].
- This is revolutionary because it addresses acne at its source without the systemic side effects of oral medications like isotretinoin.
- For people who cannot or prefer not to use systemic treatments, these lasers offer a game-changing alternative [43].
- These treatments target acne-causing bacteria and reduce inflammation, promoting clearer skin [44].
- laser-based therapies can be performed safely during or shortly after isotretinoin treatment, without an increased risk of adverse scarring or delayed healing [45].
- Laser light may be absorbed, reflected, transmitted, or scattered when applied to the skin. In order for a clinical effect to occur, light must be absorbed by tissue [46].

➤ **How it Helps:**

- Reduces oil production by shrinking sebaceous glands.
- Destroys *Cutibacterium.acnes* (acne-causing bacteria).
- Helps prevent future breakouts.
- Improves redness, swelling, and overall skin texture [47,48].

3. Chemical peel:

- Chemical peeling induces controlled removal of pathological epidermal and partial dermal tissues, promoting epidermal regeneration for scar repair [49].
- Chemical peels are specialized acid solutions that an esthetician or dermatologist with board certification applies to the face of acne patients.
- Common chemical peel solutions include salicylic acid, glycolic acid or retinoic acid.
- This procedure treats minor acne.
- The top layer of dull skin can be dissolved and removed over the course of two weeks if the acid solution is used properly.
- Smooth, healthy, new skin layer is revealed after the peel.
- Chemical peels have been used to treat a variety of skin disorders for many years [50].
- It might improve the appearance of the skin, though the change is not long lasting and repeat treatments are usually needed [51].

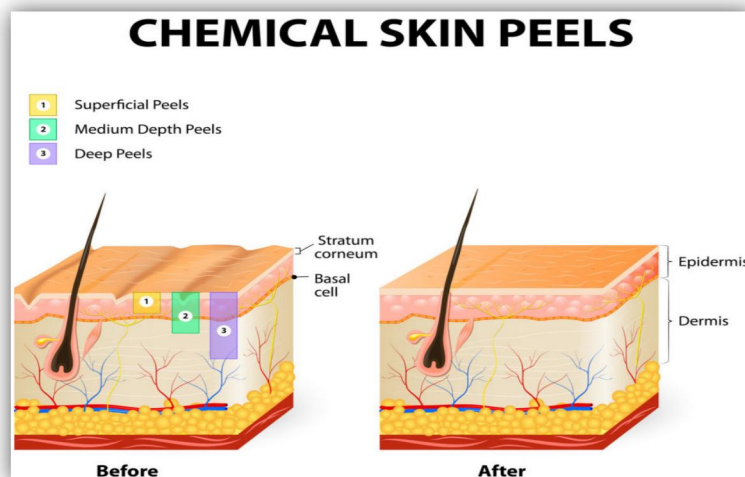


Fig 11: Representation of Chemical Peel.

4. Mechanical Peels:

- One kind of mechanical exfoliation is microdermabrasion. When treating mild to severe cases of acne vulgaris as well as acne scars, microdermabrasion is a supportive treatment. Using a stream of tiny crystals (such as aluminum oxide) and negative pressure, the mechanism of

action involves controlled, superficial exfoliation of the stratum corneum, which improves skin texture, reduces blackheads, and unblocks hair follicle outlets [52].

5. Red and blue light:

- Red light and blue light can be utilized individually or in conjunction for acne phototherapy.
- Specifically, blue light activates endogenous porphyrins to inhibit the proliferation of P.acnes, demonstrating antibacterial and anti-inflammatory properties.
- Blue light has limited dermal penetration depth. Conversely, red light irradiation alone exhibits tissue-repairing and anti-inflammatory effects with superior tissue penetration ability.
- The combination of red and blue light for acne treatment can produce synergistic effects, enhancing therapeutic outcomes and often serving as an alternative treatment for moderate inflammatory acne lesions [53].

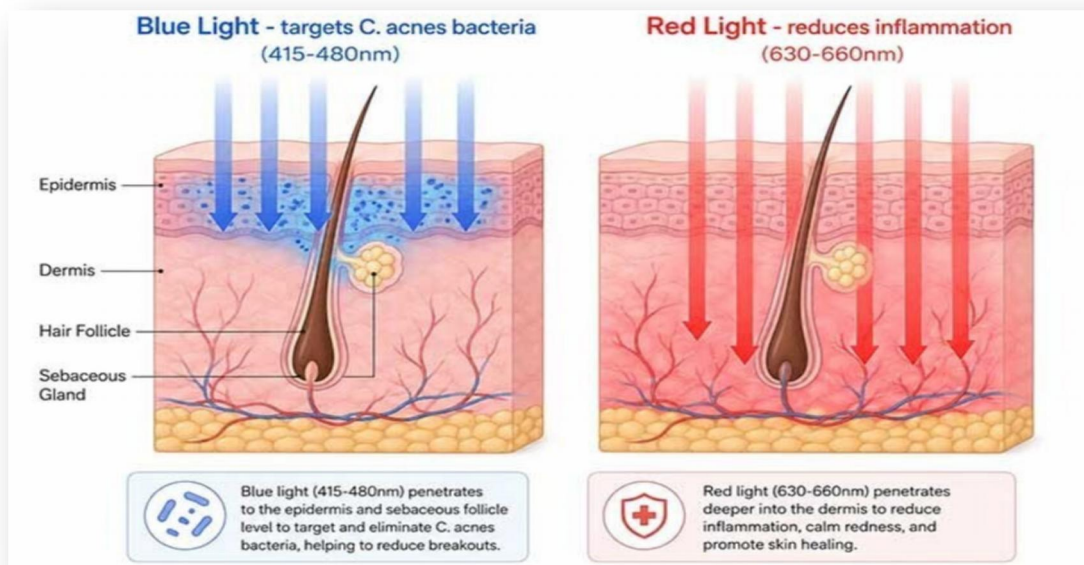


Fig 12: Representation of Red and Blue light Therapy for acne.

6. CO₂ Laser Light Therapy:

- The fractional CO₂ laser is very beneficial in treating acne scars.
- However, it can be used in the treatment of active acne lesions as it also tends to treat enlarged oil glands (especially around the nose), Sun damage, uneven skin tone, and the hyperpigmentation associated with the condition.
- Long pulse modes with low density and low fluence are preferred to prevent possible epidermal damage; multiple treatment sessions are needed to minimize complications and optimize results.
- Fractional carbon dioxide laser decreases photodamage, recent tan, and pigment at the scar base.
- Thus, decreasing the possibility of post-inflammatory hyperpigmentation [54].
- CO₂ lasers have a double effect – they encourage renewable processes of the wound and incite increased production of myofibroblasts and matrix proteins such as the hyaluronic acid [55].

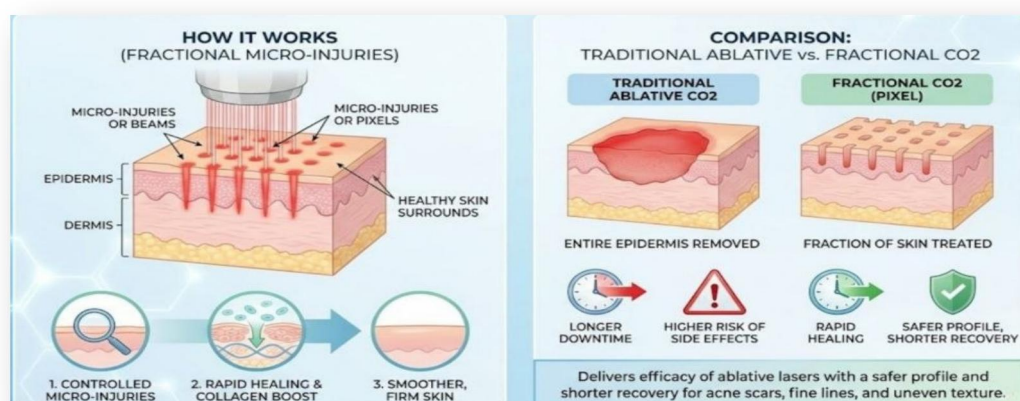


Fig 13: Representation of CO₂ Laser Light Therapy.

GENERAL FORMULATION AND EVALUATION OF POLYHERBAL TOPICAL ANTI-ACNE GEL:

1.11. General Overview:

❖ Definition and composition:

Polyherbal formulations represent medicinal products obtained from mixtures of two or more plant species according to complementarity of their therapeutic activities.

They have an historical background in traditional medical practice systems, such as in Ayurveda, in Traditional Chinese Medicine, or in Siddha medicine systems. The basic principles would be to improve efficacy; reduce toxicity; and thus, have fewer side effects. PHFs usually consist of different herbs that have different complementary pharmacological properties such as antimicrobial activity, or anti-inflammatory or wound healing properties. The forms which PHFs can be seen include powders, extracts, tablets, capsules, syrups, topical creams. Active constituents found in PHFs include bioactive compounds like alkaloids and flavonoids, saponins, tannin, and essential oils. These compounds are able to act on different physiological pathways, which provides broad-spectrum therapeutic effects, thereby making PHFs an important area of research in modern phytotherapy.

❖ Mechanisms of synergism in polyherbal formulations:

One of the foremost benefits of polyherbal formulations is the phenomenon known as synergism-it occurs when the combination results in effects that are together greater than the simple aggregation of individual effects. It might be brought about through mechanisms.

• It includes:

1. Pharmacodynamic synergy.
2. Pharmacokinetic synergy.
3. Toxicity reduction.
4. Balancing opposing effects [56].

❖ Anti-Acne Gel:

Anti-acne gels are topical semisolid formulations used for the treatment and management of acne vulgaris. These formulations help in reducing bacterial growth, inflammation, excess oil secretion and blockage of pores. Gels are widely preferred for topical application because they are non-greasy, easily washable and provide better drug release on the skin surface. Herbal anti-acne gels containing natural ingredients are considered safer and produce fewer side effects compared to synthetic formulations [57].

1.12. General Formulation:

❖ Commonly used Medicinal Plants in Polyherbal Anti-Acne Gel:

1. Neem (*Azadirachta indica*).
2. Aloe Vera (*Aloe barbadensis Miller*).
3. Turmeric (*Curcuma longa*).
4. Tea Tree Oil (*Melaleuca alternifolia*).

5. Tulsi (*Ocimum sanctum*).

1. Neem (*Azadirachta indica*):

- **Family:** Meliaceae
- **Bio. Source:** Fresh or dried leaves, bark, flowers, and fixed oil obtained from fully matured seeds of *Azadirachta indica*.

Neem being one of the widely used ayurvedic medicinal plants with strong antibacterial, antifungal, anti-inflammatory properties and also has powerful antioxidant properties.

The antimicrobial properties are present in neem leaves due to active constituents like nimbin, nimbidin, azadirachtin and quercetin which show strong antimicrobial effect against acne causing microorganisms.

Neem also works to diminish the redness, swelling, and irritation of acne lesions that are inflammatory. The antimicrobial and detoxifying effects of neem are widely used in topical skin creams [58,60].

2. Aloe Vera (*Aloe barbadensis* Miller):

- **Family:** Asphodelaceae (formerly Liliaceae)
- **Bio. Source:** Dried juice or latex and the inner leaf gel obtained from the leaves of *Aloe barbadensis* Miller.

It is common knowledge that aloe vera has anti-inflammatory, wound healing, moisturizing and soothing properties.

It comprises biologically active substances like aloin, aloe-emodin, vitamins, amino acids, enzymes and polysaccharides that are good for skin repair and hydration.

Aloe vera also has a calming effect on skin irritation and speeds up healing of acne lesions, without disturbing the moisture balance of the skin. Additionally, it helps increase patient acceptance of topical products because of its cooling effect.

3. Turmeric (*Curcuma longa*):

- **Family:** Zingiberaceae
- **Bio. source:** Dried or fresh rhizome of *Curcuma longa* Linn.

Turmeric is an important medicinal plant with curcumin as the major active ingredient.

Curcumin has anti-inflammatory, antioxidant, antimicrobial and wound healing properties. Turmeric mitigates acne inflammation and prevents the damage of skin tissues due to oxidative effect.

It has antibacterial activity against *Cutibacterium acnes*, which helps to reduce acne lesions and prevent secondary infections.

4. Tea Tree Oil (*Melaleuca alternifolia*):

- **Family:** Myrtaceae
- **Bio. Source:** Sourced from the leaves and terminal branches of the *Melaleuca alternifolia* tree.

Tea tree oil is a natural essential oil with potent antimicrobial and anti-inflammatory properties, and is commonly used in various dermatological formulations.

The main active ingredient, terpinen-4-ol, has shown to have antibacterial properties against bacteria that cause acne.

Tea tree oil also helps to combat inflammation, itching and redness caused by acne vulgaris. It is thought to be a natural alternative to topical antimicrobials.

5. Tulsi (*Ocimum sanctum*):

- **Family:** Lamiaceae
- **Bio. Source:** Fresh and dried leaves of *Ocimum sanctum* Linn.

Tulsi has antibacterial, anti-oxidant, anti-inflammatory and immunomodulatory properties. It has eugenol, ursolic acid, and flavonoids, that provides antimicrobial activity to skin pathogen.

Tulsi cleanses the skin, reduces the inflammation and prevents microbial infections involved in acne vulgaris.

These medicinal plants, when combined in a gel, yield synergistic therapeutic effects for effective management of acne. Compared to the conventional synthetic preparations, the polyherbal gel has several advantages like increased safety, decreased side effects, increased patient compliance and better therapeutic efficacy [59,60].



Fig 14: Commonly Used Medicinal Plants in Polyherbal Anti-Acne Gel.

Table 1-General Composition of Polyherbal Anti-Acne Gel.

Sr. No.	Ingredients	Quantity(%w/w)	Category
1.	Neem extract	2%	Antimicrobial agent
2.	Aloe vera gel	5%	Moisturizer and soothing agent
3.	Turmeric extract	1%	Anti-inflammatory agent
4.	Tulsi extract	2%	Antioxidant and antimicrobial agent
5.	Tea tree oil	0.5%	Antibacterial agent
6.	Carbopol 940	1%	Gelling agent
7.	Propylene glycol	5%	Humectant
8.	Methyl paraben	0.2%	Preservative
9.	Triethanolamine	q.s.	pH adjuster
10.	Distilled water	q.s. to 100g	Vehicle

1.12.1. General Formulation Techniques for Polyherbal Gels:

There are several methods for preparing polyherbal gel, and the specific method used will depend on the intended use, the properties of the herbs, and the desired texture and consistency of the gel.

Some common methods for preparing polyherbal gel include:

1. **Hot infusion method:** In this method, the herbs are steeped in hot water or oil to extract their active compounds. The resulting infusion is then mixed with a base material such as glycerine or aloe vera gel to create the gel.
2. **Cold infusion method:** This method is similar to the hot infusion method, but the herbs are steeped in cold water or oil instead. This method is often used for more delicate herbs that may be damaged by heat.
3. **Decoction method:** This involves simmering the herbs in water to extract their active compounds. The resulting liquid is then strained and mixed with a base material to create the gel.
4. **Emulsification method:** In this method, the herbal extracts are mixed with a base material and an emulsifying agent to create a stable emulsion. This method is often used for polyherbal gels that contain oils or other ingredients that are not water-soluble.
5. **Micronization method:** In this method, the herbs are ground into a fine powder, and the powder is then mixed with a base material to create the gel. This method is often used for herbs that are difficult to extract using traditional methods.
6. **Alcohol extraction method:** In this method, the herbs are soaked in alcohol to extract their active compounds. The resulting extract is then concentrated and mixed with a base material to create the gel [61].

1.13. General Evaluation of Polyherbal Topical Anti-Acne Gel:

- **It involves:**

1. **Appearance and consistency:** The physical appearance was visually checked for the appearance and consistency of Polyherbal gel formulations and observations were stated in terms of colour, clogging, homogeneity and texture.
2. **Washability:** Formulations were applied on the skin and then ease and extent of washing with water were checked manually and observations may be like stated.
3. **Extrudability determination of formulations:** The polyherbal gel formulations were filled into collapsible metal tubes or aluminium collapsible tubes. The tubes were pressed to extrude the material and the extrudability of the formulation was checked.
4. **Determination of Spreadability:** A special apparatus has been designed to study the spreadability of the formulations. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from formulation, placed between, under the application of a certain load. Lesser the time taken for the separation of two slides, better the spreadability.

- **It is calculated by using the following formula:**

$$S = M \cdot L / T$$

Where, S = Spread-ability.

M = Weight tide to upper slide.

L = Length moved on the glass slide.

T = Time taken to separate the slide completely from each other.

5. **Viscosity:** Viscosity is a measure of a fluid's resistance to flow. For a gel, viscosity tells us how thick or stiff the gel is, and how easily it can spread, pour, or be squeezed. In order to determine the viscosity of a gel, Brookfield Viscometer (Rotational Viscometer) was employed. The resistance to rotation reflected the gel's viscosity. Viscosity was record for all the formulations in *centipoise, cP*.
6. **Determination of pH:** The pH of the anti-acne gels was determined by digital pH meter. One gram of gel was dissolved in 25 ml of distilled water and the electrode was then dipped in to gel formulation until constant reading obtained and constant reading was noted. The measurements of pH of each formulation were replicated two times.
7. **Drug content:** The drug content was determined by taking 1gm of gel in 10 ml volumetric flask diluted with methanol. 2 ml of stock solution was mixed with 1 ml of Folin- Ciocalteu reagent (previously diluted with distilled water 1:10 v/v) and 1 ml (7.5g/l) of sodium carbonate. The mixture was vortexed for 15s and allowed to stand for 15min for colour development. The absorbance was measured at 765 nm using a

spectrophotometer.

8. **Antimicrobial studies:** The well diffusion method was used to determine the antibacterial activity of the polyherbal gel prepared from fruits of *Terminalia chebula* and *Phyllanthus emblica* using standard procedure. Three concentration- 25, 50 and 100mg/ml, were used for antimicrobial studies. The plates were incubated at 37°C for 24 hr. and then examined for clear zones of inhibition around the wells with particular concentration of drug.
9. **Stability Study:** The stability study was performed as per ICH guidelines. The formulated gel was filled in the collapsible tubes and stored at different temperatures and humidity conditions, viz. 25 °C ± 2 °C/ 60% ± 5% RH, 30 °C ± 2 °C/65% ± 5% RH, 40 °C ± 2 °C/ 75% ± 5% RH for a period of six months and studied for appearance, pH, viscosity and spreadability [62].
10. **In-vitro diffusion studies:** The in-vitro diffusion studies for all formulations (Fa1-Fa4) were carried out using the Franz-diffusion cell. The diffusion cell apparatus was fabricated locally as an open- ended cylindrical tube with an area of 3.7994 cm² and 100m height, having a diffusion area of 3.8cm². A weighed quantity of formulation equivalent to 1gm of the drug was placed onto the dialysis membrane-70 (Hi-Media) and was immersed slightly in 100ml of receptor medium (phosphate buffer pH 6.8 + ethanol in ratio 40:60) which was continuously stirred and the temperature was maintained at 37°C±1°C. Aliquots of 1ml were withdrawn from each of the system at time intervals of 5, 10, 15, 30, 60, 120, 240 and 360 min were analyzed for drug content using UV spectrophotometer.
11. **Drug release kinetics:** To study the release kinetics of the optimized formulation, the data obtained from invitro release studies were plotted in various kinetic models [63].
12. **Grittiness:** All the formulations were evaluated microscopically for the presence of any appreciable particulate matter which was seen under light microscope. Hence, obviously the gel preparation fulfils the requirement of freedom from particulate matter and from grittiness as desired for any topical preparation.
13. **Homogeneity:** After the gels have been set in the container, all developed gels were tested for homogeneity by visual inspection. They were tested for their appearance and presence of any aggregates.
14. **Skin irritation study:** Guinea pigs (400-500 g) of either sex were used for testing of skin irritation. The animals were maintained on standard animal feed and had free access to water. The animals were kept under standard conditions. Hair was shaved from back of guinea pigs and area of 4cm² was mark done both the sides; one side served as control while the other side was test. Gel was applied (500 mg / guinea pig) twice a day for 7 days and the site was observed for any sensitivity and the reaction if any, was graded as 0, 1, 2, 3 for no reaction, slight patchy erythema, slight but confluent or moderate but patchy erythema and severe erythema with or without oedema, respectively [64].

CONCLUSION:

Acne vulgaris remains a multifaceted and stubborn dermatological condition that significantly impacts physical appearance and psychosocial well-being of the affected individuals. The pathogenesis—driven by sebum overproduction, abnormal keratinization, bacterial proliferation, and inflammation—demands therapeutic interventions that can address multiple pathological pathways simultaneously. Although conventional synthetic agents and systemic antimicrobial regimens demonstrate clinical efficacy, their associated toxicities, localized skin reactions, and the growing concern of bacterial resistance necessitate the development of safer drug with synergistic approach.

Polyherbal topical gels represent a scientifically sound approach to modern acne therapy. The incorporation of bio-active herbal extracts into semi-solid gel networks allows for enhanced localized skin retention, improved spread-ability, optimal hydration, and minimal systemic exposure. Through synergistic phytotherapy, polyherbal systems combine anti-inflammatory, antimicrobial, antioxidant, and anti-seborrheic properties within a single matrix.

In conclusion, the careful selection of natural actives, combined with precise formulation parameters and rigorous quality control evaluation including pH, viscosity, spread-ability, drug content uniformity, and stability assessment is essential for transforming traditional herbal remedies into standardized, commercially viable pharmaceutical gels.

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