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Recent Progress in Nanoemulsion-Loaded Herbal Creams for Enhanced Skin Delivery: A Comprehensive Review

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ABSTRACT

Nanoemulsion formulations can improve the stability and bioavailability of hydrophobic drugs. Moreover, nanoemulsions exhibit excellent skin penetration and prolonged effects, making them particularly appealing for topical and cosmetic applications. This article provides an overview of herbal nanoemulsion formulations as cosmetic products, covering their formulation, production, and characterization. Herbal nanoemulsions are effective, stable, and promising systems for cosmetic delivery. Nanoemulsions are characterized by key properties such as particle size, polydispersity index (PDI), zeta potential, viscosity, and stability. Stability tests are employed to evaluate nanoemulsion performance. Neem contains azadirachtin, nimbidin, and flavonoids, which exhibit potent antibacterial, antifungal, and antioxidant properties. The combination of these two botanicals in a gel formulation is believed to provide synergistic benefits for managing acne by reducing microbial colonization, alleviating inflammation, and promoting skin repair. This project aims to develop a stable herbal cream incorporating neem and aloe vera extracts, optimized with suitable gelling agents and preservatives. In addition to its antimicrobial activity against Propionibacterium acnes, the formulation was evaluated for physicochemical properties such as pH, viscosity, spreadability, and stability. The findings support the potential of the herbal gel as a natural alternative to synthetic acne treatments, demonstrating favourable consistency, acceptable pH, and strong antibacterial effectiveness. The results demonstrate the potential of Aloe vera–neem gel as a sustainable, safe, and effective dermatological product. Future work includes investigating commercialization pathways to meet the growing demand for herbal skincare products and conducting clinical trials to confirm efficacy in human subjects. Herbal medicines are compatible with nanoemulsion technology, making it a promising approach for environmentally friendly drug delivery. In this study, a polyherbal anti-acne cream was prepared using plant extracts, including neem and aloe vera, along with other base materials. These plants possess strong anti-inflammatory, antimicrobial, and antioxidant properties. The main goal is to develop a cream containing natural herbal extracts with fewer side effects than conventional chemical treatments. Although conventional treatments such as antibiotics, retinoids, and benzoyl peroxide are effective, they are frequently associated with side effects such as skin irritation, microbial resistance, and high costs. This has increased interest in herbal remedies that may offer more cost-effective, safer, and eco-friendly alternatives. Neem (Azadirachta indica) and aloe vera contain bioactive compounds; the polysaccharides and vitamins present in aloe vera may enhance wound healing and hydration and possess anti-inflammatory effects.

Keywords: Acne vulgaris, Propionibacterium acnes, Staphylococcus epidermidis, Azadirachta indica, Aloe barbadensis Miller, nanoemulsion

I. INTRODUCTION

Acne vulgaris is a relatively common skin disorder affecting teenagers and adults worldwide. Inflammation of the sebaceous glands can cause pimples, blackheads, and, in some cases, scarring.

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Antibiotics and retinoids are examples of synthetic drugs commonly used in conventional treatments. These drugs can cause side effects such as skin irritation, dryness, and resistance to therapy. This has increased interest in safe, effective, and affordable plant-based remedies.

Herbal formulations have garnered considerable attention owing to their bioactive compounds, which demonstrate antimicrobial, anti-inflammatory, and antioxidant properties. Aloe vera and neem (Azadirachta indica) are two promising medicinal plants for the management of acne.

- Aloe vera contains polysaccharides, vitamins, and enzymes that support wound healing, reduce swelling, and help maintain skin moisture. Its soothing properties make it useful for calming acne-prone skin.
- Neem is well known for its antibacterial and antifungal properties. It may help combat Propionibacterium acnes, the bacterium associated with acne, reduce excess oil, and help prevent new breakouts.

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit. It is characterized by comedones, papules, pustules, nodules, and, in severe cases, cysts. It primarily affects adolescents and young adults, with global prevalence estimates ranging from 70% to 90%. Contributing factors include excessive sebum production, follicular hyperkeratinization, colonization by Propionibacterium acnes, and subsequent inflammatory responses. Acne can have both physical and psychological effects, including low self-esteem, anxiety, and depression. This highlights the importance of effective approaches to its management.

Two herbal ingredients, aloe vera gel and neem, were used in this formulation. Aloe vera gel helps maintain skin moisture, manage pimples and acne, and support the treatment of burn wounds. Neem possesses antifungal and anti-inflammatory properties and may also help with scars, pigmentation, redness, and itching of the skin.

Aloe vera is an important ingredient in cosmetic products. It contains nearly 20 amino acids, minerals such as calcium, magnesium, and sodium, as well as enzymes, vitamins, polysaccharides, nitrogen, and other constituents that contribute to its cosmetic value.

Cream is a semisolid emulsion that can be either water-in-oil (w/o) or oil-in-water (o/w). These emulsions are intended for external application. Creams are applied to the skin, where they can remain for an extended period. They can protect the skin from environmental conditions, soothe the skin, and support the management of infections, tanning, and acne.

The main objective of this work is to develop a herbal cream that may help manage acne and skin irritation and improve the overall appearance of the skin. (Rodrigues et al., 2018; Sadurní et al., 2005; Jerobin et al., 2012)

II. LIMITATIONS OF CONVENTIONAL TREATMENTS

Topical retinoids, benzoyl peroxide, salicylic acid, and systemic antibiotics are among the treatments currently available for acne. Although these treatments can be effective, they also have several limitations:

- Long-term use of tetracyclines and macrolides may contribute to antibiotic resistance.
- Retinoids and benzoyl peroxide can cause skin dryness and irritation.

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- Oral antibiotics can cause systemic side effects, such as gastrointestinal disturbances.
- Long-term treatment regimens can be expensive.

These limitations have increased interest in herbal and plant-derived remedies. However, natural origin alone does not establish superior safety or efficacy; these attributes require formulation-specific evidence. (McClements, 2011)

III. ROLE OF HERBAL MEDICINE IN DERMATOLOGY

Herbal medicine has been an important component of traditional healthcare systems such as Ayurveda, Traditional Chinese Medicine, and Unani. Plant-based formulations are increasingly being investigated for dermatological applications because they contain bioactive compounds and may provide multiple therapeutic benefits. Herbs with antibacterial, anti-inflammatory, and antioxidant properties are particularly relevant to acne management. (McClements, 2011; Walker et al., 2015)

Advantages of Nanoemulsions

- The nanosized droplets and large interfacial area of nanoemulsions can facilitate the dissolution, absorption, permeation, and bioavailability of active compounds.
- Encapsulation of herbal bioactives within the nanoemulsion matrix can improve their stability.
- Nanoemulsions can be formulated using biocompatible oils and lipids, which may be well tolerated and readily metabolized.
- A lower dose may reduce adverse effects while maintaining or improving therapeutic efficacy.
- Nanoemulsions have been the focus of extensive global research because of their ability to solubilize and transport both hydrophobic and hydrophilic active compounds and their unique physical properties.
- For topical delivery, their principal relevance is improved solubilization, deposition, and skin permeation; systemic bioavailability benefits depend on the formulation and route and should not be generalized from oral or other non-topical studies.
- Nanoemulsions can provide delivery systems for nutraceuticals and dietary supplements, thereby adding functional value.

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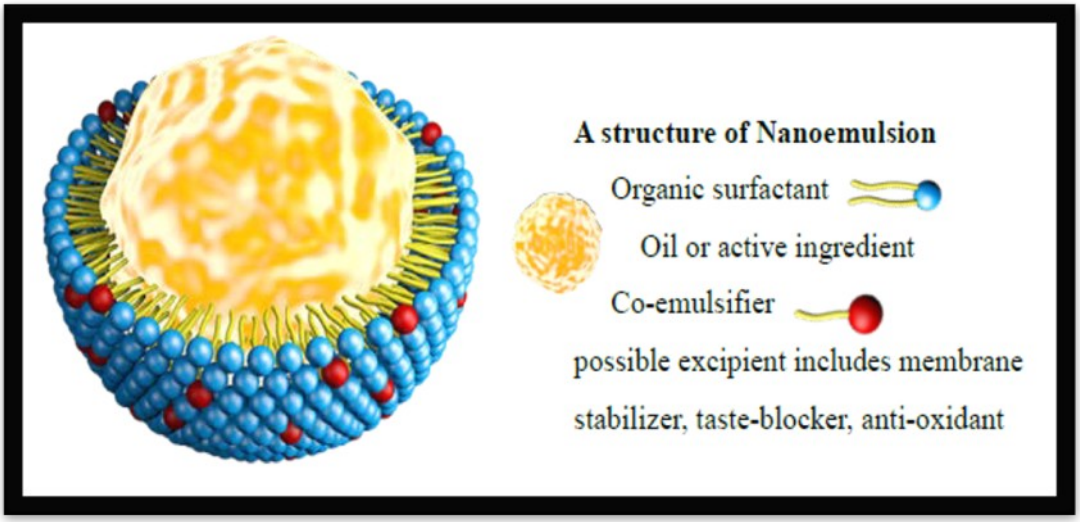


Figure 1. Structure of Nanoemulsion

IV. RATIONALE FOR ALOE VERA–NEEM FORMULATION

Combining aloe vera and neem in a cream may provide complementary effects. Aloe vera can support wound healing, soothe the skin, and provide moisture, whereas neem has antibacterial and anti-inflammatory properties. The gel base facilitates application and spreading. Compared with some conventional treatments, herbal formulations may offer complementary benefits, but reductions in irritation or antimicrobial resistance should not be assumed without comparative clinical evidence. The development of an Aloe vera–neem cream is a promising approach in herbal dermatology and is consistent with the growing interest in natural skincare products. (Ozogul et al., 2017)

Aloe vera and neem (Azadirachta indica) are scientifically justified for use together in a cream-based topical formulation because they possess complementary pharmacological properties and may provide combined benefits. (Al-Adham et al., 2000)

Synergistic Therapeutic Action: Aloe vera is a moisturizing and soothing agent with antioxidant and wound-healing properties. Neem has demonstrated antibacterial, antifungal, and anti-inflammatory activities. When combined, the bioactive compounds aloin and aloesin from aloe vera and azadirachtin and nimbidin from neem may work together to provide protection against acne-associated microorganisms and support skin healing.

Benefits for the Skin: The combination may help reduce redness, swelling, itching, and microbial load on the skin. Neem acts against Propionibacterium acnes and other microorganisms associated with acne and skin infections, while aloe vera may support collagen production and skin hydration. Together, neem and aloe vera may provide complementary benefits for skin care. The formulation may also improve the stability of herbal actives, promote uniform drug release, and provide a cooling effect, which may be

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beneficial for inflamed or acne-prone skin. The natural origin of these ingredients may also improve patient acceptability and adherence. (Jaiswal et al., 2015; Harwansh, Deshmukh, & Rahman, 2019)

In Line with Global Trends: As more consumers choose natural, plant-based skincare products, Aloe vera–neem gel aligns with current market trends emphasizing herbal dermatological solutions that are effective, plant-based, and environmentally friendly. (Yukuyama et al., 2017; Zhang et al., 2015; Harwansh et al., 2017; Yukuyama et al., 2016; Rates, 2001; Gumus et al., 2015)

Main Advantages of Nanoemulsions for Delivering Herbal Drugs

- Better Solubility and Bioavailability: Nanoemulsions can effectively solubilize lipophilic (oil-soluble) herbal extracts, potentially improving their absorption and increasing drug availability.
- Better Stability: These formulations can protect active herbal compounds from degradation by hydrolysis and enzymatic processes, thereby potentially extending their stability.
- High Permeability for Topical Delivery: Nanoemulsions can improve skin penetration in topical and transdermal applications, facilitating the delivery of herbal active ingredients for localized or systemic effects.
- Release and skin deposition can be modulated through formulation composition and droplet characteristics, but sustained or targeted delivery should be demonstrated experimentally rather than assumed from nanoscale droplet size alone.
- Taste masking is mainly relevant to oral formulations and is not a primary advantage of a topical herbal nanoemulsion cream.
- Better Therapeutic Efficacy: Improved bioavailability of herbal drugs may reduce the dose required to achieve the desired therapeutic effect and may lower the risk of adverse effects. (Shu, 1998; Ajazuddin & Saraf, 2010; Piazzini et al., 2017; Aburjai & Natsheh, 2003; Thornfeldt, 2005; Mazumder et al., 2004)

V. GREEN AND SUSTAINABLE CONSIDERATIONS

Herbal medicines and formulations are becoming increasingly important worldwide for the management of various illnesses. There is growing awareness of the constituents of daily diets, their potential health benefits, and their mechanisms of action. Plants contain numerous bioactive compounds that contribute to the therapeutic potential of traditional medicine systems.

Natural remedies have been used to manage a wide range of illnesses because plants contain phytochemicals such as glycosides, tannins, alcohols, and aldehydes. Herbal medicine is often preferred because it is perceived as having fewer side effects and lower toxicity.

People are increasingly exposed to lifestyle-related factors and environmental pollution, which may contribute to various skin disorders. (Ramos-e-Silva & Da Silva Carneiro, 2007; Afaq & Mukhtar, 2006; F'guyer et al., 2003)

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VI. ALOE VERA: MEDICINAL AND DERMATOLOGICAL QUALITIES

Aloe vera (Aloe barbadensis Miller) has been extensively studied for its dermatological applications. The gel contains polysaccharides such as acemannan, which may support wound healing by promoting fibroblast proliferation and collagen production. Aloe vera also contains vitamins A, C, and E, which have antioxidant properties and may help protect against free-radical-induced skin damage. (Aburjai & Natsheh, 2003).

- Anti-inflammatory Activity: Aloe vera may inhibit cyclooxygenase activity and reduce prostaglandin E2 production, thereby helping to reduce redness and swelling.
- Antimicrobial Properties: Numerous studies have reported the inhibitory effects of Aloe vera against Staphylococcus aureus and Propionibacterium acnes.
- Moisturizing Effect: Aloe vera contains mucopolysaccharides that help retain moisture in the skin, improving hydration and flexibility.
- Wound Healing: Aloe vera may promote epithelialization and reduce scarring, making it potentially useful for acne-related scars. Aloe vera gel has also been reported in clinical studies to reduce the number of acne lesions and improve skin condition when applied topically.

VII. NEEM: MEDICINAL AND DERMATOLOGICAL PROPERTIES

Neem (Azadirachta indica) is considered one of the important medicinal plants in Ayurveda. It is often referred to as the “village pharmacy” because of its diverse traditional uses. Neem contains bioactive compounds such as azadirachtin, nimbidin, quercetin, nimbolide, flavonoids, tannins, and polyphenols. These compounds contribute to its antimicrobial, anti-inflammatory, antioxidant, and wound-healing properties. These characteristics make neem useful in skincare, particularly for acne and other skin infections. Neem may reduce bacterial growth on the skin, inhibit fungal infections, reduce inflammation, protect against oxidative damage, and support wound healing. Because of these activities, neem is used in topical herbal products intended for acne, inflammation, and skin infections. (Mireles-Rocha et al., 2002; Naik et al., 2006; Chanchal & Swarnlata, 2008; Čilek et al., 2006; Hu et al., 2011; Sermkaew et al., 2013; Bergonzi et al., 2014)

- Antibacterial Activity: Neem extracts can inhibit acne-associated bacteria, particularly Propionibacterium acnes.
- Antifungal Activity: Neem is active against dermatophytes and Candida species, which may make it useful in managing secondary fungal infections.
- Anti-inflammatory Effects: Nimbidin and quercetin may reduce prostaglandin production and modulate neutrophil activity, thereby reducing inflammation.
- Antioxidant Activity: Flavonoids and polyphenols in neem can scavenge free radicals and may protect skin cells from oxidative damage.

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TABLE 1. COMPARISON OF HERBAL AND SYNTHETIC TREATMENTS

Parameters	Herbal Treatments (Aloe vera, Neem)	Conventional Synthetic Treatments (Benzoyl peroxide, Retinoids, Antibiotics)
Mechanism	Multiple potentially complementary activities, including antimicrobial and anti-inflammatory effects	Established mechanisms including antimicrobial, keratolytic, comedolytic, and anti-inflammatory effects depending on the agent
Speed of action	Often slower or less predictable; evidence is formulation-dependent	Generally better characterized and more predictable for approved therapies
Tolerability	May be favorable in some formulations, but irritation and sensitization remain possible	Irritation, dryness, erythema, and other adverse effects are agent- and dose-dependent
Long-term use	Requires formulation-specific safety and clinical evidence	Established safety/monitoring considerations vary by drug and duration
Resistance	Resistance risk cannot be assumed absent; evidence is limited for standardized herbal combinations	Antibiotic resistance is an important concern with prolonged or inappropriate antibiotic use
Skin-barrier impact	May be supportive or neutral depending on formulation; surfactants/fragrance may irritate	Some agents can disrupt or dry the skin barrier, particularly when overused
Overall suitability	Potential adjunct for mild-to-moderate acne; should complement evidence-based care where appropriate	Selection depends on acne severity, patient factors, and established clinical guidelines

VIII. CRITICAL COMPARATIVE DISCUSSION

The evidence does not support a simple conclusion that herbal nanoemulsion creams are universally superior to conventional acne therapies. Established synthetic treatments generally have stronger clinical evidence, standardized active-ingredient content, and clearer dose–response relationships. In contrast, Aloe vera and neem offer multiple potentially complementary activities, but their efficacy can vary substantially with plant source, extraction method, phytochemical composition, concentration, and formulation. Therefore, comparisons should distinguish pharmacological potential from clinically demonstrated benefit.

The nanoemulsion platform may address several limitations of conventional herbal creams, particularly poor aqueous solubility, chemical instability, and inconsistent skin delivery of selected phytoconstituents. However, smaller droplet size alone does not guarantee improved therapeutic performance. Surfactant concentration, oil composition, interfacial properties, viscosity, pH, droplet-size distribution, and the physicochemical properties of the botanical constituents can all influence release, deposition, and tolerability. A formulation that increases skin permeation may also increase exposure to viable skin cells, so delivery enhancement and safety must be evaluated together.

A further limitation is the scarcity of head-to-head clinical studies comparing standardized Aloe vera–neem nanoemulsion creams with conventional herbal creams or guideline-supported acne treatments. Much of the supporting literature is based on laboratory, ex-vivo, animal, or non-topical nanoemulsion studies. Such evidence is useful for establishing mechanistic plausibility, but it cannot by itself establish clinical superiority. Future comparative studies should use standardized botanical extracts, validated

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analytical methods, clinically relevant endpoints, appropriate controls, and sufficient follow-up to evaluate both efficacy and tolerability.

IX. COSMETOLOGICAL IMPORTANCE OF ALOE VERA

Aloe vera has long been used traditionally for the management of infections and burns. With advances in cosmetology, Aloe vera has become an important ingredient in cosmetic products. It contains nearly 20 amino acids, minerals such as calcium, magnesium, and sodium, as well as enzymes, vitamins, polysaccharides, nitrogen, and other constituents that contribute to its cosmetic value.

The most important cosmetic applications of Aloe vera include:

- Itching and Blisters: Aloe vera may help relieve itching and soothe blisters. Vitamins B1, B2, B6, B12, and C present in aloe may support healthy skin.
- Skin Aging: Aloe vera may support collagen and elastin production. These proteins are important for maintaining skin structure and elasticity.
- Acne: Aloe vera may help reduce acne-related inflammation and the appearance of acne scars. Aloe vera-based cosmetic products may help reduce the severity of acne and support skin health.
- Freshness: Aloe vera may provide a soothing and refreshing effect and may support healthy skin circulation.
- Sunburns: Aloe vera may help soothe the discomfort associated with sunburn. It can be applied topically, and Aloe vera after-sun lotions or fresh plant gel may be used for soothing purposes.
- Moisture: Aloe vera can help soften and moisturize the skin. Many cosmetic products contain Aloe vera for this purpose, and it can be applied after bathing to improve skin softness. Aloe vera may also help reduce the appearance of dark spots and pigmentation. Creams containing Aloe vera may soothe skin rashes, while Aloe vera gels are commonly used to soothe minor burns and cuts. Aloe vera may also support skin regeneration and exhibit antibacterial and antifungal properties. (Akhtar et al., 2016; Sunintaboon et al., 2012; Shen et al., 2011; Wang et al., 2008; Pant et al., 2014; Sugumar et al., 2014; Nagi et al., 2017; Fofaria et al., 2016)

X. COSMETOLOGICAL IMPORTANCE OF NEEM LEAVES

- Supports Collagen Production: Neem leaves contain vitamin C and antioxidant compounds that may support collagen synthesis and help maintain skin firmness and elasticity.
- Lightening of Scars and Spots: Neem preparations are traditionally used for acne, pimples, minor burns, and scars. Its antioxidant and anti-inflammatory properties may help improve the appearance of post-acne marks and uneven skin tone.
- Anti-Acne Activity: Neem leaves possess antimicrobial and anti-inflammatory properties that may help reduce acne-associated microorganisms, redness, and inflammation.
- Antioxidant Activity: Neem contains flavonoids, polyphenols, and other bioactive constituents that can help protect skin from oxidative stress caused by free radicals.
- Anti-Inflammatory Effect: Neem may help soothe irritated and inflamed skin and is traditionally used for conditions associated with redness, itching, and skin irritation.

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- Astringent and Sebum-Control Properties: The astringent nature of neem may help reduce excessive oiliness and support cleansing of oily and acne-prone skin.
- Traditional Ayurvedic Use: Neem has a long history of topical and traditional use in Ayurveda. It is described as having Tikta (bitter) and Kashaya (astringent) properties and is traditionally regarded as a "blood purifier." However, such traditional claims should not be interpreted as evidence of systemic detoxification from topical cosmetic preparations.
- Skin-Protective Potential: Neem may help maintain healthy skin by combining antimicrobial, antioxidant, and soothing effects, making it useful in herbal creams, gels, lotions, face washes, soaps, and other cosmetic formulations.
- Use in Herbal Cosmetics: Neem leaf extracts are commonly considered for incorporation into anti-acne creams, face packs, cleansers, lotions, and other herbal skincare products because of their multifunctional biological properties (Ahmad et al., 2017; Ribeiro et al., 2015; Osanloo et al., 2017; Anjali et al., 2012; Mostafa et al., 2015; Kotta et al., 2012).

TABLE 2. EXCIPIENTS AND HERBAL INGREDIENTS WITH THEIR ROLES

S. No.	Ingredients	Role
1	Aloe vera gel	Anti-aging, anti-inflammatory, moisturizing, and acne- and pimple-reducing properties.
2	Neem	Promotes wound healing and relieves skin dryness, itching, and redness.
3	Beeswax	Emulsifying agent and stabilizer; provides thickness to the cream.
4	Liquid paraffin	Lubricating agent.
5	Borax	Alkaline agent that reacts with the emulsifying agent to form soap.
6	Methyl paraben	Preservative.
7	Rose oil	Fragrance.

XI. EXTRACTION AND CREAM FORMULATION PROCESSES

Aloe vera gel:

Aloe vera gel was prepared from mature, healthy, and fresh Aloe vera leaves. The leaves were collected and washed with distilled water. After drying in a hot-air oven, the outer portion of each leaf was cut lengthwise using a sterile knife. The Aloe vera gel, consisting of colourless parenchymatous tissue, was then removed using the sterile knife. The gel was filtered through muslin cloth to remove fibres and other

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unwanted materials. The resulting clear filtrate was used in the formulation. (Harwansh, Deshmukh, Barkat, et al., 2019; Szakács et al., 2006; B. P. Sahu et al., 2016; Rose, 1999; Bajerski et al., 2016; P. Sahu et al., 2017)

- **Neem leaves:**

Neem leaves were collected, washed with distilled water, and dried in a hot-air oven. After drying, the leaves were ground into a powder. Five grams of neem leaf powder were processed at a

temperature of 80-100 °C. Dimethyl sulfoxide was added to a volumetric flask, and the mixture was shaken for three days using a REMI RSB-12 mechanical shaker. The solution was then heated

in a water bath at 80-100 °C until the volume was reduced to 20 mL and subsequently filtered through muslin cloth to remove impurities. The clear filtrate, or neem leaf extract, was then used

in the formulation. (Mahato, 2017; Greish, 2007; Cho et al., 2014; Li et al., 2017)



Figure 2. Aloe vera



Figure 3. Neem

Formulation of Cream: (METHODOLOGY)

- Place liquid paraffin and beeswax in a borosilicate glass beaker and heat them to 75 °C. Maintain this temperature to prepare the oil phase.
- Place borax, methylparaben, and distilled water in a second beaker and heat them to 75 °C to dissolve the borax and methylparaben and obtain a clear solution (aqueous phase).
- Slowly add the aqueous phase to the hot oil phase while mixing.
- Add measured quantities of Aloe vera gel and neem extract. Stir the mixture until a smooth cream is obtained.
- Add a few drops of rose oil to provide fragrance.
- Place the cream on a slab and incorporate a few drops of distilled water, if required.
- To obtain a smooth cream and ensure uniform mixing of all ingredients, mix the cream on the slab using a geometric dilution pattern.
- This method is known as the slab technique or extemporaneous method for cream preparation. (Muhamad et al., 2018; Neubert, 2011; WEISS, 2011)

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TABLE 3. FORMULA FOR 100 mg OF CREAM

Ingredients	Function	Quantity (mg)
Aloe vera gel	Active (soothing, moisturizing)	20
Neem leaves extract	Active (antibacterial)	10
Beeswax	Thickening agent	8
Liquid paraffin	Oil phase (emollient)	15
Borax	Emulsifying agent	1
Methyl paraben	Preservative	0.2
Rose oil	Fragrance	0.3
Distilled water	Vehicle (aqueous phase)	45.5
Total		100



Figure 4. Formulation Process

XII. TOXICITY, SAFETY, AND REGULATORY CONSIDERATIONS

12.1 Toxicity and Safety Considerations

Potential local safety concerns include erythema, burning, itching, dryness, irritation, and allergic or sensitization reactions. Surfactants and co-surfactants may contribute to irritation when used at excessive concentrations, and fragrance components such as rose oil may also require sensitization assessment. For a topical product intended for acne-prone or inflamed skin, evaluation should therefore include skin irritation and sensitization testing, together with assessment of formulation pH and compatibility with the skin barrier. The manuscript itself recognizes that formulation components can contribute to irritation and that their concentrations require careful optimization.

Botanical quality is another critical safety issue. Plant extracts can vary in chemical composition because of differences in species, geographical origin, harvesting, processing, storage, and extraction procedures. Standardization should therefore include authenticated plant material, defined extraction parameters, phytochemical characterization, marker-compound estimation, and control of contaminants such as heavy metals, pesticide residues, and microbial contamination. Microbiological quality is especially

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important for creams containing aqueous Aloe vera gel. Appropriate preservative efficacy and microbiological-limit testing should be established for the finished product.

A staged safety-testing strategy is recommended before clinical or commercial use: first characterize the raw materials and formulation; then assess physicochemical and microbiological quality; followed by in-vitro cytotoxicity and skin irritation/sensitization studies where appropriate; and finally conduct suitable in-vivo and human safety studies according to the intended regulatory category and claims. Importantly, the finished formulation should be evaluated rather than assuming that safety of individual ingredients automatically establishes safety of the combination.

12.2 Regulatory Considerations

For an Aloe vera–neem nanoemulsion marketed as a cosmetic, the manufacturer should establish a documented quality and safety package covering raw-material specifications, botanical identity, extraction controls, microbiological quality, preservative effectiveness, physical stability, packaging compatibility, finished-product specifications, and appropriate safety substantiation. If therapeutic claims are made, the regulatory pathway may differ from that for a cosmetic product; therefore, claims should be defined early during product development.

Nanoemulsion-specific regulatory assessment should also consider droplet size distribution, polydispersity, zeta potential where relevant, physical stability, changes during storage, and the possibility that the nanostructure alters dermal exposure. These parameters are particularly relevant because the manuscript identifies droplet size, PDI, zeta potential, viscosity, pH, spreadability, content, and stability as key quality characteristics.

Internationally, regulatory expectations similarly emphasize safety substantiation rather than assuming that a product is safe because its ingredients are natural. For example, the U.S. FDA states that cosmetic manufacturers are responsible for ensuring product safety and maintaining adequate safety substantiation; its guidance also notes that the complete formulation should be considered when substantiating safety.

XIII. EXPECTED OUTCOMES, RESEARCH GAPS, AND FUTURE PERSPECTIVES

1. Enhanced Skin Penetration
   Nanoemulsion-loaded herbal creams are expected to improve the penetration and deposition of herbal bioactive compounds through the stratum corneum because of their small droplet size and ability to interact with skin lipids.
2. Improved Solubility and Bioavailability
   Nanoemulsions are expected to increase the solubility and effective availability of poorly water-soluble phytoconstituents, thereby improving their therapeutic performance after topical application.
3. Improved Stability of Herbal Constituents
   Encapsulation within the nanoemulsion system may protect sensitive herbal constituents from degradation and improve the physical stability of the formulation. This is particularly relevant for volatile oils and oxidation-sensitive phytochemicals.

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4. Enhanced Therapeutic Activity
   The improved delivery of herbal constituents is expected to enhance their antimicrobial, antioxidant, anti-inflammatory, wound-healing, and anti-acne activities, depending on the selected herbal ingredients.
5. Controlled and Prolonged Drug Release
   Nanoemulsion-based creams may improve residence or skin deposition compared with conventional herbal creams, but the magnitude and duration of any release or retention advantage should be demonstrated using validated in-vitro, ex-vivo, or in-vivo studies.
6. Better Patient Acceptability
   The incorporation of nanoemulsions into cream bases is expected to produce formulations with good spreadability, moisturizing properties, skin feel, and ease of application, potentially improving patient compliance.
7. Potential Improvement in Tolerability
   Proper optimization of oil, surfactant, and co-surfactant concentrations may improve topical tolerability. However, surfactant concentration and formulation composition must be carefully optimized because nanoemulsion components themselves can contribute to skin irritation.
8. Improved Physicochemical Characteristics
   Optimized formulations are expected to demonstrate desirable droplet size, polydispersity index (PDI), zeta potential, viscosity, pH, spreadability, drug/extract content, and physical stability. These are important parameters for evaluating herbal nanoemulsions.
9. Potential for Treatment of Various Skin Disorders
   The review is expected to establish the potential application of herbal nanoemulsion creams in conditions such as acne, inflammation, microbial skin infections, wounds, psoriasis, and other dermatological disorders.
10. Identification of Research Gaps and Future Opportunities
    The review should identify important gaps involving standardization of herbal extracts, long-term stability, toxicity, scale-up, regulatory requirements, and clinical validation. Recent systematic evidence also indicates that heterogeneity among studies and limited high-quality clinical evidence remain important barriers to translation.

XIV. Limitations of the Current Evidence

Interpretation of the available evidence is limited by heterogeneity in botanical materials, extraction procedures, nanoemulsion composition, evaluation methods, and study designs. The limited number of standardized clinical studies means that reported improvements in permeability, stability, or antimicrobial activity should be interpreted as formulation-dependent findings rather than proof of clinical superiority.

XV. CONCLUSION

Herbal creams formulated with nanoemulsions represent a promising approach to topical delivery because nanoscale droplets can improve the solubilization, stability, skin deposition, and delivery of

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selected herbal bioactives. However, these advantages are formulation-dependent and should not be interpreted as evidence of superior clinical efficacy or safety over conventional acne treatments. The available literature remains heterogeneous, with substantial variation in plant material, extraction procedures, nanoemulsion composition, characterization methods, and study models. Direct clinical comparisons of standardized Aloe vera–neem nanoemulsion creams with established acne therapies are limited. Consequently, the current evidence supports further development and investigation rather than definitive claims of therapeutic superiority. Future work should prioritize authenticated and standardized botanical materials, validated analytical methods, complete-formulation toxicology, microbiological quality, long-term stability, dermal permeation and retention studies, scale-up, and well-designed clinical trials. Regulatory classification and product claims should also be defined early so that quality, safety, and efficacy requirements are addressed throughout development.

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AUTHOR CONTRIBUTIONS

Sehrabpreet Singh: Conceptualization and overall development of the review; formulation of the research objectives and scope; comprehensive literature search on herbal nanoemulsions, topical drug delivery, Aloe vera, neem, and herbal cream formulations; collection, organization, and critical interpretation of the scientific literature; development of the formulation approach; analysis of extraction and cream preparation methods; assessment of physicochemical and stability-related parameters; preparation of the initial manuscript; integration of the toxicity, safety, regulatory, and research-gap sections; critical revision of the manuscript; and coordination of the overall work.

Amanpreet Singh: Conducted an extensive literature search related to herbal medicines, herbal dermatology, Aloe vera and neem, their pharmacological and cosmetological properties, and their applications in topical formulations; contributed to the compilation and organization of scientific information; reviewed literature concerning conventional and herbal approaches for acne management; contributed to the preparation of sections describing the therapeutic properties and dermatological applications of the selected herbal ingredients; assisted in formulation-related literature collection; critically reviewed the manuscript and contributed to its revision.

Shruti: Contributed to the literature review and scientific compilation related to nanoemulsion-based drug delivery systems, their advantages, formulation principles, physicochemical characteristics, stability, and potential applications in topical delivery; assisted in reviewing information related to herbal bioactive compounds and their incorporation into nanoemulsion and cream-based systems; contributed to the organization and interpretation of formulation and evaluation parameters; assisted in preparation and editing of the manuscript; reviewed the scientific content for consistency and clarity.

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Gaurav Saini: Contributed to the critical evaluation of the scientific literature with particular emphasis on toxicity, safety, tolerability, and regulatory considerations associated with herbal and nanoemulsion-based topical formulations; reviewed potential skin irritation, sensitization, microbiological safety, botanical standardization, formulation-related risks, and long-term safety considerations; contributed to the regulatory discussion concerning cosmetic classification, quality and safety requirements, product claims, and nanoemulsion-specific quality attributes; assisted in identifying research and regulatory gaps; critically revised the manuscript and strengthened its scientific interpretation.

Manjot Kaur: Contributed to the review and compilation of literature concerning the medicinal and Cosmetological properties of Aloe vera and neem; evaluated their reported antimicrobial, anti-inflammatory, antioxidant, moisturizing, and wound-healing activities; contributed to the description of extraction procedures for Aloe vera gel and neem leaf extract; assisted in reviewing the composition and functional roles of herbal ingredients and excipients used in cream formulation; contributed to the organization of formulation-related information and critically reviewed the relevant sections of the manuscript.

Sanjeev Kumar: Contributed to the evaluation of formulation and drug-delivery aspects of herbal nanoemulsion-loaded creams; reviewed literature concerning formulation composition, preparation techniques, physicochemical characteristics, stability, spreadability, viscosity, pH, droplet characteristics, and related quality attributes; assisted in the compilation and verification of references; contributed to interpretation and organization of scientific information; critically reviewed the manuscript for technical accuracy, coherence, and consistency; and participated in manuscript editing and revision.

Gurleen Kaur: Contributed to literature screening and compilation of evidence concerning the current status and future potential of herbal nanoemulsion-based topical formulations; assisted in identifying research gaps related to standardization, toxicity, long-term stability, scale-up, clinical validation, and regulatory requirements; contributed to the preparation of the sections concerning expected outcomes, research gaps, future perspectives, and conclusion; critically reviewed the manuscript for scientific clarity, organization, and completeness; and participated in proofreading and final revision.

All Authors: All authors contributed to the critical review and revision of the manuscript, approved the final version for submission, and agreed to be accountable for the accuracy, integrity, and overall content of the work.

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