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Research Paper

Advances in Herbal Anti-Acne Delivery Systems: Role of Marigold and Neem in Polyherbal Patch Technology

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ABSTRACT

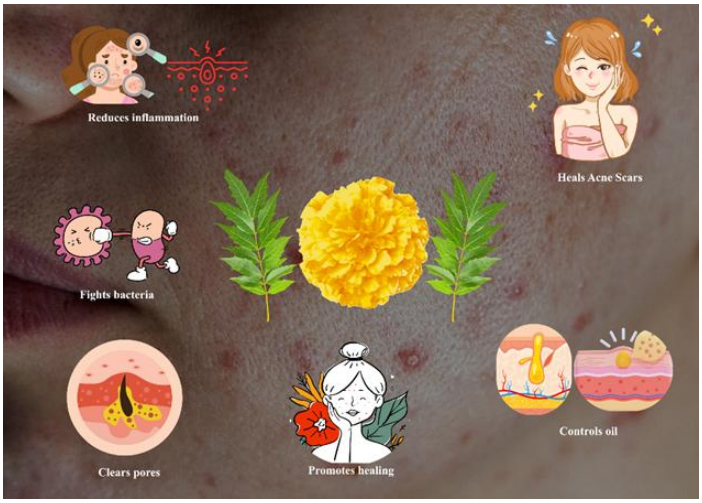
Acne vulgaris is a prevalent dermatological disorder characterized by excessive sebum production, follicular hyperkeratinization, bacterial colonization, and inflammation. While conventional therapies such as antibiotics, retinoids, and chemical peels offer clinical benefits, they are often associated with side effects, irritation, microbial resistance, and reduced patient compliance. This has led to growing interest in herbal remedies, which provide a gentler and holistic approach to skin health. Among these, neem (Azadirachta indica) and marigold (Calendula officinalis) have shown significant potential due to their complementary pharmacological activities. Neem exhibits antimicrobial and sebum-regulating properties, reducing bacterial load and controlling oiliness, whereas marigold offers anti-inflammatory, antioxidant, and regenerative benefits, promoting healing of damaged skin. Polyherbal patch technology emerges as an innovative strategy to deliver these botanicals directly to affected areas in a controlled and sustained manner, enhancing therapeutic efficacy while minimizing systemic exposure and improving patient compliance. Modern formulation approaches, including solvent casting, biocompatible polymers, and nanocarrier integration, have enabled the development of stable, effective, and safe herbal patches. Preclinical and limited clinical studies support their anti-acne potential and skin tolerability. Despite these promising outcomes, challenges such as batch-to-batch variability, skin permeability barriers, stability concerns, and regulatory considerations must be addressed. Future research focusing on smart patches, nanotechnology, eco-friendly polymers, and rigorous clinical evaluation could pave the way for translating these polyherbal systems into practical, patient-friendly therapies. In conclusion, neem–marigold polyherbal patches represent a convergence of traditional herbal wisdom and modern drug delivery science, offering a safe, multi-targeted, and sustainable approach to acne management

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INTRODUCTION

Acne vulgaris is one of the most common dermatological conditions worldwide, affecting millions of individuals, particularly adolescents and young adults. Beyond its physical manifestations—such as comedones, papules, pustules, and scarring—acne can significantly impact a person's emotional well-being, self-esteem, and overall quality of life[1]. Despite its prevalence, effective management remains a challenge, as conventional anti-acne therapies, including topical retinoids, antibiotics, and systemic agents, often come with undesirable side effects such as skin irritation, dryness, or, in some cases, antibiotic resistance. This has led to a growing interest in herbal remedies, which are perceived to be gentler, safer, and capable of targeting multiple aspects of acne pathophysiology. Among these, Neem (*Azadirachta indica*) and marigold (*Calendula officinalis*) have stood out due to their traditional use in skin care and a wealth of bioactive compounds[2].



Neem is rich in azadirachtin, nimbidin, and nimbolide, known for their antibacterial, anti-inflammatory, and sebum-regulating properties. Marigold, on the other hand, contains flavonoids, triterpenoids, and essential oils that promote wound healing, reduce inflammation, and protect the skin from oxidative stress[3]. Combining these herbs in a polyherbal system offers a synergistic approach, where multiple bioactive compounds work together to target acne from different angles—controlling bacterial growth, reducing inflammation, and supporting skin regeneration—while potentially minimizing side effects. This review aims to provide a comprehensive overview of advances in herbal anti-acne delivery systems, with a special focus on the role of neem and marigold in polyherbal patch technology. It explores the scientific evidence supporting their efficacy, the formulation strategies employed, and the potential of patch-based delivery systems to improve therapeutic outcomes and patient compliance[4].

Pathogenesis of Acne Vulgaris.

Acne vulgaris is a common yet complex skin disorder that arises from the intricate interplay of multiple physiological processes within the pilosebaceous units. At the forefront of acne development is **excessive sebum production**. Sebum, the natural oily secretion of sebaceous glands, provides a nutrient-rich environment that facilitates pore blockage and microbial proliferation, creating the ideal conditions for acne formation. Another critical factor is hyperkeratinization of the pilosebaceous follicles. Under normal conditions, skin cells are shed in a

regulated manner[6]. However, in acne-prone skin, this process becomes disrupted, leading to the accumulation of dead cells that mix with sebum to form microcomedones. These microcomedones can evolve into visible blackheads or whiteheads, further contributing to the disease's progression. The role of microbial colonization, particularly by *Cutibacterium acnes* (formerly *Propionibacterium acnes*), is central in acne pathogenesis. These bacteria thrive in the sebum-rich follicles and release pro-inflammatory substances, which activate the immune system and trigger an inflammatory cascade[7]. This inflammation manifests clinically as papules, pustules, and, in severe cases, nodules or cysts, all of which are hallmark features of acne. Beyond these primary mechanisms, acne development is influenced by a variety of other factors, including genetic predisposition, hormonal fluctuations (especially androgens), environmental triggers, dietary habits, and psychological stress. The combination of these elements makes acne a multifactorial condition, necessitating treatments that can address multiple pathogenic pathways simultaneously[8]. Understanding these underlying mechanisms is critical for designing effective and targeted therapies, whether conventional or herbal. Herbal interventions, such as those involving neem and marigold, hold promise because they can simultaneously address sebum overproduction, microbial colonization, and inflammation, offering a holistic approach to acne management[9].

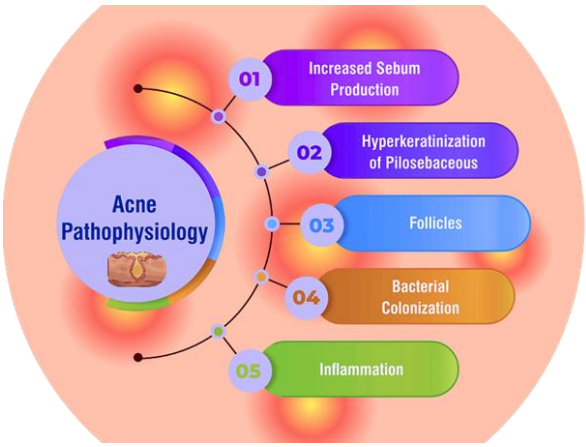


Figure 1 illustrates the complex pathophysiology of acne vulgaris.

Development of Acne

The development of acne is a dynamic process that involves a series of interconnected events within the pilosebaceous units of the skin. It typically begins with **overactive sebaceous glands**, which produce an excess of sebum. While sebum naturally protects and moisturizes the skin, an overabundance creates a lipid-rich environment that favors the accumulation of dead skin cells and the growth of acne-causing bacteria[9].

Simultaneously, follicular hyperkeratinization occurs. Normally, skin cells within the hair follicle are shed gradually, but in acne-prone skin, this process is disrupted. The resulting build-up of keratinocytes combines with excess sebum to form microcomedones, the earliest, often invisible, lesions of acne. Over time, these microcomedones can enlarge and become visible as open comedones (blackheads) or closed comedones (whiteheads)[10]. The colonization of follicles by *Cutibacterium acnes* further drives acne progression. This bacterium metabolizes sebum and releases inflammatory mediators, attracting immune cells and triggering an inflammatory response. As a result, the skin may develop

papules, pustules, nodules, or cysts, depending on the severity of inflammation and follicular damage[11]. Several modulating factors influence acne development. Hormonal fluctuations, particularly during puberty or menstrual cycles, can increase sebum production. Genetic predisposition, stress, dietary habits, and environmental factors can also exacerbate lesion formation and inflammation[12].

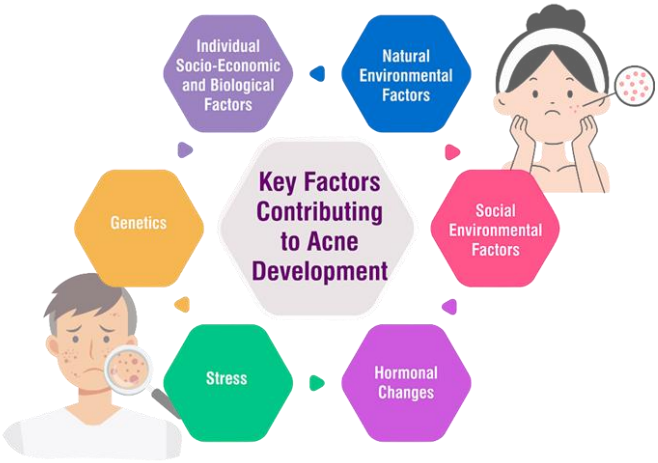


Figure 2 illustrates the complex Development of acne vulgaris.

Herbal Anti-Acne Agents

Herbal remedies continue to gain scientific attention in acne management, especially because many botanicals can act on multiple acne-related pathways (bacteria, inflammation, sebum). Two stars in this space are **neem (*Azadirachta indica*)** and **marigold (*Calendula officinalis*)**, both of which have seen promising recent research.

***Neem* (Azadirachta indica)**

Neem's traditional skin-healing credentials are being reinforced by modern studies. For instance, a network pharmacology and molecular docking study (2023) identified that key compounds in neem oil show strong binding affinity to several molecular targets involved in acne, such as STAT1, CSK, CRABP2, and SYK, suggesting anti-inflammatory and antibacterial effects[13]. Also, in vitro work has confirmed that neem leaf powder incorporated into a herbal hydrogel strongly inhibits *Staphylococcus aureus* (a bacterium associated with skin infections) using agar well diffusion assays — showing neem's direct antimicrobial potential. Another recent formulation study (2024) developed a turmeric + neem nanoemulgel, which demonstrated good antimicrobial activity, promising for treating microbe-associated skin issues[14]. These modern investigations reaffirm neem's broad-spectrum capabilities: not just killing bacteria but also modulating inflammation and facilitating deeper skin penetration in advanced formulations.

Marigold (Calendula officinalis)

While neem often gets the spotlight, marigold's gentle but powerful skin effects are backed by growing evidence too. A notable in vitro study (2023) used a simple herbal formulation made from marigold (Calendula) tea and showed strong anti-inflammatory activity (via protein denaturation and anti-protease assays) and antioxidant capacity (DPPH assay) even at low concentrations[15]. On a molecular level, more recent work (2025) has identified C16-hydroxylated triterpenoids in *C. officinalis* flowers as the key anti-inflammatory compounds — these molecules appear to suppress interleukin-6 (IL-6), a cytokine often elevated in acne-related inflammation[16]. There is also a pharmaceutics

study (2022/23) where an anti-acne topical gel containing marigold extracts was formulated and evaluated, showing potential as a gentle alternative to synthetic acne gels[17]. Additionally, a broader phytochemical profiling review (2022) catalogued hundreds of metabolites in *Calendula officinalis* (flavonoids, triterpenoids, phenols) that could underlie its skin-beneficial and anti-inflammatory effects[18].

Polyherbal Synergy & Patch-Relevance

Importantly, neem and marigold are being studied together in advanced delivery systems. A recent (2024) formulation study developed a polyherbal anti-acne patch using ethanol extracts of neem leaves (*A. indica*) and marigold (Tagetes / Calendula species). They tested it against *P. acnes* and *S. aureus* and found significant inhibition, showing good compatibility, release properties, and stability of the patch[19]. This synergy is promising because neem is tackling more of the *microbial and sebaceous* side of acne, while marigold is providing anti-inflammatory and antioxidant support, which can together reduce lesion severity and promote healing.

Transdermal and Topical Delivery Systems

Conventional Topical Formulations

When it comes to treating acne, the most familiar forms are **creams, gels, and ointments**. These have been the go-to for decades because they are relatively easy to formulate and apply. However, they come with important limitations:

- **Stability**: Many active herbal ingredients degrade over time, particularly in water-based gels or creams, reducing their effectiveness.
- **Skin penetration**: Getting actives through the tough outer layer of the skin (stratum corneum) is difficult. In many cases, only a fraction of the active ingredient actually penetrates to the deeper layers where it's needed.
- **Patient compliance**: Frequent reapplication, greasy residue, or stickiness can make users drop off. Ointments, especially, feel heavy; gels might dry out too quickly; creams may irritate sensitive skin.

These constraints motivate the search for more advanced delivery systems that can overcome these drawbacks[20].

Novel Drug Delivery Approaches

To address the shortcomings of conventional topicals, researchers have turned to innovative delivery systems such as:

- **Patches / Films**: These are adhesive or flexible matrices that stick to the skin and release active compounds over time.
- **Hydrogels**: Water-rich networks that can hold herbal actives, maintain moisture, and mimic skin-like environments.
- **Nanocarriers**: These include nanoparticles, liposomes, ethosomes, invasomes, and other vesicles that can encapsulate plant extracts and improve their skin permeation[21].

Advantages of these systems include:

- **Controlled release**: They can release actives slowly or in a sustained fashion, reducing dosing frequency.
- **Targeted delivery**: By controlling where and when the drug is released, they can deliver actives closer to the acne lesion.
- **Improved bioavailability**: Nanocarriers, for instance, can enhance penetration, protect fragile herbal molecules from degradation, and increase their effectiveness[22].

Recent scientific reviews have highlighted the increasing use of **nanotechnology in transdermal herbal delivery**, as it allows potent plant-derived actives to cross the skin barrier more

effectively[23]. One such example is a **herbal extract-loaded hydrogel** developed for acne: it combined green tea, ginger, *Phyllanthus emblica*, and salicylic acid into a gelatin/CMC matrix. This gel demonstrated strong anti-inflammatory activity, good mechanical properties, and in vivo efficacy. In a small study, more than half of the participants showed at least a 50% improvement in moderate-to-severe acne after 14 days[24]. Additionally, a 2023–2024 review of novel herbal drug delivery systems emphasized how plant-based actives are being reformulated into modern platforms to improve stability and performance[25].

Polyherbal Patch Technology

Polyherbal patch technology is particularly exciting. The idea is to combine multiple herbal extracts into a single adhesive patch that delivers actives in a controlled way. Rather than relying on one plant, you leverage **synergy** — where different botanical compounds work together to address various factors of acne (bacteria, inflammation, oil production)[26].

Materials

Designing such a patch requires careful selection of:

- **Polymers** (for the patch base): Common ones include hydroxypropyl methylcellulose (HPMC), ethyl cellulose, or other biocompatible polymers that form the backbone.
- **Adhesives**: To make sure the patch sticks to the skin without irritating it.
- **Release modifiers / plasticizers**: These adjust how quickly the actives are released and how flexible the patch is — e.g., glycerol, propylene glycol.

Mechanism of Drug Release and Skin Permeation

Once applied, the patch hydrates slightly (through contact with skin moisture), which causes the polymer matrix to swell. This swelling helps control the **diffusion** of herbal actives from the patch into the skin. Depending on formulation, you can design a patch for *sustained release* (slow, continuous) or *burst + sustained* (an initial fast release followed by slower diffusion). The actives then penetrate into skin layers, aided by permeation enhancers (if used) or the inherent diffusivity of the matrix. A very recent (2024) study developed a polyherbal anti-acne patch using ethanol extracts of neem (Azadirachta indica) and marigold (Tagetes erecta)[27]**.** They characterized the patches for moisture content**,** pH**,** thickness**,** folding endurance, and swelling**.** In microbiological tests (agar diffusion + broth microdilution), the patches showed significant inhibition of *Propionibacterium acnes* (now *Cutibacterium acnes*) and *Staphylococcus aureus[27]*. patches combine neem's antibacterial power with marigold's antioxidant and anti-inflammatory benefits, potentially offering a more balanced, gentler, and effective treatment. This study strongly supports the feasibility of using polyherbal patches for acne not just as a cosmetic convenience, but as a scientifically valid, multi-target therapeutic system.

Mechanism of Action in the Polyherbal Patch

In a polyherbal patch combining **neem** (*Azadirachta indica*) and **marigold** (*Calendula officinalis / Tagetes* species), the two botanicals act in a beautifully30 complementary way — each contributing its strengths, and together addressing key drivers of acne. Here's a detailed breakdown of how this synergy works, especially when delivered via a patch:

1. Reduction of Bacterial Load

- **Neem's Antimicrobial Action**: Neem is rich in compounds like azadirachtin, nimbidin, and other triterpenoids, which are well-known for their strong antimicrobial activity. In the patch formulation developed in a 2022 study, ethanol extracts of neem leaves showed significant inhibition of *Propionibacterium acnes* (now *Cutibacterium acnes*) and *Staphylococcus aureus* in both agar diffusion and broth microdilution assays. The patch format helps by maintaining close contact with the skin, allowing these compounds to gradually diffuse into the follicular environment where acne-causing bacteria persist[28].

2. Inflammation Modulation

- **Marigold's Anti-inflammatory Power**: Marigold flower extracts contain flavonoids, triterpenoids, and carotenoids, which are known to reduce inflammation. In the same 2024 patch study, marigold's bioactivity was leveraged to provide antioxidant and anti-inflammatory benefits[29].
- **Neem's Immune Modulation**: Beyond killing bacteria, neem's active compounds can also modulate immune signaling. Recent reviews suggest that neem triterpenoids may suppress pro-inflammatory pathways (e.g., NF-κB), thereby reducing cytokines like IL-6 and TNF-α, which are central to acne inflammation[30]. Together in a patch, these anti-inflammatory mechanisms lower inflammation in localized acne lesions, reducing redness, swelling, and the discomfort associated with breakouts.

3. Sebum Regulation

While the 2024 patch study primarily focused on antimicrobial and antioxidant activities, the traditional uses and phytochemistry of neem suggest that it can help regulate sebum production. The astringent properties of certain neem constituents help tighten pores and reduce excess oil, which is a major factor in acne formation. By reducing sebum locally through sustained diffusion from the patch, neem may help prevent the "oiliness + pore blockage" cycle that feeds acne[31].

4. Wound Healing & Skin Regeneration

Marigold's Regenerative Role: Calendula is renowned for its ability to promote wound healing. Its triterpenoids and flavonoids aid in re-epithelialization and help repair the skin barrier. Indeed, a very recent (2025) polyherbal gel study demonstrated that a formulation containing Azadirachta indica + Calendula officinalis +Turmeric + Aloe vera significantly enhanced wound healing and skin repair. Synergistic Tissue Repair: Neem too plays a role in regeneration, its antioxidant compounds reduce oxidative stress in skin, while its antimicrobial effect prevents infection, creating a favorable environment for healing[31].

5. Synergy in Patch Format

The patch ensures that both neem and marigold act right where they are needed. Instead of the actives washing off or being spread over a large area, they release slowly at the site of the acne. Because the actives are focused on one site, systemic absorption is minimal, which may reduce the risk of irritation or unwanted systemic effects. The patch matrix (typically made of a polymer such as HPMC) swells upon contact with skin moisture. This swelling modulates how quickly the actives diffuse out: the patch is designed so that neem's antibacterial compounds and marigold's anti-inflammatory molecules are released in a controlled manner. Neem fights microbes,

controls oil, and soothes; marigold calms inflammation, scavenges free radicals, and helps repair skin. This combination addresses not just the cause of acne but also the damage that acne leaves behind[19].

Formulation and Evaluation of Herbal Patches

Creating a successful herbal patch—especially a polyherbal one using neem and marigold—requires thoughtful design, precise formulation, and rigorous evaluation. Here's how this typically works, and how you might approach it in your review.

Selection of Polymers and Excipients

When developing an herbal anti-acne patch, the choice of materials is just as important as the active ingredients themselves. The polymer base forms the backbone of the patch and determines its strength, flexibility, and release behavior. Polymers such as hydroxypropyl methylcellulose (HPMC) and ethyl cellulose (EC) are commonly used because they produce films that are stable, flexible, and gentle on the skin. In one polyherbal anti-inflammatory patch study, researchers successfully combined HPMC with cassava starch to create a smooth and durable film matrix[31]. To prevent brittleness and ensure comfortable skin adhesion, plasticizers like PEG 400, glycerol, or dibutyl phthalate are added. These ingredients also help control how quickly the herbal compounds are released from the patch, allowing for either faster or more sustained diffusion. Permeation enhancers are another important component[32]. They help herbal molecules pass through the outer layer of the skin so they can reach deeper areas where acne develops. Natural oils are often chosen for herbal formulations. For example, a recent neem-based patch formulation used niaouli oil as a permeation enhancer and achieved noticeably better penetration of antimicrobial compounds. Finally, because a patch must remain on the skin for several hours, it requires a skin-friendly adhesive and an appropriate backing layer. These ensure that the patch stays in place without causing irritation, while also preventing the active ingredients from evaporating or diffusing away from the skin[32].

Preparation Techniques

Several common methods can be used to manufacture herbal patches. Depending on your formulation goals and scale, you might choose one of the following:

1. **Solvent Casting**:

This is perhaps the most widely used technique. Here, you dissolve the polymer(s), plasticizer, and herbal extract in a suitable solvent (e.g., a mixture of ethanol, water, or other solvents), cast the solution into a mold or petri dish, and allow the solvent to evaporate slowly. This method was used effectively in many herbal patch studies, and is well-suited for delicate plant extracts[33].

Hot-Melt Extrusion :

Useful when dealing with polymers that melt without degrading the herbal actives. The mixture is heated, extruded, and then cooled to form a film or patch. While less common for heat-sensitive herbal extracts, it offers advantages in scalability and solvent-free production[34].

2. **Electrospinning**:

Advanced technique, especially for nano- or micro-fibrous patches. It allows the creation of very fine fibers with high surface area, potentially improving the release profile and skin contact. May not always be practical for all types of herbal extracts, but could be a direction for future research[35].

Characterization of the Patch

Once the patch is made, you need to evaluate a variety of properties to ensure it is physically robust, chemically stable, and functionally effective.

Physical Characterization

- **Thickness**: Measured at several points using a micrometer or screw gauge to ensure uniformity.
- **Tensile Strength**: To check how strong the patch film is, how much force it can withstand before breaking.
- **Folding Endurance**: How many times the patch can be folded at the same point before it cracks or breaks. This indicates flexibility and durability. Many studies use folding endurance as a key test[36].
- **Moisture Content and Uptake**: Determines how much water the patch absorbs (which can affect stability) and how much moisture it loses. Good patches should balance moisture so that they don't become brittle or overly soft[37].

Chemical Characterization

- **Drug Content / Active Content**: Measure how much of the herbal actives (neem / marigold extracts) are present uniformly across the patch. This can be done by dissolving a portion of the patch in a suitable solvent and measuring by UV-Vis, HPLC, or other suitable assays[38].
- **Stability Studies**: Accelerated stability testing over time (temperature, humidity) to make sure actives don't degrade, patch doesn't lose adhesion, and physical properties remain consistent. For example, in a natural-polymer patch study, a batch was checked for drug content and folding endurance over 3 months[39].
- **Compatibility / Interactions**: Techniques like FTIR (Fourier-transform infrared spectroscopy) or DSC (Differential Scanning Calorimetry) are used to make sure there are no adverse interactions between extracts and polymers. A curcumin-film optimization study did exactly this to confirm compatibility[40].

In Vitro Release Studies

- **Franz Diffusion Cell**: This is the classic method. The patch is placed on a membrane (synthetic or biological), and the release of the actives into a receptor fluid is measured over time. Many herbal patch studies use this to profile how quickly and how much of the herbal extract is released[41].
- **Release Kinetics**: Analyze how the active diffuses (zero-order, first-order, Higuchi, etc.) to understand the mechanism of release and predict in-use behavior. For example, in formulation studies, one optimized patch displayed zero-order kinetics and non-Fickian diffusion, indicating a sustained and controlled release[42].

Biological / Functional Evaluation

Because the goal is anti-acne (or anti-inflammatory) effect, it's important to test antimicrobial and anti-inflammatory activity in vitro (and potentially in vivo):

Antimicrobial Testing: Patch samples (or the extracted actives) are tested against acne-relevant bacteria (e.g., *Cutibacterium acnes*, *S. aureus*) using agar diffusion or broth dilution methods to check inhibition. In a polyherbal patch research (though not exactly neem + marigold), antimicrobial zones and MIC (minimum inhibitory concentration) tests were carried out[43].

Anti-inflammatory Activity:

Use in vitro cell-based assays (e.g., measuring cytokine release) or simpler chemical assays (e.g., protein denaturation, albumin denaturation) to check if the patch extract reduces inflammation. In the Dashmool transdermal patch study, the anti-inflammatory potential was assessed by **albumin denaturation inhibition**, a common biochemical test[44].

- **Skin Irritation / Permeation Studies** (optional but valuable):

Ex vivo skin permeation (using animal or human skin) to assess how well the actives penetrate. Skin irritation tests to ensure that the patch is safe for regular use.

Clinical Evidence and Safety

Neem (Azadirachta indica):

- A **clinical study** in healthy adults tested the *Purifying Neem Face Wash* (which contains neem + turmeric) over four weeks in people with mild-to-moderate acne or oily skin. The results showed a significant reduction in both inflammatory and non-inflammatory acne lesions**,** along with reduced sebum levels and good skin hydration. Importantly, no side effects or skin irritation were reported[45]. In preclinical models, a nanoemulsion-based gel containing neem extract and vitamin E showed strong anti-acne and anti-inflammatory effects in Wistar rats, and no erythema or edema was observed in skin irritation tests[45]. Another study formulated a gel by incorporating neem microspheres into a topical system. When tested in rats, it demonstrated antibacterial activity and good skin compatibility in irritation studies[46]. A more mechanistic study used network pharmacology and molecular docking to explore neem oil's action in acne; it identified several molecular targets (e.g., STAT1, SYK) that could explain neem's anti-inflammatory and antimicrobial potential[47].

Marigold (Calendula officinalis):

Safety data from a **safety-assessment panel** (Cosmetic Ingredient Review) indicate that extracts from *C. officinalis* (flower extract, oil) are *not significantly irritating or sensitizing* in clinical or animal tests[48]. In a **controlled irritation study**, healthy volunteers who applied a cream containing marigold extract were protected against experimentally induced skin irritation (using sodium lauryl sulfate). The marigold cream significantly reduced signs of inflammation compared to control[49]. A randomized controlled trial in women undergoing **radiation therapy** compared calendula cream to a standard moisturiser. Although the study was underpowered, it found no significant increase in severe skin reactions, suggesting acceptable tolerability[50]. On a more functional level, a study on healthy skin showed that a cream with *Calendula officinalis* extract improved mechanical properties of the skin (elasticity, resilience) over 8 weeks, with no major safety issues[51]. In animal models (albino rats), a cream with calendula essential oil showed **protective antioxidant effects** and no signs of acute toxicity when applied topically.

Safety Profile & Irritancy

Neem oil is generally considered *low-toxicity* for topical use. However, it can cause contact dermatitis or allergic reactions in some individuals. It's recommended to do a patch test before broader use. In dermocosmetic reviews, ethanolic neem extracts up to a certain concentration (e.g., ~0.5%) have been well tolerated without serious adverse effects. While calendula is broadly safe, some individuals — especially those with allergies to plants in the

Asteraceae (Compositae) family (like ragweed, daisies) — may experience contact dermatitis**.** Precautions: According to regulatory assessments, topical calendula is generally safe when used as intended, but data in pregnancy and lactation are limited**,** so caution is advised[52].

Regulatory Considerations

In the **European Union**, herbal medicinal products (including topical ones) fall under specific regulatory pathways. The **EMA's Committee on Herbal Medicinal Products (HMPC)** provides monographs and guidance for safe use and marketing. For *Calendula officinalis*, a European assessment concluded that products for external use (e.g., creams) can be categorized as **traditional herbal medicinal products**, given their long history of use and favorable safety profile. As with all herbal products, **quality control is critical**: regulatory dossiers usually require consistent sourcing, good manufacturing practices, phytochemical standardization, and stability/safety data[53].

Challenges and Future Perspectives

While the development of a neem–marigold polyherbal patch holds great promise for acne therapy, several challenges remain. At the same time, future research directions offer exciting opportunities to overcome these hurdles and translate this technology into a real-world product.

Challenges

Standardization & Batch-to-Batch Variability

One of the biggest obstacles in herbal formulations is *inconsistency* in phytochemical content: the concentration of active compounds in neem and marigold extracts can vary depending on plant source, harvest time, extraction method, and even geographic factors. This variability can make it hard to ensure consistent efficacy and safety[54]. For a patch formulation, this is particularly critical: since the active is delivered at a fixed rate, any variability in concentration could lead to under-dosing or overdosing.

Skin Permeability Barrier

The skin's outermost layer, the **stratum corneum**, remains a formidable barrier. Even with a well-designed patch, some herbal actives—especially larger or more hydrophilic molecules—may struggle to permeate efficiently[55]. While permeation enhancers or nanocarriers can help, they may also interact unfavorably with sensitive phytochemicals, potentially degrading them or reducing their activity[55].

Stability of Herbal Compound

Natural extracts are often susceptible to degradation via oxidation, hydrolysis, or photodegradation. Over time, this can reduce the potency of neem or marigold actives in the patch matrix. Ensuring long-term stability (shelf life) without compromising bioactivity is a significant formulation challenge[56].

Patch Adhesion and Skin Irritation

Ensuring that the patch adheres well to human skin under daily use is non-trivial — sweat, movement, and skin texture can all interfere. There's also a risk of irritation or sensitization, especially with prolonged application; even natural compounds can trigger skin reactions, and polymer matrices or adhesives may also contribute[57].

Regulatory Hurdles

Regulatory pathways for herbal transdermal patches are not always straightforward. Unlike synthetic drugs, herbal products often lack well-defined monographs or standardized requirements,

which makes regulatory approval more complex. Demonstrating consistent quality, reproducibility, and safety (especially for a novel combination patch) will require rigorous data[58].

Sustainability and Material Concerns

Many patches use synthetic polymers, which can raise environmental sustainability issues. There is a growing demand (and research) for *eco-friendly*, biodegradable patch materials. Balancing ecological materials with performance (adhesion, controlled release) is still a tough engineering problem[59].

Future Perspectives

1. **Advanced Delivery Technologies**
   Incorporating **microneedles** or *smart patches* could help circumvent the stratum corneum barrier. Researchers are increasingly exploring microneedle-based transdermal systems for precise and more efficient delivery[60]. **Nanotechnology** (e.g., nanoemulsions, polymeric nanoparticles) can further enhance permeation and protect sensitive herbal actives[61]. *Eco-friendly polymers*: The use of biodegradable, natural polymer matrices (like chitosan, cellulose, etc.) is becoming more popular to make sustainable patches.
2. **Standardization & Quality Control**
   Development of phytochemical fingerprinting methods (e.g., HPLC, LC-MS) for neem and marigold to ensure batch-to-batch consistency.Use of good agricultural and collection practices (GACP) and uniform extraction protocols to minimize variability.Establishing release specifications and bioassays for each batch of patch to confirm efficacy[62].
3. **Smart & Responsive Patches**
   The concept of *smart patches* that respond to skin pH, temperature, or other triggers could optimize release of herbal actives when and where they are most needed. Integrating sensors or digital health technologies (wearable sensors) to monitor patch adherence, drug release, or even local skin inflammation in real time[63].
4. **Sustainability & Green Manufacturing**
   Further research into **green synthesis routes** for patch materials: using plant-derived or biodegradable polymers to reduce environmental impact. Lifecycle assessments of patches to ensure eco-friendliness from production to disposal[63].
5. **Robust Clinical Studies**
   While preliminary patch studies (like the neem–marigold patch) show promise, **well-designed clinical trials** are needed: randomized controlled trials in acne patients, long-term safety studies, and real-world usability assessments. Comparative studies against standard acne treatments to establish relative effectiveness, tolerability, and cost-benefit[64].
6. **Regulatory Strategy Development**
   Collaborate early with regulatory agencies to define the right pathway: whether the patch will be treated as a cosmetic**,** medical device, **or** phytopharmaceutical. Develop quality-by-design (QbD) frameworks for herbal patches to streamline regulatory submission.

CONCLUSION

Acne vulgaris is more than just a cosmetic concern—it is a complex skin condition that can affect self-esteem, social interactions, and overall quality of life. While conventional treatments such as antibiotics, retinoids, and chemical peels are effective, they often come with drawbacks like side effects, irritation, or the risk of microbial resistance. These limitations have sparked a

growing interest in herbal remedies, which offer a gentler, holistic approach to skin health. Among herbal candidates, neem (Azadirachta indica) and marigold (Calendula officinalis) stand out for their remarkable properties. Neem is celebrated for its antimicrobial and sebum-regulating effects, helping to reduce the bacterial load and control excess oil that fuel acne. Marigold, on the other hand, brings anti-inflammatory, antioxidant, and skin-regenerative benefits, soothing irritated skin and supporting natural healing. When combined in a polyherbal patch, these two botanicals work in harmony, tackling multiple aspects of acne at once—bacteria, inflammation, and skin repair. The patch format itself adds another layer of innovation. By delivering the actives directly to the affected area in a controlled, sustained manner, polyherbal patches improve efficacy, reduce the need for frequent application, and enhance patient compliance. Modern formulation techniques—such as solvent casting, use of biocompatible polymers, and incorporation of nanocarriers—have made it possible to produce stable, safe, and effective herbal patches. Early in vitro and animal studies, along with available clinical evidence, suggest these patches are well-tolerated, non-irritating, and capable of addressing acne more holistically than conventional topical formulations. Despite the promise, challenges remain. Ensuring consistent quality of herbal extracts, achieving optimal skin penetration, maintaining stability over time, and navigating regulatory requirements are key hurdles that researchers must overcome. Future research focusing on advanced delivery technologies, smart responsive patches, eco-friendly materials, and rigorous clinical trials will be crucial in bringing these innovations from the lab to real-world use. In essence, neem–marigold polyherbal patches represent a perfect marriage of traditional herbal wisdom and modern drug delivery science. They offer a gentle, multi-targeted, and patient-friendly approach to acne management—highlighting how nature and technology can work together to create effective and safe therapeutic solutions.

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