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A REVIEW ON FORMULATION AND EVALUATION OF HERBAL BIOACTIVES LOADED NANOEMULSION FOR TREATMENT OF PSORIASIS AND ACNE VULGARIS

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ABSTRACT

Psoriasis and acne vulgaris are prevalent and chronic dermatological disorders. Psoriasis is an autoimmune-mediated condition characterized by the hyperproliferation of keratinocytes, resulting in erythematous, pruritic, and scaly plaques, while acne vulgaris is primarily driven by follicular hyperkeratinization, excess sebum production, and bacterial colonization, leading to severe inflammatory lesions. Conventional topical therapeutics often exhibit limited clinical efficacy due to the formidable barrier properties of the stratum corneum, which severely restricts the cutaneous permeation of active pharmaceutical ingredients. Furthermore, the prolonged administration of synthetic agents and topical corticosteroids is frequently associated with severe adverse effects, including cutaneous atrophy and the development of antimicrobial resistance. To mitigate these adverse effects, contemporary research has increasingly focused on phytotherapeutics and plant-derived bioactives, such as curcumin, tea tree oil, and aloe vera. While these natural compounds possess significant anti-inflammatory and antimicrobial properties alongside a favorable safety profile, their clinical translation is significantly impeded by their highly lipophilic nature and poor aqueous solubility. This inherent insolubility results in suboptimal skin penetration and restricted bioavailability when formulated in conventional topical vehicles. Nanoemulsion technology offers a robust strategy to overcome these physiochemical limitations. As thermodynamically stable, isotropic systems comprising oil, water, and an optimized blend of surfactants featuring nanometer-sized droplets, nanoemulsions markedly enhance the solubility of lipophilic herbal bioactives by encapsulating them within the internal lipid phase. Furthermore, the nanometric droplet size facilitates superior transdermal permeation across the stratum corneum, ensuring the targeted, deep delivery of therapeutic agents directly into the viable epidermal layers and pilosebaceous units to address the pathogenesis of psoriasis and acne vulgaris at their respective cellular sites of action.

KEYWORDS: Nanoemulsion, Herbal Bioactives, Phytotherapeutics, Psoriasis, Acne Vulgaris, Topical Drug Delivery, Transdermal Permeation, Bioavailability Enhancement.

INTRODUCTION

Psoriasis and acne vulgaris represent two of the most prevalent and clinically challenging chronic dermatological pathologies worldwide, both of which significantly impair patients' psychosocial well-being and overall quality of life. Psoriasis is a T-cell-mediated autoimmune disorder characterized by the abnormal hyperproliferation and incomplete differentiation of epidermal keratinocytes, culminating in the formation of well-demarcated, erythematous, and hyperkeratotic plaques.[1] Conversely, acne vulgaris is a multifactorial inflammatory disease of the pilosebaceous unit, primarily driven by androgen-induced seborrhea, altered follicular keratinization, and the pathogenic proliferation of the anaerobic bacterium *Cutibacterium acnes*. The conventional pharmacological management of these localized conditions relies heavily on synthetic topical formulations containing corticosteroids, retinoids, and antibiotics. While these regimens offer acute symptomatic relief, their long-term clinical utility is severely compromised by a spectrum of dose-limiting adverse effects, including epidermal atrophy, localized erythema, systemic toxicity, and the increasing global emergence of antibiotic-resistant bacterial strains.[2] Consequently, there remains an urgent and unmet biopharmaceutical need for safer, alternative therapeutic modalities that provide sustained anti-inflammatory and antimicrobial efficacy without compromising epidermal integrity.[3]

Figure 1: Image show Psoriasis and acne vulgaris condition.

In recent years, phytotherapeutics have emerged as a highly promising clinical alternative, leveraging the pleiotropic anti-inflammatory, antioxidant, and antimicrobial properties of herbal bioactives such as curcumin, tea tree oil, and aloevera. However, much like other poorly water-soluble pharmaceutical compounds, the clinical translation of these botanical agents is severely hindered by their complex physicochemical properties. The highly lipophilic nature of these active phytoconstituents presents a fundamental challenge in solubility enhancement a critical prerequisite for any effective topical formulation.[4,5] This inherent poor aqueous solubility restricts their thermodynamic activity, thereby limiting their partition coefficient and subsequent transdermal permeation across the formidable lipid barrier of the stratum corneum. When incorporated into conventional dermatological vehicles such as standard macro-emulsions or ointments, these bioactives exhibit sub-therapeutic tissue concentrations and poor localized bioavailability.

To circumvent these biopharmaceutical limitations and achieve requisite solubility enhancement, advanced nanoscale drug delivery systems specifically nanoemulsions—have garnered significant attention in dermatological research.[6,7]

Nanoemulsions are kinetically stable, isotropic colloidal dispersions comprising an oil phase, an aqueous phase, and an optimized interfacial film of surfactants and co-surfactants. By encapsulating lipophilic bioactives within nanometer-

sized lipid droplets (typically 20–200 nm), these systems fundamentally alter the solvation dynamics, dramatically improving thermodynamic stability and achieving complete drug solubilization. This engineered nanoscale architecture not only resolves the inherent solubility constraints of herbal extracts but also provides a massive interfacial surface area that facilitates superior cutaneous penetration through both the intercellular lipid matrix and transappendageal pathways. Ultimately, nanoemulsion-based delivery systems ensure the targeted, sustained release of phytotherapeutics directly into the viable epidermis and pilosebaceous units, offering a highly effective and biocompatible paradigm for the management of psoriasis and acne vulgaris.[8]

Herbal Bioactives in Dermatology

Herbal medicines have long been used in the treatment of skin disorders due to their wide spectrum of biological activities and relatively low incidence of adverse effects. In the field of dermatology, botanical bioactives are particularly favored because they offer multi-targeted mechanisms of action, such as simultaneously exerting antimicrobial, anti-inflammatory, antioxidant, and wound-healing effects.[9,10] This multi-targeted action aligns well with the multifactorial pathogenesis of chronic skin conditions like acne vulgaris and psoriasis.

However, the therapeutic application of herbal actives is often limited by poor aqueous solubility, chemical instability, volatility, unpleasant odor, and inadequate skin penetration. Many natural phytoconstituents are highly lipophilic, which leads to poor aqueous solubility and subsequently limits their overall bioavailability when applied topically through conventional vehicles like standard creams or ointments. Advanced drug delivery systems, such as nanoemulsions, are therefore required to overcome these physicochemical challenges to maximize clinical efficacy.

Pathophysiology of Psoriasis

Psoriasis is a chronic, immune-mediated inflammatory skin disorder characterized by dysregulated interactions between the innate and adaptive immune systems and epidermal keratinocytes. Its pathogenesis involves a complex interplay between genetic susceptibility and environmental triggers, including infections, psychological stress, trauma, certain medications, smoking, and alcohol consumption.[11] In genetically predisposed individuals, activation of dendritic cells initiates an inflammatory cascade that promotes the activation and differentiation of T-lymphocytes, particularly Th1 and Th17 cells. These activated immune cells release a range of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-17, and IL-23, which play central roles in the initiation and perpetuation of psoriatic inflammation. The IL-23/Th17 axis is considered a key pathogenic pathway, with IL-17 acting directly on keratinocytes to stimulate the production of additional inflammatory mediators and chemokines, thereby amplifying the inflammatory response. Persistent cytokine signaling promotes excessive proliferation and abnormal differentiation of keratinocytes, resulting in epidermal hyperplasia (acanthosis), parakeratosis, and accelerated epidermal turnover.[12]

Concurrent inflammatory and vascular changes, including dilation of dermal blood vessels and infiltration of immune cells, contribute to the characteristic clinical appearance of psoriasis, namely well-demarcated, erythematous, raised plaques covered with silvery-white scales. The interaction between immune activation, cytokine release, keratinocyte hyperproliferation, and abnormal differentiation establishes a self-sustaining inflammatory cycle that contributes to the chronic and recurrent nature of the disease. Furthermore, the marked epidermal hyperplasia and accumulation of hyperkeratotic scales may reduce the penetration and bioavailability of topical therapeutic agents within affected lesions, potentially limiting their efficacy in patients with extensive or thick plaques. Consequently, the pathophysiological complexity of psoriasis provides the rationale for a multimodal therapeutic approach involving

topical agents, phototherapy, conventional systemic therapies, and targeted biologic treatments directed against key inflammatory pathways, particularly the TNF-α, IL-17, and IL-23 pathways.[13,14]

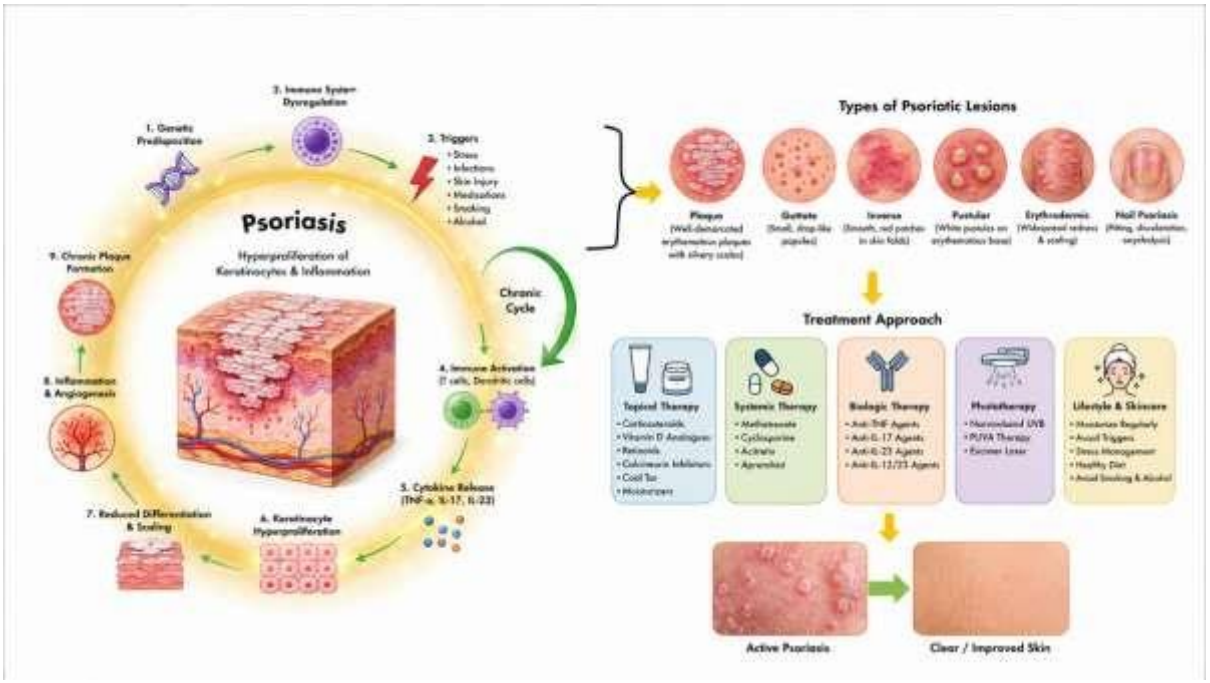

Figure 2: Pathogenesis of Psoriasis.

Pathophysiology of Acne Vulgaris

Unlike psoriasis, acne vulgaris is a chronic inflammatory disorder primarily affecting the pilosebaceous unit and resulting from a complex interplay of hormonal, follicular, microbial, and immunological factors. The pathogenesis involves four interrelated processes: increased sebum production, abnormal follicular keratinization, proliferation and dysbiosis of *Cutibacterium acnes* (formerly *Propionibacterium acnes*), and inflammation. The process typically begins with androgen-mediated stimulation of sebaceous glands, leading to excessive sebum production, which, together with abnormal shedding and hyperproliferation of follicular keratinocytes, promotes the formation of a microcomedone, the earliest precursor lesion of acne.[15] The accumulation of sebum and keratinous material within the follicular canal creates a lipid-rich, relatively anaerobic microenvironment that favors the proliferation of *C. acnes*. Although *C. acnes* is a normal component of the skin microbiota, alterations in the follicular microenvironment and microbial composition can promote its pathogenic activity. *C. acnes* activates innate immune pathways through interactions with Toll-like receptors (particularly TLR2) and other inflammatory mechanisms, leading to the release of pro-inflammatory cytokines and chemokines, including IL-1β, TNF-α, and IL-8, and recruitment of inflammatory cells. This inflammatory cascade contributes to the progression of initially non-inflammatory open and closed comedones into inflammatory lesions such as papules and pustules, while deeper inflammation may result in nodules and cysts. Additional factors, including oxidative stress, alterations in sebum composition, and genetic and environmental influences, may further amplify the inflammatory response.[16] Thus, acne vulgaris is best understood as a dynamic and multifactorial disease in which follicular occlusion, sebaceous gland hyperactivity, microbial dysbiosis, and immune-mediated inflammation interact to produce the diverse spectrum of clinical lesions characteristic of the disorder.

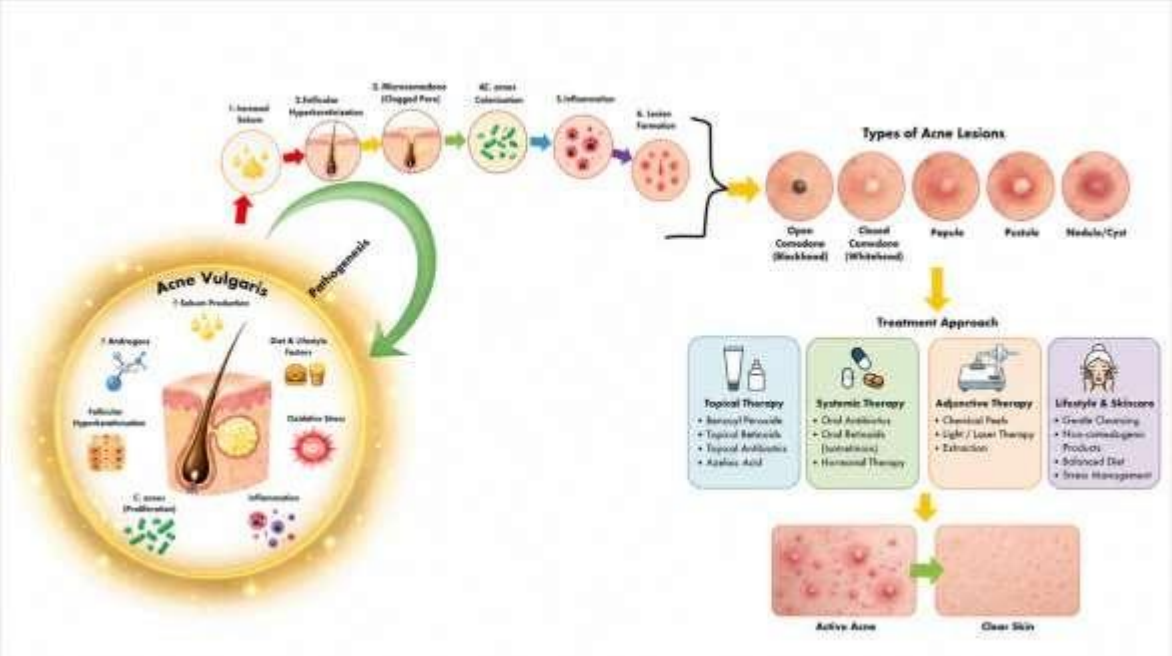

Figure 3: Pathogenesis of Acne Vulgaris.

Detailed Profiles of Key Herbal Bioactives

- **Garlic Oil (*Allium sativum L.*)**: Garlic oil is obtained from the bulbs of *Allium sativum* and is heavily relied upon for its rich concentration of organosulfur compounds, including allicin, ajoene, diallyl disulfide, and diallyl trisulfide. These compounds provide garlic with its broad antimicrobial potential, which acts by interacting with thiol-containing enzymes in microbial cells and inhibiting their essential metabolic pathways. Additionally, garlic oil modulates inflammatory mediators like prostaglandins and cytokines, and it exhibits potent antioxidant activity to reduce the oxidative stress involved in acne pathogenesis. While its topical use is normally limited by a strong odor, volatility, and skin irritation potential, encapsulating it within a nanoemulsion masks the odor, improves stability, and enhances deep skin penetration.[17,18]
- **Manuka Honey (*Leptospermum scoparium*)**: Produced from the nectar of the *Leptospermum scoparium* plant native to New Zealand, Manuka honey is distinguished by its high content of methylglyoxal (MGO) and its Unique Manuka Factor (UMF). It exerts pronounced antibacterial action through multiple synergistic mechanisms, including osmotic effects, an acidic pH, hydrogen peroxide production, and the presence of MGO. Crucially, bacterial resistance to honey has not been reported, making it a highly attractive option for long-term dermatological management. It also demonstrates significant anti-inflammatory and wound-healing activity by downregulating pro-inflammatory cytokines and promoting tissue repair via enhanced epithelialization and collagen synthesis. In topical formulations, it serves as an excellent natural humectant that improves skin hydration and barrier function.[19]
- **Tea Tree Oil (*Melaleuca alternifolia*)**: Extensively studied for acne management, tea tree oil's primary active component is terpinen-4-ol, which exhibits strong antimicrobial and anti-inflammatory properties. It has been shown to successfully reduce acne lesion counts and severity with an efficacy comparable to conventional benzoyl peroxide, but with fewer side effects. Because high concentrations can sometimes cause skin irritation or sensitization, formulating tea tree oil into a nanoemulsion helps reduce adverse effects by improving dispersion, preventing direct concentrated contact, and enabling a controlled release.

- **Neem (*Azadirachta indica*):** Neem contains powerful bioactive compounds such as azadirachtin, nimbidin, quercetin, and nimbin. These constituents contribute directly to its renowned antimicrobial, anti-inflammatory, and antioxidant properties.[20] Neem extracts and oils effectively target acne-causing bacteria and are widely known to reduce the redness, swelling, and irritation associated with inflammatory lesions.
- **Turmeric (*Curcuma longa*)** Rich in curcuminoids, particularly curcumin, turmeric possesses potent anti-inflammatory and antioxidant activity. Curcumin inhibits nuclear factor-kappa B (NF-kB) signaling and effectively downregulates the pro-inflammatory cytokines involved in acne and psoriasis pathogenesis. It also promotes active wound healing and exhibits antibacterial activity. Because the poor aqueous solubility of curcumin severely limits its traditional topical application, nanoemulsion systems are utilized to significantly enhance its solubility, stability, and bioavailability.
- **Green Tea Extract (*Camellia sinensis*)** Green tea extract is abundant in polyphenols, particularly epigallocatechin gallate (EGCG), which provides multi-targeted antioxidant, anti-inflammatory, and sebum-regulating effects. EGCG has been shown to actively inhibit the growth of *Cutibacterium acnes* and reduce excess sebum production by modulating androgen activity in the sebaceous glands.
- **Aloe Vera (*Aloe barbadensis Miller*)** Widely used across dermatology for its soothing, moisturizing, and wound-healing properties, aloe vera contains a complex matrix of polysaccharides, vitamins, enzymes, and amino acids that aid in anti-inflammatory and skin-repair effects. In anti-acne and anti-psoriasis formulations, it helps reduce the irritation, redness, and dryness often associated with active antimicrobial agents, and is frequently used as a supportive component to drastically enhance overall skin tolerability.

Table 1: Herbal actives commonly used in nanoemulsion-based Anti-acne formulations.

Herbal active	Major constituents	Primary activity
Garlic oil	Allicin, ajoene	Antibacterial, anti- inflammatory
Manuka honey	Methylglyoxal, phenolics	Antibacterial, wound healing
Tea tree oil	Terpinen-4-ol	Antimicrobial
Neem	Azadirachtin	Antibacterial, antioxidant
Turmeric	Curcumin	Anti-inflammatory, antioxidant
Green tea	Epigallocatechin gallate	Sebum regulation, antioxidant
Aloe vera	Polysaccharides	Soothing, wound healing

The Polyherbal Concept and Scientific Rationale

Polyherbal formulations are intentionally designed to integrate multiple botanicals with complementary biological actions, enabling broader therapeutic coverage of complex disease pathways. Because multiple pathogenic factors operate simultaneously in conditions like acne vulgaris (e.g., altered keratinization, sebum overproduction, bacterial colonization, and inflammation), a polyherbal approach is particularly advantageous. Instead of relying on a single active pharmaceutical ingredient that may only target one aspect of a disease, a polyherbal formulation offers a multi-pronged therapeutic strategy.

Polyherbal nanoemulsion systems can simultaneously target different aspects of pathogenesis, including bacterial proliferation, local inflammation, oxidative stress, and impaired wound healing. For example, a single formulation might combine garlic oil to provide strong antibacterial activity, Manuka honey to enhance antimicrobial action while promoting healing, turmeric to reduce inflammation, and aloe vera to improve skin hydration and tolerability. The synergistic interaction among these specific components results in enhanced clinical efficacy while reducing the likelihood of adverse effects that are common when using high concentrations of single synthetic agents.[21,22]

Furthermore, integrating this polyherbal synergy with nanoemulsion technology resolves the formulation challenges of mixing diverse plant extracts. It ensures the uniform distribution of multiple herbal actives, superior penetration into the pilosebaceous unit, and a highly controlled release directly at the target site. By combining the holistic, multi-targeted benefits of traditional herbal medicine with advanced nanotechnology, polyherbal nanoemulsions represent a highly rational and innovative strategy for the modern management of dermatological disorders.

Nanoemulsion as a Drug Delivery System

To overcome the significant physicochemical limitations of herbal extracts, nanoemulsions are heavily employed as advanced topical nanocarriers. The transition from traditional topical vehicles to nanocarriers represents a critical advancement in dermatological therapies, specifically tailored to handle the complex properties of natural phytoconstituents.[23]

By design, nanoemulsions are kinetically stable, isotropic systems characterized by ultra-fine droplet sizes, typically ranging between 5 and 200 nm. Structurally, these advanced delivery vehicles consist of an oil phase, an aqueous phase (water), and an optimized blend of surfactants and co-surfactants designed to stabilize the system.

Structural Composition

The fundamental architecture of a nanoemulsion requires a precise combination of phases to ensure kinetic stability:

- **Oil Phase:** Acts as the primary solubilizing core for highly lipophilic herbal bioactives.
- **Aqueous Phase:** The water-based continuous medium that allows the system to remain isotropic.
- **Surfactants & Co-surfactants:** Form an optimized boundary layer to lower interfacial tension and stabilize the ultra-fine droplets.

Therapeutic and Commercial Advantages

The application of nanoemulsions in dermatology offers several distinct therapeutic and commercial advantages that directly address the failures of conventional treatments when attempting to deliver natural phytoconstituents:

- **Enhanced Skin Permeation:** The nanometric size of the droplets creates a massive surface area for interaction with the skin. Additionally, the lipidic nature of the nanoemulsion fluidizes the lipid matrix of the stratum corneum. They successfully extract and expand the lipids of the stratum corneum, which facilitates deep dermal penetration and allows the bioactives to reach deeper skin layers. They can also penetrate through the stratum corneum and preferentially accumulate in hair follicles and sebaceous glands, which are the primary sites involved in acne vulgaris.[24,25]
- **High Solubilization Capacity:** Many herbal bioactives suffer from poor aqueous solubility, but nanoemulsions can easily encapsulate highly lipophilic phytoconstituents. This effectively solubilizes them, protects them from environmental or enzymatic degradation, and provides a controlled release of active ingredients.
- **Aesthetic Appeal and Patient Compliance:** Unlike traditional, heavy ointments, nanoemulsions offer high cosmetic elegance. Due to their transparent or translucent nature and their non-greasy texture, they are highly appealing to patients, which in turn significantly boosts treatment adherence and patient compliance.[26]

Formulation into Nanoemulgels: Overcoming Physical Limitations

While nanoemulsions possess excellent delivery capabilities, their physical consistency can present a practical challenge. Because low-viscosity nanoemulsions run off the skin easily upon application, they are frequently

incorporated into a hydrogel matrix to form what is known as a "nanoemulgel" or incorporated into semisolid bases to form nanoemulsion creams.

This physical modification is highly beneficial for the clinical management of both psoriasis and acne vulgaris. The transition into a nanoemulgel or cream format increases the formulation's contact time on the skin and provides a localized, controlled release of the herbal bioactives directly to the affected psoriatic plaques or acne lesions.[27] By locking the kinetically stable nano-droplets within a structured gel network, the formulation merges the superior skin permeation of a nanoemulsion with the structural and practical advantages of a standard topical gel.

Formulation Approaches

The successful formulation of a nanoemulsion requires a delicate balance of excipients and appropriate emulsification techniques. The strategic selection of each phase and the method of emulsification are critical to ensuring the kinetic stability, skin compatibility, and overall therapeutic efficacy of the final delivery system.

Components of Nanoemulsion Systems

A standard topical nanoemulsion consists of three primary components: an oil phase, an aqueous phase, and an optimized blend of surfactants and co-surfactants.

- **Oil Phase** The oil phase plays a crucial role in determining the solubilization capacity and therapeutic performance of the nanoemulsion. It must possess the maximum solubilizing capacity for the highly lipophilic herbal bioactives being delivered. Additionally, the oil itself can provide therapeutic value. Essential oils such as garlic oil, tea tree oil, and neem oil can serve dually as both the solubilizing oil phase and as active antimicrobial agents. Incorporating oils with inherent skin-healing properties, such as kalonji oil or jojoba oil, can further provide synergistic therapeutic effects in managing dermatological conditions.
- **Surfactants & Co-surfactants** Surfactants are carefully selected based on their ability to lower the interfacial tension between the oil and water phases, enabling the formation of stable, nano-sized droplets. For topical nanoemulsions, non-ionic surfactants, such as polysorbates (e.g., Tween 20, Tween 80) and Span 20, are generally preferred. These are favored due to their lower irritation potential, low toxicity, skin compatibility, and their ability to form stable emulsions over a wide pH range. Furthermore, biosurfactants are increasingly being utilized as a "green," eco-friendly alternative to synthetic agents.[28]
- **Aqueous Phase** The aqueous phase typically consists of purified water or buffered solutions. This phase serves as the continuous medium in oil-in-water (O/W) nanoemulsions and allows for the incorporation of hydrophilic botanical actives, such as Manuka honey and aloe-vera extract, further enhancing the polyherbal synergy of the formulation.

Emulsification Methods

Nanoemulsions can be formulated using either high-energy or low-energy methods, depending on the available equipment and the physicochemical properties of the herbal actives.

- **High-Energy Methods** These methods utilize intense mechanical forces to physically disrupt oil droplets, breaking them down into the nanometer range. Common high-energy techniques include high-pressure homogenization and ultrasonication.[29] Ultrasonication is particularly popular and widely used at the laboratory scale due to its simplicity and overall effectiveness in producing uniform nano-droplets.
- **Low-Energy Methods** Unlike high-energy methods, low-energy techniques rely on the spontaneous formation of

nanoemulsions. This is achieved by systematically altering specific system parameters, such as changes in composition or temperature, to induce nanoemulsion formation. Prominent examples include the Phase Inversion Temperature (PIT) method and the Phase Inversion Composition (PIC) method.

Pseudo-Ternary Phase Diagrams

A critical step in the formulation process is the construction of pseudo-ternary phase diagrams. These diagrams help in identifying the specific concentration ranges of the oil, surfactant, co-surfactant, and aqueous phases required to form a stable emulsion.[30] By mapping these regions, formulators can successfully select optimal formulation compositions that yield kinetically stable nanoemulsions while requiring minimal energy input.

Characterization and Evaluation Parameters

Rigorous physicochemical and biological evaluations are imperative to ensure the stability, safety, consistency, and functional performance of nanoemulsion-based topical systems. Because these formulations rely on intricate interfacial phenomena and sub-micron structures, a comprehensive assessment matrix is required before they can be deemed suitable for clinical application.

Physicochemical Characterization

- **Globule Size and Polydispersity Index (PDI)**

The droplet size and its distribution are critical determinants of a nanoemulsion's performance. These parameters are typically analyzed using light-scattering analytical techniques, specifically Dynamic Light Scattering (DLS). Smaller droplet sizes significantly enhance skin penetration by providing a larger surface area for interaction with the stratum corneum, and they also contribute to the kinetic stability of the system. A droplet size below 200 nm coupled with a PDI value less than 0.3 indicates a stable, uniform nanoemulsion with a narrow size distribution, reflecting good physical stability.[31]

- **Zeta Potential**

Zeta potential measures the surface charge of the nanoemulsion droplets and provides direct insight into the formulation's long-term stability. Generally, zeta potential values greater than +30 mV or less than -30 mV confer high kinetic stability by preventing droplet coalescence through strong electrostatic repulsion. However, it is important to note that many topical nanoemulsions utilize non-ionic surfactants, which may result in low overall zeta potential values; in these cases, the system relies heavily on steric stabilization to ensure adequate stability against aggregation.

- **pH, Viscosity, and Spreadability**

For topical applications, physical parameters like pH, viscosity, and spreadability dictate both safety and patient compliance. The pH of topical nanoemulsion creams must be strictly compatible with natural skin physiology, typically falling within the acidic mantle range of 5.0 to 6.5. Furthermore, optimized viscosity and spreadability are vital as they directly influence the formulation's application behavior, its retention time on the skin, and ultimate patient acceptance.[32]

Release and Permeation Studies in Vitro Drug Release

To evaluate the therapeutic potential of the nanocarrier, *in vitro* release studies are conducted using Franz diffusion cells equipped with synthetic membranes. These studies determine the release kinetics of the herbal bioactive from the

core of the nanoemulsion matrix into a receptor compartment, providing essential insights into the formulation's controlled-release capabilities.

Ex Vivo Permeation Studies

While *in vitro* models provide kinetic data, *ex vivo* permeation studies are necessary to map the actual transdermal flux and skin retention of the active compound. These studies typically utilize excised human cadaver skin or relevant animal skin models (such as porcine or rat skin) mounted on Franz diffusion cells to simulate real-world topical application and penetration behavior.

Stability Assessment

Comprehensive stability studies are required to predict the shelf life and physical integrity of the formulation under various environmental stressors.[33] This involves subjecting the nanoemulsions to different storage conditions (including varying temperatures and humidity levels) as well as rigorous mechanical stress tests like centrifugation and freeze-thaw cycles to evaluate both physical and chemical stability over time.

Biological and Safety Evaluations

In Vivo Efficacy: To confirm the therapeutic relevance of the *in vitro* data, formulations are tested on specific *in vivo* animal models. For dermatological applications, this includes the imiquimod-induced psoriasis mouse model or testosterone-induced acne models. These studies allow researchers to observe tangible clinical improvements, actual reductions in local inflammation, and histopathological restoration of the affected tissue.

Skin Irritation and Toxicity Studies Finally, safety is paramount when applying formulations to already compromised, inflamed skin. Skin irritation and toxicity studies are essential to definitively confirm that the selected synthetic excipients (like surfactants) and the concentrated herbal bioactives do not cause adverse reactions such as erythema or edema upon repeated topical application.

Biological Evaluation and Therapeutic Efficacy

Biological evaluation is a critical component in establishing the therapeutic potential of herbal bioactive-loaded nanoemulsions for the management of psoriasis and acne vulgaris. Although physicochemical characterization provides valuable information regarding droplet size, polydispersity index, zeta potential, pH, viscosity, drug content, entrapment efficiency, stability, and in vitro drug-release behavior, these parameters alone are insufficient to predict the actual biological performance of a formulation. Therefore, systematic biological evaluation is necessary to determine the safety, skin compatibility, permeation behavior, pharmacological activity, and therapeutic effectiveness of nanoemulsion-based delivery systems. Such studies help bridge the gap between the formulation characteristics observed during in vitro development and the potential clinical performance of the final product.

For psoriasis, biological evaluation primarily focuses on assessing the anti-inflammatory, antioxidant, immunomodulatory, and anti-proliferative activities of the incorporated herbal bioactives. Psoriasis is a chronic immune-mediated inflammatory skin disorder characterized by excessive keratinocyte proliferation, abnormal differentiation, immune-cell infiltration, and increased production of pro-inflammatory cytokines. Therefore, the efficacy of herbal bioactive-loaded nanoemulsions can be evaluated by investigating their ability to suppress inflammatory mediators, modulate immune responses, and reduce abnormal epidermal hyperproliferation. In vitro

cellular assays, including studies using keratinocytes and immune-related cell models, can provide valuable information regarding the effects of bioactive compounds on inflammatory signaling pathways and cytokine production. Ex vivo skin permeation and skin-retention studies are also important for determining whether the nanoemulsion can effectively overcome the barrier function of the stratum corneum and facilitate enhanced deposition of the herbal bioactive within the epidermal and dermal layers. In vivo evaluation using appropriate experimental models may further assess reductions in erythema, scaling, epidermal thickness, inflammatory-cell infiltration, and other histopathological changes associated with psoriatic lesions.

In the treatment of acne vulgaris, biological evaluation focuses on the antimicrobial, anti-inflammatory, antioxidant, and seboregulatory properties of herbal bioactives incorporated into nanoemulsion systems. Acne vulgaris is a multifactorial inflammatory disorder involving excessive sebum production, abnormal follicular keratinization, microbial proliferation, and inflammation. The biological efficacy of herbal nanoemulsions may therefore be evaluated through antimicrobial assays against acne-associated microorganisms, particularly *Cutibacterium acnes*, along with studies assessing inhibition of inflammatory mediators and oxidative stress. The ability of the nanoemulsion to improve penetration into the pilosebaceous unit is particularly relevant because the hair follicle and sebaceous gland represent important therapeutic targets in acne. Enhanced follicular delivery may increase the local concentration of bioactive compounds at the site of disease while minimizing unnecessary systemic exposure. In vitro antimicrobial studies, anti-inflammatory assays, antioxidant evaluations, cell viability studies, and ex vivo skin permeation or follicular penetration experiments can collectively provide evidence of the therapeutic potential of these formulations.

Herbal bioactives such as Curcumin, Thymoquinone, Tea Tree Oil, Aloe vera constituents, Neem-derived compounds, and other plant-based phytoconstituents have demonstrated various pharmacological activities relevant to inflammatory skin disorders. However, their therapeutic application may be limited by poor aqueous solubility, chemical instability, low bioavailability, rapid degradation, or inadequate penetration through the skin. Nanoemulsion-based delivery systems can potentially overcome these limitations by improving the solubilization, stability, skin permeation, and localized deposition of poorly water-soluble herbal compounds. The nanoscale droplets and large interfacial surface area of nanoemulsions may facilitate enhanced interaction with the skin and promote efficient delivery of bioactive molecules to the target site. Consequently, improved topical delivery may enhance the anti-inflammatory, antimicrobial, antioxidant, and immunomodulatory effects of herbal bioactives in both psoriasis and acne vulgaris.

Application and Efficacy in Psoriasis

The thick, hyperkeratotic, and scaly plaques characteristic of psoriatic skin present a significant barrier to the effective delivery of conventional topical drugs. The highly organized lipid structure of the stratum corneum restricts the penetration of many therapeutic molecules, often preventing them from reaching the deeper epidermal layers at concentrations sufficient to produce the desired pharmacological effect. As a result, conventional topical formulations may show limited efficacy and, in some cases, prolonged or repeated application can lead to local irritation and reduced patient compliance.

Nanoemulsion-based drug delivery systems have emerged as a promising strategy to overcome these limitations by enhancing the penetration and targeted delivery of bioactive compounds into psoriatic skin. Nanoemulsions containing natural anti-inflammatory agents such as Thymoquinone and Curcumin can interact with and disrupt the lipid organization of the stratum corneum, thereby improving drug permeation across the skin barrier.[34] Their nanoscale

droplets provide a large surface area and facilitate closer interaction with the skin, allowing the encapsulated bioactive compounds to penetrate more efficiently into the affected epidermal layers. This enhanced delivery may enable the active agents to reach inflammatory immune cells, including dendritic cells and T-cells, which play a central role in the pathogenesis of psoriasis. By modulating these immune pathways, nanoemulsion-based formulations may help reduce the production of pro-inflammatory cytokines, suppress abnormal keratinocyte proliferation, and alleviate the characteristic redness, scaling, and inflammation associated with psoriatic lesions. Therefore, nanoemulsions have considerable potential as an advanced topical delivery system for improving the efficacy, penetration, and therapeutic performance of anti-psoriatic agents while potentially minimizing the limitations associated with conventional topical formulations.

Application and Efficacy in Acne Vulgaris

Acneic skin suffers from blocked, inflamed pores heavily colonized by bacteria. To combat this, antibacterial activity of these formulations is commonly assessed against acne-associated microorganisms, primarily *Cutibacterium acnes* and *Staphylococcus aureus*.

Herbal nanoemulsions containing bioactives like Tea Tree Oil or Garlic Oil are highly effective because they penetrate deep into the pilosebaceous unit. The nano-sized droplets provide a targeted antimicrobial assault against *C. acnes* while simultaneously regulating sebum secretion and rapidly soothing local inflammation. This localized delivery avoids the systemic toxicity commonly seen with oral retinoids, as well as the resistance associated with long-term topical clindamycin use.

Specific bioactives demonstrate distinct pathways of antibacterial efficacy. For instance, garlic oil nanoemulsions have shown strong inhibitory effects on Gram-positive bacteria by disrupting essential thiol-containing enzymes.[35]

Meanwhile, the inclusion of Manuka honey contributes additional antibacterial action through the presence of methylglyoxal and potent osmotic effects.

Antioxidant Activity

Furthermore, oxidative stress plays a significant role in acne pathogenesis by promoting inflammation and tissue damage. Therefore, evaluating the antioxidant capacity of the formulation is a critical component of assessing therapeutic efficacy.

Antioxidant activity is typically evaluated using widely accepted free radical scavenging assays, such as DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) assays. Formulations containing actives like turmeric and green tea extracts consistently demonstrate strong radical scavenging activity, indicating their high potential to neutralize reactive oxygen species and drastically reduce oxidative damage within skin lesions.

A growing body of preclinical evidence strongly supports the use of nanoemulsion systems for topical anti-acne and anti-psoriasis therapy. Various published studies have demonstrated that herbal nanoemulsions containing botanical agents like tea tree oil, neem oil, curcumin, and garlic oil consistently show superior antimicrobial and anti-inflammatory activity when directly compared to conventional creams and gels.

Polyherbal nanoemulsions, in particular, have been shown to demonstrate profound synergistic effects in laboratory models, successfully targeting multiple pathogenic mechanisms of skin disorders simultaneously. For instance, *in vivo* efficacy testing on specific animal models—such as the imiquimod-induced psoriasis mouse model and testosterone-induced acne models—has repeatedly proven that herbal nanoemulsions yield visible clinical improvements, drastic reductions in local inflammation, and notable histopathological restoration of the skin barrier. While large-scale human clinical trials on polyherbal nanoemulsions remain somewhat limited, the existing *in vitro* and *ex vivo* permeation studies confirm exceptional transdermal flux and skin retention of the active compounds.

Challenges and Limitations

Despite the highly promising therapeutic potential and encouraging results of polyherbal nanoemulsion-based formulations, several significant challenges currently hinder their widespread commercial adoption and successful translation from laboratory research to commercial products.

- **Standardization of Herbal Raw Materials:** Natural phytoconstituents suffer from inherent variability in their phytochemical composition due to geographical, environmental, and seasonal harvesting factors. Standardizing these herbal extracts to ensure batch-to-batch consistency remains a major manufacturing hurdle.
- **Stability and Volatility Concerns:** Many highly effective botanical extracts, particularly essential oils and other bioactive compounds, are highly volatile and prone to chemical degradation. Consequently, maintaining long-term stability represents an ongoing formulation challenge.
- **Surfactant-Related Toxicity:** While surfactants are necessary for formulation, utilizing high concentrations of synthetic surfactants and co-surfactants to stabilize the nanoemulsion can lead to potential skin irritation upon repeated application on compromised skin.
- **Regulatory Ambiguity:** There is currently a lack of clear, harmonized regulatory guidelines globally for the approval of herbal nanoformulations and complex nanophytopharmaceuticals.
- **Limited Clinical Data:** There is a distinct need for extensive, large-scale human clinical trials. Currently, there is insufficient clinical data to definitively establish long-term safety and confirm therapeutic efficacy in human patients.[36]

Future Perspectives

The integration of nanotechnology with traditional herbal medicine holds significant promise for the development of safe, effective, and patient-friendly topical therapies for dermatological conditions. To fully realize the clinical and commercial potential of polyherbal nanoemulsion formulations for psoriasis and acne vulgaris, future research and development must focus on several key areas:

- **Standardization and Quality Control:** There is a critical need for the development of standardized herbal extracts using validated biomarkers. This will help address the natural variability in phytochemical compositions and ensure batch-to-batch consistency.
- **Formulation Advancements:** Future formulations should increasingly prioritize the use of green and biodegradable surfactants to improve the overall safety and skin tolerability of these nanocarriers. Additionally, research should explore advanced targeting strategies specifically designed to enhance follicular delivery, which is especially crucial for treating acne.
- **Manufacturing and Stability:** Optimizing large-scale manufacturing techniques is essential for commercial viability. Alongside this, comprehensive long-term stability and shelf-life studies must be conducted to ensure the

physical and chemical integrity of the formulations over time.

- **Clinical Validation:** The transition from bench to bedside requires well-designed, large-scale human clinical trials. Rigorous clinical data is paramount to definitively establish the therapeutic efficacy and long-term safety of these complex nanophytopharmaceuticals in diverse patient populations.
- **Regulatory Harmonization:** There must be a push toward regulatory harmonization globally to provide clear guidelines for the approval of herbal nanoformulations, thereby facilitating their smoother commercialization.
- The integration of nanotechnology with traditional herbal medicine holds significant promise for the development of safe, effective, and patient-friendly antiacne therapies.

SUMMARY

Nanoemulsion-based polyherbal topical formulations represent a paradigm shift and a highly promising therapeutic approach for the management of dermatological disorders like acne vulgaris and psoriasis. By integrating multiple bioactive herbal constituents, such as garlic oil and Manuka honey—these advanced systems are capable of addressing multiple pathogenic mechanisms simultaneously. The application of nanoemulsion technology effectively resolves the traditional bottlenecks associated with natural phytoconstituents, namely poor aqueous solubility, volatility, and inadequate skin penetration. These nanocarriers provide distinct formulation advantages, including the improved solubilization of lipophilic compounds, uniform drug distribution, and enhanced interaction with the skin barrier. By facilitating deep-dermal and targeted delivery, polyherbal nanoemulsions achieve superior antimicrobial and anti-inflammatory performance while minimizing the limitations and adverse effects associated with conventional synthetic therapies. Despite the encouraging outcomes highlighted in existing studies, further investigations focusing on formulation optimization, long-term safety, and rigorous clinical validation are warranted. Ultimately, the continued exploration and successful commercialization of these nanophytopharmaceuticals hold the potential to vastly improve clinical outcomes and boost patient compliance in global dermatology.

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