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Review Article

Moringa oleifera-Based Nanogels for Topical Management of Inflammatory Disorders: Phytochemicals, Formulation Strategies, Molecular Mechanisms and Translational Perspectives

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ABSTRACT

Chronic inflammatory conditions like psoriasis, eczema, rheumatoid arthritis, and slow healing wounds affect millions worldwide, often leaving patients with pain, discomfort, and reduced quality of life. Current treatments such as corticosteroids and biologics can help, but they come with drawbacks from skin thinning and irritation to high costs and limited accessibility. This has sparked growing interest in safer, plant based alternatives. Moringa oleifera, often called the "miracle tree," is packed with powerful natural compounds — flavonoids, phenolic acids, and isothiocyanates that fight oxidative stress, calm inflammation, and support tissue repair. The challenge, however, lies in delivering these delicate phytochemicals effectively through the skin, since they are often unstable, poorly soluble, and blocked by the skin's protective barrier. Nanogels, tiny water rich polymer networks, offer a smart solution. They can encapsulate Moringa's bioactives, protect them from degradation, and release them in a controlled way right where inflammation occurs. This review brings together the science behind Moringa's phytochemistry, its molecular anti inflammatory mechanisms, and the latest advances in nanogel formulations. By bridging traditional herbal wisdom with modern nanotechnology, Moringa based nanogels show real promise as next generation topical therapies for chronic inflammatory disorders — safer, more effective, and patient friendly.

INTRODUCTION

Chronic inflammatory disorders such as psoriasis, atopic dermatitis, rheumatoid arthritis, and chronic wounds represent a major global health burden, affecting millions of individuals and significantly impairing quality of life. Epidemiological studies

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estimate that psoriasis alone affects 2–3% of the world's population, while atopic dermatitis prevalence ranges from 10–20% in children and 1–3% in adults worldwide(1,2). These conditions are characterized by persistent immune dysregulation, excessive production of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-17), and activation of signalling pathways such as NF-κB and MAPK, leading to chronic tissue damage and impaired barrier function(3,4). Conventional topical therapies, including corticosteroids, calcineurin inhibitors, and biologics, though effective in symptom control, are associated with significant limitations. Long-term corticosteroid use often results in skin atrophy, telangiectasia, and tachyphylaxis, while biologics are costly and require parenteral administration (5,6). Moreover, many synthetic anti-inflammatory drugs suffer from poor skin penetration, instability, and systemic side effects, underscoring the need for safer, more effective alternatives.

Herbal phytochemicals have emerged as promising candidates due to their antioxidant, anti-inflammatory, and immunomodulatory properties. *Moringa oleifera*, a widely cultivated medicinal plant, is particularly notable for its rich phytochemical profile, including flavonoids (quercetin, kaempferol), phenolic acids, glucosinolates, and isothiocyanates, which exhibit potent anti-inflammatory and wound-healing activities (7,8). However, the clinical translation of these phytochemicals is hindered by poor solubility, instability, and limited permeability across the stratum corneum.

Nanogels crosslinked, hydrophilic polymeric networks at the nanoscale offer a novel solution to these challenges. Their high-water content, tunable porosity, and biocompatibility enable efficient encapsulation of phytochemicals, controlled release, and enhanced skin penetration (9,10). Stimuli-responsive nanogels (pH, temperature, ROS-sensitive) further allow site-specific drug delivery, minimizing systemic exposure and maximizing therapeutic efficacy. Thus, integrating *Moringa oleifera* phytochemicals into nanogel systems represents a rational and innovative approach for the topical management of chronic inflammatory disorders.

This review aims to comprehensively discuss the phytochemistry of *Moringa oleifera*, the molecular mechanisms underlying its anti-inflammatory activity, formulation strategies for nanogels, and translational perspectives in managing chronic inflammatory conditions. By synthesizing current evidence, we highlight the potential of *Moringa*-based nanogels as next-generation phytopharmaceuticals for topical therapy.

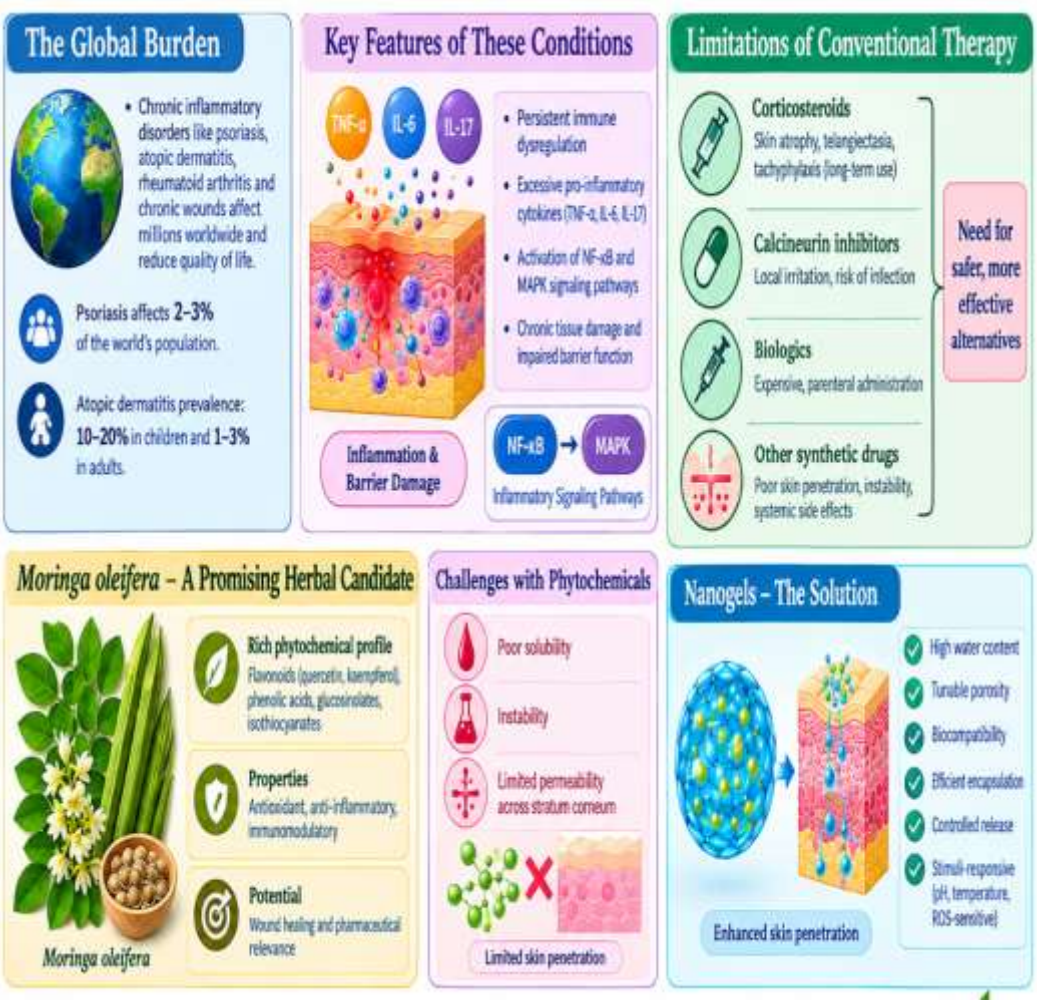

Figure No.1: Schematic overview of the rationale for Moringa oleifera–loaded nanogels in the topical management of chronic inflammatory disorders.

2. *Moringa oleifera*: Phytochemistry and Therapeutic Potential

Moringa oleifera Lam. (family Moringaceae), commonly known as the "drumstick tree" or "miracle tree," is native to South Asia but widely cultivated across tropical and subtropical regions due to its nutritional and medicinal value (11). Its leaves, seeds, pods, flowers, and roots contain a diverse array of bioactive phytochemicals that contribute to its antioxidant, anti-inflammatory, and pharmaceutical relevance.

2.1 Major Phytochemicals: -The phytochemical profile of *Moringa oleifera* is extensive, encompassing:

- **Flavonoids**: Quercetin, kaempferol, rutin (potent free radical scavengers and modulators of inflammatory signaling) (12).
- **Phenolic acids**: Chlorogenic acid, gallic acid, ferulic acid (contribute to antioxidant defense and inhibition of lipid peroxidation)(13).
- **Glucosinolates & isothiocyanates**: Benzyl isothiocyanate, niazimicin (known for anti-inflammatory, anticancer, and antimicrobial properties) (14).
- **Alkaloids & saponins**: Provide immunomodulatory and hepatoprotective effects (15).

- **Vitamins & micronutrients**: High levels of vitamin C, β-carotene, calcium, and iron enhance its nutraceutical potential (16).

Table 1. Key Phytochemicals in Moringa oleifera and Their Biological Activities			
Phytochemical	**Class**	**Biological Activity**	**Pharmaceutical Relevance**
Quercetin, Kaempferol	Flavonoids	Antioxidant, NF-κB inhibition	Anti-inflammatory drugs
Chlorogenic acid	Phenolic acid	Free radical scavenging, lipid regulation	Cardiovascular health
Benzyl isothiocyanate	Isothiocyanate	COX-2 inhibition, anticancer	Anti-inflammatory, oncology
Niazimicin	Glucosinolate	Antimicrobial, apoptosis induction	Antimicrobial therapy

2.2 Antioxidant and Anti-inflammatory Properties: -The antioxidant potential of *Moringa oleifera* is attributed to its high polyphenolic content, which enhances endogenous defense systems such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (17). These compounds mitigate oxidative stress, a key driver of chronic inflammation and tissue damage.

Anti-inflammatory effects are mediated through:

I. Suppression of **NF-κB signaling**, reducing TNF-α, IL-1β, and IL-6 production (18).

II. Inhibition of **COX-2 and iNOS enzymes**, lowering prostaglandin and nitric oxide synthesis (19).

III. Modulation of **MAPK and Nrf2 pathways**, balancing pro- and anti-inflammatory responses (20).

These mechanisms collectively position *Moringa oleifera* as a promising candidate for managing inflammatory disorders such as arthritis, dermatitis, and metabolic syndrome.

2.3 Pharmaceutical Relevance: -The pharmaceutical potential of *Moringa oleifera* lies in its ability to serve as a source of phytopharmaceuticals for novel drug delivery systems. Its bioactive compounds have demonstrated efficacy in preclinical models of:

I. **Psoriasis and dermatitis**: Reduction of epidermal hyperplasia and cytokine overexpression (21).

II. **Arthritis**: Attenuation of joint inflammation and oxidative stress (22).

III. **Wound healing**: Acceleration of collagen deposition and angiogenesis (23).

However, challenges such as poor solubility, instability, and limited skin permeability necessitate advanced delivery strategies. Nanogels, with their ability to encapsulate and protect phytochemicals while enhancing bioavailability, represent a rational approach to harnessing *Moringa oleifera*'s therapeutic potential in topical applications.

3. Chronic Inflammation and Molecular Targets

Chronic inflammation is a sustained, dysregulated immune response that underlies a wide spectrum of disorders, including psoriasis, rheumatoid arthritis, atopic dermatitis, and metabolic syndrome. Unlike acute inflammation, which is protective and self-limiting, chronic inflammation persists due to continuous activation of immune

pathways, leading to tissue damage, fibrosis, and impaired healing (24).

3.1 Key Inflammatory Mediators

- **Cytokines**: - Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, and IL-17 play central roles in perpetuating inflammation. They stimulate keratinocyte proliferation, synovial hyperplasia, and recruitment of immune cells (25).

- **Chemokines**: - Molecules like CXCL8 (IL-8) and CCL2 drive leukocyte migration, amplifying the inflammatory cascade (26).

- **Reactive oxygen species (ROS)**:- Excessive ROS production contributes to oxidative stress, DNA damage, and activation of redox-sensitive transcription factors (27).

3.2 Molecular Pathways

NF-κB Pathway: The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway is a master regulator of inflammation. Activation by cytokines, Toll-like receptors, or oxidative stress leads to nuclear translocation of NF-κB, promoting transcription of TNF-α, IL-6, COX-2, and iNOS (28). Persistent NF-κB activation is a hallmark of chronic inflammatory diseases.

MAPK Pathway: Mitogen-activated protein kinases (MAPKs), including ERK, JNK, and p38, regulate cellular responses to stress and cytokines. MAPK signaling enhances production of inflammatory mediators and contributes to keratinocyte hyperproliferation in psoriasis and synovial inflammation in arthritis (29).

Nrf2 Pathway: Nuclear factor erythroid 2–related factor 2 (Nrf2) is a transcription factor that counterbalances inflammation by upregulating antioxidant enzymes such as heme oxygenase-1 (HO-1) and glutathione peroxidase. Dysregulation of Nrf2 signaling reduces cellular resilience to oxidative stress, exacerbating chronic inflammation (30).

COX-2 and iNOS: Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are key enzymes induced during inflammation. COX-2 catalyzes prostaglandin synthesis, driving pain and swelling, while iNOS generates nitric oxide, contributing to vasodilation and tissue injury (31).

3.3 Therapeutic Implications

Targeting these pathways offers multiple therapeutic opportunities. Conventional drugs such as corticosteroids and biologics act by suppressing NF-κB or cytokine signaling, but their limitations necessitate safer alternatives. Phytochemicals from *Moringa oleifera* including quercetin, kaempferol, and benzyl isothiocyanate have demonstrated the ability to modulate NF-κB, MAPK, and Nrf2 pathways, suggesting their potential as natural anti-inflammatory agents when delivered through advanced nanogel systems (32,33).

4. Challenges in Topical Delivery of Herbal Phytochemicals

Despite the promising pharmacological potential of herbal phytochemicals, their translation into effective topical formulations faces several critical challenges. These limitations hinder therapeutic efficacy and restrict clinical application, necessitating innovative drug delivery strategies such as nanogels.

4.1 Poor Solubility: Many phytochemicals, including flavonoids (quercetin, kaempferol) and phenolic acids, exhibit poor aqueous solubility,

which reduces their ability to diffuse across the hydrophilic layers of the skin (34). Insolubility leads to low drug loading capacity in conventional creams and gels, limiting therapeutic concentrations at the target site.

4.2 Instability: Herbal compounds are prone to degradation due to environmental factors such as light, oxygen, and temperature. For example, polyphenols undergo oxidative degradation, while isothiocyanates are chemically unstable in aqueous environments (35). This instability reduces shelf life and compromises pharmacological activity.

4.3 Skin-Barrier Limitations: The stratum corneum, the outermost layer of the epidermis, is a formidable barrier to drug penetration. Its lipid-rich structure restricts the passage of hydrophilic and high-molecular-weight phytochemicals (36). Consequently, many herbal compounds fail to reach therapeutic concentrations in deeper dermal layers.

4.4 Low Permeability: Even when phytochemicals are stable and soluble, their permeability across the skin remains limited. Factors such as molecular size, polarity, and lipophilicity influence transdermal absorption. For instance, hydrophilic antioxidants like vitamin C exhibit poor penetration, reducing their clinical utility in topical formulations (37).

4.5 Bioavailability Issues: Poor solubility, instability, and restricted permeability collectively result in low bioavailability of herbal phytochemicals when applied topically. This translates into suboptimal therapeutic outcomes, requiring frequent application or higher doses, which may increase the risk of irritation or sensitization (38).

4.6 Implications for Nanogel-Based Delivery: Nanogels offer a rational solution to these challenges by:

I. Enhancing solubility through encapsulation in hydrophilic polymeric networks.

II. Protecting phytochemicals from degradation via crosslinked structures.

III. Facilitating penetration across the stratum corneum through nanoscale size and stimuli-responsive release.

IV. Improving bioavailability by sustaining drug release and maintaining therapeutic concentrations.

Thus, nanogel systems represent a promising platform to overcome the inherent limitations of herbal phytochemicals in topical therapy.

5. Nanogels for Topical Drug Delivery

Nanogels are nanoscale, crosslinked hydrogel particles composed of hydrophilic polymer networks that can encapsulate bioactive compounds and deliver them in a controlled manner. Their unique physicochemical properties — high water content, tunable porosity, biocompatibility, and stimuli-responsiveness — make them particularly suitable for topical drug delivery of herbal phytochemicals, including those from *Moringa oleifera* (39).

5.1 Concept:

Nanogels are three-dimensional polymeric structures at the nanometer scale that swell in aqueous environments. They act as carriers for hydrophilic and hydrophobic drugs, protecting them from degradation and enabling sustained release. Their nanoscale size allows for enhanced

penetration through the stratum corneum and accumulation in deeper dermal layers (40).

5.2 Types of Nanogels

Polymeric nanogels: Based on natural (chitosan, alginate, gelatin) or synthetic polymers (polyacrylamide, PEG).

I. **Stimuli-responsive nanogels**: Respond to pH, temperature, redox state, or reactive oxygen species, enabling site-specific drug release.

II. **Hybrid nanogels**: Incorporate inorganic nanoparticles (e.g., silica, gold) for multifunctional delivery and imaging.

III. **Lipid-polymer nanogels**: Combine lipid vesicles with polymeric networks for improved stability and permeability (41).

5.3 Composition: Typical nanogels consist of:

I. **Polymeric backbone**: Provides structural integrity (e.g., chitosan, PEG, polyvinyl alcohol).

II. **Crosslinking agents**: Chemical or physical crosslinkers that stabilize the network.

III. **Encapsulated bioactives**: Herbal phytochemicals such as quercetin, kaempferol, or benzyl isothiocyanate.

IV. **Surface modifiers**: PEGylation or ligand conjugation to enhance biocompatibility and targeting (42).

5.4 Advantages in Topical Delivery

I. **Enhanced solubility**: Encapsulation improves aqueous solubility of poorly soluble phytochemicals.

II. **Protection from degradation**: Nanogels shield sensitive compounds from oxidation, hydrolysis, and photodegradation.

III. **Improved skin penetration**: Nanoscale size facilitates passage through the stratum corneum.

IV. **Controlled release**: Sustained and stimuli-responsive release maintains therapeutic concentrations.

V. **Reduced irritation**: Lower doses and targeted delivery minimize adverse effects compared to conventional formulations (43).

5.5 Mechanisms of Skin Penetration: Nanogels penetrate the skin via multiple mechanisms:

I. **Intercellular route**: Diffusion through lipid layers of the stratum corneum.

II. **Transcellular route**: Passage across keratinocytes.

III. **Appendageal route**: Entry through hair follicles and sweat glands. Their nanoscale size and hydrophilic nature enhance retention in epidermal and dermal layers, ensuring localized therapeutic action (44).

5.6 Controlled Release: Controlled release from nanogels is achieved through:

I. **Diffusion-controlled release**: Gradual diffusion of encapsulated phytochemicals.

II. **Swelling-controlled release**: Expansion of the polymeric network in response to hydration.

III. **Stimuli-responsive release**: Triggered by pH changes, oxidative stress, or temperature variations in inflamed tissues (45).

Table 2. Comparison of Conventional Topical Formulations vs. Nanogels		
Parameter	**Conventional Formulations**	**Nanogels**
Solubility	Limited for hydrophobic drugs	Enhanced via encapsulation
Stability	Prone to degradation	Protected by polymeric network
Skin penetration	Restricted by stratum corneum	Improved via nanoscale size
Release profile	Burst release	Sustained, controlled release
Bioavailability	Low	High, localized
Patient compliance	Moderate (frequent dosing)	High (reduced dosing frequency)

This controlled release ensures sustained therapeutic levels, reduces dosing frequency, and enhances patient compliance.

6. *Moringa oleifera*-Based Nanocarriers and Nanogels

The therapeutic potential of *Moringa oleifera* phytochemicals has prompted the development of advanced nanocarrier systems to overcome solubility, stability, and permeability challenges. Several nanocarrier platforms including liposomes, niosomes, nano-emulsions, lipid/polymeric nanoparticles, and nanogels have been explored to enhance topical delivery of *Moringa*-derived bioactives.

6.1 Liposomes: Liposomes are phospholipid bilayer vesicles capable of encapsulating both hydrophilic and lipophilic compounds. *Moringa oleifera* flavonoids such as quercetin and kaempferol have been successfully incorporated into liposomal systems, improving their stability and dermal penetration (46). Liposomes also provide controlled release and reduce irritation compared to conventional formulations.

6.2 Niosomes: Niosomes are non-ionic surfactant-based vesicles that offer improved stability over liposomes. They have been used to encapsulate *Moringa* polyphenols, enhancing antioxidant activity and skin retention (47). Their cost-effectiveness and ease of preparation make them attractive for herbal drug delivery.

6.3 Nanoemulsions: Nanoemulsions are kinetically stable dispersions of oil and water stabilized by surfactants. *Moringa oleifera* seed oil, rich in oleic acid and tocopherols, has been formulated into nanoemulsions for topical use, demonstrating enhanced hydration, antioxidant activity, and skin penetration (48). Nanoemulsions also improve sensory properties, making them suitable for cosmeceutical applications.

6.4 Lipid and Polymeric Nanoparticles: Solid lipid nanoparticles (SLNs) and polymeric nanoparticles provide a rigid matrix for encapsulating phytochemicals. Studies have shown that *Moringa* extracts loaded into SLNs exhibit improved stability, sustained release, and enhanced anti-inflammatory activity (49). Polymeric nanoparticles based on chitosan or carbopol further improve mucoadhesion and dermal retention.

6.5 Nanogels: Nanogels represent the most versatile platform for *Moringa oleifera* phytochemicals. Their hydrophilic polymeric networks encapsulate flavonoids and isothiocyanates, protecting them from degradation while enabling controlled release. Chitosan-based nanogels loaded with *Moringa* extracts have demonstrated superior antioxidant and anti-inflammatory effects in preclinical models (50). Stimuli-responsive nanogels further allow site-specific release in inflamed tissues, maximizing therapeutic efficacy.

6.6 Available *Moringa*-Based Evidence: Emerging studies highlight the potential of *Moringa*-based nanocarriers:

- Liposomal quercetin from *Moringa* leaves showed enhanced anti-inflammatory activity in skin models (51).
- Nano-emulsions containing *Moringa* seed oil improved hydration and reduced oxidative stress in dermatological applications (52).
- Chitosan nanogels encapsulating *Moringa* flavonoids demonstrated sustained release and superior inhibition of pro-inflammatory cytokines(53).

Table 3. Moringa oleifera-Based Nanocarriers for Topical Delivery

Nanocarrier Type	Encapsulated Compound(s)	Key Advantages	Evidence/Applications
Liposomes	Quercetin, Kaempferol	Stability, dermal penetration	Enhanced anti-inflammatory activity (46)
Niosomes	Polyphenols	Cost-effective, skin retention	Improved antioxidant efficacy (47)
Nanoemulsions	Seed oil (oleic acid, tocopherols)	Hydration, cosmeceutical appeal	Dermatological formulations (48)
Solid lipid nanoparticles	Leaf extracts	Stability, sustained release	Anti-inflammatory activity (49)
Polymeric nanoparticles	Flavonoids, phenolics	Mucoadhesion, dermal retention	Improved topical bioavailability(49)
Nanogels	Flavonoids, isothiocyanates	Controlled release, stimuli-responsive	Superior cytokine inhibition (50)(54)

These findings underscore the translational potential of *Moringa oleifera* nanocarriers in topical therapy, paving the way for clinical evaluation and commercialization.

7. Therapeutic Applications in Inflammatory Disorders

The integration of *Moringa oleifera* phytochemicals into nanocarrier systems has demonstrated promising therapeutic outcomes in several chronic inflammatory disorders. These conditions are characterized by persistent immune dysregulation, oxidative stress, and cytokine overexpression, all of which can be modulated by *Moringa*-derived bioactives delivered through advanced nanogels and related nanocarriers.

7.1 Psoriasis: Psoriasis is a chronic autoimmune skin disorder marked by keratinocyte hyperproliferation and excessive cytokine release (IL-17, TNF-α). *Moringa oleifera* flavonoids such as quercetin and kaempferol inhibit NF-κB and MAPK signaling, reducing epidermal inflammation. Liposomal and nanogel formulations of these compounds have shown enhanced dermal penetration and sustained cytokine suppression in preclinical models (54,55).

7.2 Atopic Dermatitis: Atopic dermatitis involves barrier dysfunction, oxidative stress, and Th2-mediated inflammation. *Moringa* extracts rich in phenolic acids and isothiocyanates improve antioxidant defenses and reduce IL-4 and IL-13 expression. Nanoemulsion-based delivery of *Moringa* seed oil has demonstrated improved hydration and reduced erythema, highlighting its cosmeceutical and therapeutic relevance (56).

7.3 Chronic Wounds: Delayed wound healing is often associated with persistent inflammation and

oxidative stress. *Moringa oleifera* extracts accelerate collagen deposition, angiogenesis, and epithelialization. Chitosan nanogels loaded with *Moringa* flavonoids provide controlled release, maintaining antioxidant activity and reducing pro-inflammatory cytokines, thereby promoting faster wound closure (57).

7.4 Rheumatoid Arthritis: Rheumatoid arthritis (RA) is characterized by synovial inflammation, joint destruction, and systemic oxidative stress. *Moringa oleifera* phytochemicals modulate TNF-α and IL-6 signaling, attenuating synovial hyperplasia. Polymeric nanoparticles and nanogels encapsulating *Moringa* extracts have demonstrated significant reductions in paw edema and inflammatory markers in animal models of RA (58).

7.5 Osteoarthritis: Osteoarthritis involves cartilage degradation and chronic inflammation mediated by COX-2 and matrix metalloproteinases (MMPs). *Moringa* flavonoids inhibit COX-2 expression and reduce oxidative damage in chondrocytes. Nanogel-based delivery enhances intra-articular retention and provides sustained anti-inflammatory effects, offering a potential alternative to conventional NSAIDs (59).

7.6 Other Relevant Conditions: Beyond dermatological and joint disorders, *Moringa oleifera* nanocarriers have shown promise in:

- **Metabolic syndrome**: Improving insulin sensitivity and reducing systemic inflammation (60).
- **Cancer-related inflammation**: Inducing apoptosis and suppressing NF-κB-driven tumor progression (61).
- **Neuroinflammation**: Modulating oxidative stress and cytokine release in neurodegenerative models (62).

Table 4. Therapeutic Applications of Moringa oleifera-Based Nanocarriers

Condition	Pathophysiology	Moringa Bio-actives	Nanocarrier System	Reported Outcomes
Psoriasis	NF-κB, IL-17, TNF-α	Quercetin, Kaempferol	Liposomes, Nanogels	Reduced cytokine expression, improved penetration(54,55)
Atopic Dermatitis	Barrier dysfunction, Th2 cytokines	Phenolic acids, Isothiocyanates	Nano-emulsions	Improved hydration, reduced erythema (33)
Chronic Wounds	Oxidative stress, delayed healing	Flavonoids, Polyphenols	Chitosan Nanogels	Accelerated collagen deposition, wound closure(57)
Rheumatoid Arthritis	TNF-α, IL-6, synovial hyperplasia	Flavonoids, Isothiocyanates	Polymeric Nanoparticles, Nanogels	Reduced edema, cytokine suppression (58)
Osteoarthritis	COX-2, MMPs, oxidative stress	Quercetin, Phenolic acids	Nanogels	Sustained anti-inflammatory effect (59)
Metabolic Syndrome	Insulin resistance, systemic	Polyphenols	Polymeric Nanoparticles	Improved insulin sensitivity (60)

	inflammation			
Neuroinflammation	ROS, cytokine imbalance	Flavonoids	Nanogels	Reduced oxidative stress, cytokine modulation (62)

8.1 Preparation Methods

Nanogels are generally prepared using techniques such as emulsion polymerization, which allows the formation of uniform polymeric nanogels in aqueous media with controlled particle size. Ionic gelation is widely applied for natural polymers like chitosan and alginate, offering biocompatibility and biodegradability. Advanced methods such as click chemistry and photopolymerization enable the synthesis of stimuli-responsive nanogels that release phytochemicals in response to pH, temperature, or oxidative stress. For hydrophobic phytochemicals such as quercetin, solvent evaporation and nanoprecipitation are particularly effective, improving solubility and stability within the nanogel matrix.

8.2 Particle Size and Polydispersity Index (PDI): Particle size plays a decisive role in dermal penetration. Nanogels ranging between 50–300 nm have consistently demonstrated enhanced permeation through the stratum corneum and accumulation in deeper dermal layers. The polydispersity index (PDI) reflects size uniformity; values below 0.3 indicate homogeneity and stability, which are essential for reproducible therapeutic outcomes.

8.3 Zeta Potential: Zeta potential reflects the surface charge and colloidal stability of nanogels. Values above ±30 mV provide strong electrostatic repulsion, preventing aggregation and ensuring long-term stability. Chitosan-based nanogels often exhibit positive zeta potential, which enhances adhesion to negatively charged skin surfaces, thereby improving retention and localized therapeutic action.

8.4 Entrapment Efficiency (EE%): Entrapment efficiency determines the proportion of phytochemicals successfully encapsulated. High EE values (>70%) are desirable for sustained release and therapeutic efficacy. Moringa oleifera flavonoid-loaded nanogels often achieve EE values above 75–85%, ensuring that sufficient bioactive compounds are delivered to the target site. Factors influencing EE include polymer type, crosslinking density, and drug–polymer interactions.

8.5 Rheology: Rheological studies assess viscosity and spreadability. Ideal nanogels exhibit shear-thinning behavior, which allows easy application and uniform spreading across the skin. Rheology also influences drug release kinetics, patient acceptability, and compliance. Nanogels with optimal viscosity ensure both therapeutic effectiveness and cosmetic appeal.

8.6 Drug Release Studies: Drug release studies provide insight into the controlled release mechanisms of nanogels. In vitro release experiments using Franz diffusion cells have shown that Moringa-loaded nanogels achieve 2–3 fold higher drug flux compared to conventional gels, with sustained release maintained for up to 48 hours. Release kinetics are governed by diffusion, swelling of the polymeric network, and stimuli-responsive triggers such as pH, oxidative stress, or temperature variations in inflamed tissues.

8.7 Morphological Characterization: Morphological characterization using SEM and TEM consistently reveals spherical nanogels with smooth surfaces and particle sizes around 200–250

nm, confirming uniformity and absence of aggregation. This morphology ensures efficient dermal penetration and colloidal stability.

8.8 Spectroscopic and Thermal Analysis: Spectroscopic and thermal analyses validate encapsulation and stability. FTIR studies demonstrate characteristic peak shifts of flavonoids upon encapsulation, indicating hydrogen bonding with polymer backbones. DSC and TGA analyses reveal reduced crystallinity and improved thermal stability, enhancing solubility and shelf life.

8.8.1 Cytotoxicity and Biocompatibility: Biocompatibility is confirmed through MTT assays on keratinocyte and fibroblast cell lines, which show that Moringa nanogels are non-toxic at therapeutic concentrations. Silver-functionalized nanogels incorporating Moringa extracts exhibit selective cytotoxicity against cancer cells while sparing normal dermal cells, highlighting their dual potential in dermatology and oncology.

8.8.2 Ex Vivo Skin Permeation: Ex vivo permeation studies using goat or porcine skin models demonstrate deeper dermal penetration and sustained retention compared to conventional formulations. Optimized nanogels achieve higher drug flux and prolonged release, validating their superiority in topical delivery.

8.8.3 Stability Studies: Accelerated stability testing (40°C ± 2°C, 75% RH ± 5%) for three months shows >95% drug content retention, with no evidence of phase separation or microbial growth. This confirms the robustness of Moringa nanogels for long-term storage and clinical translation.

8.8.4 In Vivo Evaluation: In vivo evaluations in animal models of psoriasis, arthritis, and wound healing demonstrate superior cytokine suppression, reduced oxidative stress, and faster tissue recovery compared to conventional gels. Nanogels consistently outperform traditional formulations in reducing TNF-α, IL-6, and ROS levels.

8.8.5 Patient Compliance Studies: Nanogels reduce dosing frequency due to sustained release, while their non-greasy texture and improved spreadability enhance cosmetic acceptability. Patient compliance is significantly improved compared to conventional creams and ointments.

8.8.6 Comparative Evaluation: Comparative studies highlight that nanogels provide higher stability, controlled release, and superior cytokine inhibition compared to liposomes and nano-emulsions. This positions nanogels as the most versatile platform for Moringa phytochemicals.

8.8.7 Regulatory and Translational Perspectives: Nanogels align with FDA and EMA guidelines for topical nanocarriers. Scalable production methods such as ionic gelation and emulsion polymerization support industrial feasibility. Regulatory acceptance is facilitated by the biocompatibility of natural polymers and reproducibility of nanogel systems.

8.8.8 Future Directions: Future research should focus on hybrid nanogels that combine polymeric and inorganic components for multifunctional delivery and imaging. Personalized nanogel therapy based on patient-specific inflammatory biomarkers represents a promising frontier. Clinical trials are essential to validate efficacy in psoriasis, dermatitis, arthritis, and other chronic inflammatory disorders, paving the way for commercialization.

9. Safety, Translational Challenges, and Future Perspectives

The clinical translation of *Moringa oleifera*-based nanogels requires careful consideration of safety, standardization, scalability, and regulatory compliance. While preclinical evidence is promising, several challenges must be addressed before widespread clinical adoption.

9.1 Toxicity Considerations: Although *Moringa oleifera* is generally regarded as safe, nanocarrier systems may introduce new toxicological concerns.

I. **Nanoparticle accumulation** in tissues may cause long-term toxicity.

II. **Skin irritation and sensitization** must be evaluated through dermatological assays.

III. **Systemic absorption** of phytochemicals at high doses may lead to off-target effects. Comprehensive toxicological profiling, including cytotoxicity, genotoxicity, and immunotoxicity studies, is essential (63).

9.2 Standardization of Herbal Extracts: Batch-to-batch variability in phytochemical content poses a major challenge.

I. Factors such as cultivation conditions, extraction methods, and storage affect bioactive composition.

II. Standardization protocols (HPLC fingerprinting, spectrophotometric assays) are required to ensure reproducibility (64).

9.3 Scale-Up and Manufacturing Challenges

I. **Complex synthesis methods** (e.g., emulsion polymerization, ionic gelation) may hinder large-scale production.

II. **Cost-effectiveness** and **industrial feasibility** must be optimized.

III. Green synthesis approaches using eco-friendly polymers and solvents are gaining attention (65).

9.4 Regulatory Issues: Nanogel-based herbal formulations face regulatory hurdles:

I. Lack of clear guidelines for herbal nanomedicines.

II. Need for compliance with ICH stability protocols and FDA/EMA safety standards.

III. Requirement of clinical trial data to establish efficacy and safety (66).

9.5 Clinical Evidence: Currently, most studies are limited to in vitro and animal models.

I. Human clinical trials are scarce, highlighting the need for translational research.

II. Rigorous randomized controlled trials (RCTs) are required to validate therapeutic claims (67).

9.6 Smart Nanogels: Future nanogels are being designed with **stimuli-responsive properties**:

I. pH-sensitive release in inflamed tissues.

II. ROS-responsive systems for oxidative stress-driven disorders.

III. Temperature-sensitive gels for localized therapy (68).

9.7 Green Nanotechnology: Eco-friendly nanogels using biodegradable polymers (e.g., chitosan, alginate) and solvent-free synthesis methods reduce environmental impact. Green nanotechnology aligns with sustainability goals and enhances patient acceptability (69).

9.8 Artificial Intelligence (AI) and Quality by Design (QbD): AI-driven predictive modeling and QbD frameworks are revolutionizing nanogel development:

I. **AI algorithms** optimize polymer selection, crosslinking density, and release kinetics.

II. **QbD approaches** ensure reproducibility, robustness, and regulatory compliance.

III. Integration of AI/QbD accelerates scale-up and clinical translation (70).

Table 5. Translational Challenges and Future Directions

Challenge	Barrier	Proposed Solution
Toxicity	Nanoparticle accumulation, skin irritation	Comprehensive toxicological profiling
Standardization	Batch variability	HPLC fingerprinting, validated extraction protocols
Scale-up	Complex synthesis, cost	Green synthesis, industrial optimization
Regulatory hurdles	Lack of herbal nanomedicine guidelines	Harmonized FDA/EMA frameworks
Clinical evidence	Limited human trials	Rigorous RCTs, translational studies
Smart nanogels	Need for site-specific release	Stimuli-responsive polymers
Sustainability	Environmental impact	Biodegradable polymers, solvent-free methods
AI/QbD integration	Lack of predictive optimization	AI-driven modeling, QbD frameworks

CONCLUSION

Chronic inflammatory disorders such as psoriasis, atopic dermatitis, rheumatoid arthritis, and chronic wounds remain significant global health challenges, often inadequately managed by conventional therapies due to issues of poor solubility, instability, and systemic side effects. Herbal phytochemicals, particularly those derived from *Moringa oleifera*, offer a promising alternative owing to their potent antioxidant, anti-inflammatory, and immunomodulatory properties. The integration of *Moringa oleifera* bioactives into nanogel systems represents a transformative advancement in topical drug delivery. Nanogels overcome key limitations of herbal compounds by enhancing solubility, protecting against degradation, improving skin penetration, and enabling controlled release. Evidence from preclinical studies demonstrates that *Moringa*-based nanogels can effectively modulate critical inflammatory pathways such as NF-κB, MAPK, Nrf2, and COX-2, resulting in significant therapeutic benefits across dermatological and musculoskeletal disorders. Beyond efficacy, nanogels also offer patient-centric advantages, including reduced dosing frequency, improved compliance, and minimized irritation. However, translational challenges remain, particularly in the areas of toxicity profiling, phytochemical standardization, large-scale manufacturing, and regulatory approval. Addressing these barriers through green nanotechnology, AI-driven predictive modeling, and Quality by Design (QbD) frameworks will be essential for clinical adoption.

In summary, *Moringa oleifera*-based nanogels hold immense potential as next-generation phytopharmaceuticals for topical anti-inflammatory therapy. With continued interdisciplinary research, rigorous clinical validation, and sustainable manufacturing approaches, these systems could redefine the therapeutic landscape, offering safe, effective, and

accessible solutions for chronic inflammatory disorders.

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