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Betulin-Loaded Topical Gels: A Novel Phytotherapeutic Approach for Arthritis Management.

Manisha Bharti*[1], Dr. Kehar singh Dhaker[1]

[1]LNCT University, J.K. Town Road, Sarvadharam, Kolar Road, Bhopal-462042, Madhya Pradesh.

***Corresponding Author:**

Manisha Bharti,

LNCT University, J.K. Town Road, Sarvadharam, Kolar Road, Bhopal-462042, Madhya Pradesh

Email ID : bhartimanisha85@gmail.com

ABSTRACT

Arthritis, encompassing osteoarthritis and rheumatoid arthritis, remains a leading cause of disability, affecting over 350 million individuals globally and contributing significantly to the socioeconomic burden of chronic disease management. Conventional therapeutic regimens such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs) provide symptomatic relief but are associated with gastrointestinal, renal, cardiovascular, and immunological adverse effects, thereby necessitating safer and more sustainable alternatives. In this context, natural triterpenoids have attracted considerable attention as phytopharmaceutical candidates. Betulin, a pentacyclic lupane-type triterpenoid abundantly derived from the bark of Betula species, exhibits a broad pharmacological spectrum, including anti-inflammatory, antioxidant, chondroprotective, and analgesic activities. Emerging experimental evidence demonstrates its ability to modulate nuclear factor kappa B (NF-κB), cyclooxygenase-2 (COX-2), and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), positioning it as a potential disease-modifying anti-arthritic agent. Despite its therapeutic promise, betulin suffers from limitations of low aqueous solubility and poor systemic bioavailability. To address these challenges, recent advances in formulation science have emphasized topical gel delivery systems, which offer localized action, enhanced dermal penetration, reduced systemic toxicity, and improved patient compliance compared to oral or injectable counterparts. Gels based on carbopol, hydroxypropyl methylcellulose, and nano-carrier assisted systems have been evaluated for their physicochemical stability, rheological properties, in vitro drug release, ex vivo permeation, and in vivo anti-arthritic efficacy. Preclinical studies highlight the potential of betulin-loaded gels to attenuate joint inflammation, cartilage degradation, and oxidative stress in arthritic models, underscoring their translational relevance. This review synthesizes current knowledge on the botanical origin, phytochemistry, pharmacological mechanisms, formulation strategies, and evaluation parameters of betulin topical gels for arthritis management. Comparative insights with conventional anti-arthritic agents, safety and toxicity considerations, and regulatory perspectives are critically examined. Future research directions emphasize the need for clinical validation, standardization of quality markers, and integration of nanotechnology-driven delivery approaches. Collectively, betulin-loaded topical gels represent a novel, plant-based, and scientifically validated therapeutic strategy, holding promise for next-generation arthritis management within the evolving framework of phytopharmaceuticals.

Keywords: *Betulin; Topical gel; Arthritis; Phytopharmaceuticals; Triterpenoids; Anti-inflammatory; Drug delivery systems*

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1. INTRODUCTION

Arthritis is one of the most prevalent chronic inflammatory disorders worldwide, contributing to significant morbidity, disability, and economic burden. It affects over 350 million people globally, with osteoarthritis (OA) and rheumatoid arthritis (RA) being the most common subtypes. Both conditions are characterized by joint pain, stiffness, progressive cartilage degeneration, and loss of mobility, ultimately reducing quality of life [1]. With the increasing prevalence of arthritis in aging populations, the demand for effective, safe, and affordable therapies continues to rise. Conventional treatment strategies rely on nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biologics [2]. While these therapies provide symptomatic relief and delay disease

progression, they are often associated with significant side effects, including gastrointestinal irritation, hepatotoxicity, nephrotoxicity, cardiovascular risk, and compromised immunity during long-term administration [3]. Moreover, biologics and advanced DMARDs remain costly and inaccessible to a large proportion of patients, especially in low- and middle-income countries. These limitations underscore the urgent need for alternative therapeutic approaches that combine efficacy with safety and affordability [4]. In recent years, phytochemicals have emerged as promising candidates for the management of chronic inflammatory conditions, including arthritis. Plant-derived bioactives are increasingly being recognized for their pleiotropic pharmacological effects, biocompatibility, and reduced toxicity profiles [5]. Among them, pentacyclic triterpenoids represent a structurally diverse group with strong anti-inflammatory and antioxidant potential. Betulin, a lupane-type triterpenoid abundantly obtained from the bark of Betula species, has gained substantial attention in this regard [6]. Preclinical studies have demonstrated that betulin exhibits anti-inflammatory, antioxidant, chondroprotective, wound-healing, and analgesic properties, making it a compelling candidate for arthritis management [7].

Mechanistically, betulin modulates key molecular pathways involved in arthritis pathogenesis, including inhibition of nuclear factor kappa B (NF-κB), suppression of cyclooxygenase-2 (COX-2), downregulation of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and mitigation of oxidative stress [8]. These actions collectively contribute to the reduction of synovial inflammation, cartilage degradation, and joint pain. However, despite its broad pharmacological potential, clinical translation of betulin is hindered by poor aqueous solubility, low systemic bioavailability, and limited oral absorption [9].

To overcome these limitations, topical drug delivery systems have been explored as an alternative platform for betulin administration [10]. Topical gels offer several advantages over conventional oral or parenteral routes, including localized drug action at the site of inflammation, reduced systemic exposure, enhanced patient compliance, and minimized adverse effects [11]. Advances in formulation science, particularly the development of polymeric gels, hydrogel matrices, and nanocarrier-assisted gels, have further enhanced the dermal penetration and therapeutic efficacy of botulin [12]. These delivery systems have demonstrated promising results in preclinical arthritis models, highlighting their translational relevance. The present review provides a comprehensive synthesis of the botanical and ethnomedicinal sources of betulin, its phytochemical characteristics, and its pharmacological potential in arthritis management [13]. It further emphasizes the formulation strategies employed in developing betulin-loaded topical gels, their evaluation parameters, safety and regulatory aspects, and future research prospects. By integrating multidisciplinary insights, this review aims to establish betulin-based topical gels as a novel, plant-derived, and scientifically validated therapeutic option for arthritis, bridging the gap between traditional knowledge and modern pharmaceutical innovation [14].

Phytochemistry of Betulin

Betulin is a lupane-type pentacyclic triterpenoid characterized by a rigid hydrophobic skeleton with hydroxyl groups at C-3 and C-28, which impart limited aqueous solubility but significant biological activity. It occurs naturally in crystalline form within the cork layer of *Betula* bark and is considered one of the most abundant plant triterpenoids, representing up to 30% of bark dry weight. Chemical modifications of betulin have yielded a wide range of derivatives, including betulinic acid, betulonic acid, and betulone, which further expand its pharmacological potential [15]. Phytochemically, betulin and its derivatives exhibit strong anti-inflammatory, antioxidant, anticancer, antiviral, and wound-healing activities, many of which are directly relevant to arthritis management. For instance, betulinic acid demonstrates enhanced anti-inflammatory activity through suppression of NF-κB signaling and downregulation of cyclooxygenase-2 (COX-2), while lupeol (a structurally related triterpenoid) shows cartilage-protective properties in experimental models [16]. These findings support the pharmacological diversity of betulin derivatives and provide a strong foundation for formulating topical gels aimed at arthritis. As shown in Table 1, betulin and its structural derivatives collectively contribute to anti-inflammatory and chondroprotective activities that directly address key pathological mechanisms of arthritis. Their presence in birch bark and related medicinal plants highlights a rich phytochemical basis that supports the modern development of betulin-loaded topical gels [17].

Table 1. Phytochemistry of betulin and its derivatives with pharmacological relevance to arthritis

Compound/Derivative	Structural class	Source plants	Pharmacological activities	Relevance in arthritis	References
Betulin	Lupane-type triterpenoid	*Betula pendula*, *B. pubescens*, *Ziziphus jujuba*	Anti-inflammatory, antioxidant, analgesic, wound-healing	Inhibits NF-κB, reduces cytokine production, alleviates joint inflammation	[18]

Betulinic acid	Oxidized derivative of betulin (C-28 carboxyl)	*Betula alba*, *Mimosa tenuiflora*	Anti-inflammatory, anticancer, hepatoprotective	Suppresses COX-2, decreases PGE2, protects cartilage	[19]
Betulonic acid	Ketone derivative of betulin	Birch bark extracts	Antimicrobial, anti-inflammatory	Reduces oxidative stress and tissue degeneration	[20]
Lupeol	Structurally related lupane triterpenoid	Mango peel, birch bark, legumes	Chondroprotective, antioxidant, anti-arthritic	Prevents cartilage erosion, modulates immune response	[21]
Allobetulin	Rearranged triterpenoid from betulin	Semi-synthetic from betulin	Antiviral, cytotoxic, anti-inflammatory	Potential synergist in arthritis formulations	[22]

Botanical and Ethnomedicinal Source of Betulin

Betulin is a naturally occurring lupane-type pentacyclic triterpenoid predominantly found in the outer bark of *Betula* species (family: Betulaceae). Among these, *Betula pendula* (silver birch), *Betula pubescens* (downy birch), and *Betula alba* are considered the richest sources, where betulin can constitute up to 20–30% of the dry weight of the outer bark [23]. The distinctive white color of birch bark is directly attributed to the high concentration of betulin crystals embedded within its cork tissue. In addition to birch, trace amounts of betulin and its derivatives have been reported in plants such as *Ziziphus jujuba*, *Mimosa tenuiflora*, and *Syzygium claviflorum*, further highlighting its widespread distribution in medicinal flora [24].

Birch trees have held a significant place in traditional medicine across diverse cultures. In Russian and Siberian folk practices, birch bark decoctions and poultices were applied to alleviate joint pain, arthritis, rheumatism, and inflammatory skin disorders. Native American tribes traditionally used birch bark for treating wounds, burns, and swelling, while birch sap was consumed as a detoxifying tonic. In Scandinavian ethnomedicine, birch-derived preparations were prescribed for fever, gout, and musculoskeletal pain. In Traditional Chinese Medicine, birch extracts were believed to dispel "heat," reduce inflammation, and promote tissue repair, thus justifying their use in chronic inflammatory conditions [25]. The ethnomedicinal applications of birch bark align closely with the pharmacological activities of betulin, particularly its anti-inflammatory and analgesic properties. Historical usage across continents suggests an empirical understanding of its therapeutic benefits, which modern pharmacological studies have validated through mechanistic insights into NF-κB inhibition, cytokine modulation, and oxidative stress reduction. These findings underscore the relevance of traditional knowledge in guiding contemporary formulations of betulin, including topical gels for arthritis [26]. In Table 2, the ethnomedicinal evidence demonstrates a strong and consistent association between birch bark preparations and the management of inflammatory and musculoskeletal disorders. This historical knowledge provides a rational basis for modern pharmaceutical research focused on the development of betulin-loaded topical gels as targeted anti-arthritic

therapies.

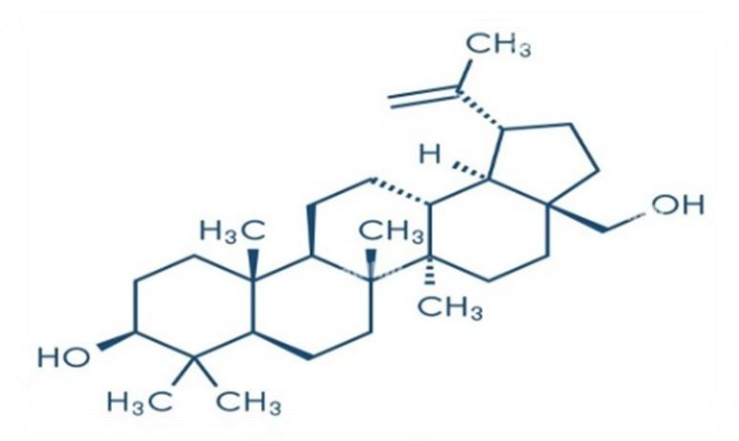

Figure 1. Chemical Structure of Betulin

Table 2. Ethnomedicinal uses of birch bark across different cultures and their pharmacological correlation

Region/Culture	Traditional preparation & uses	Ethnomedicinal indication	Pharmacological correlation	References
Russian & Siberian folk medicine	Decoction, poultice of birch bark	Arthritis, rheumatism, skin inflammation	Anti-inflammatory, analgesic, wound-healing	[27]
Native American practices	Birch bark poultices, birch sap tonic	Burns, wounds, joint swelling, detoxification	Antioxidant, tissue repair, anti-edema	[28]
Scandinavian ethnomedicine	Birch leaf/bark extracts in herbal teas	Fever, gout, musculoskeletal pain	Anti-inflammatory, antipyretic	[29]
Traditional Chinese Medicine	Birch bark decoctions	"Heat-clearing," rheumatic pain, chronic inflammation	Cytokine suppression, COX-2 inhibition	[30]

Pharmacological Potential of Betulin in Arthritis

Arthritis is primarily driven by chronic inflammation, oxidative stress, and progressive cartilage degradation. Betulin and its derivatives have been extensively studied for their pharmacological activities that directly target these pathological mechanisms. Evidence from in vitro and in vivo models highlights their potential as anti-inflammatory, antioxidant, and chondroprotective agents, making them suitable candidates for arthritis management [31].

Anti-inflammatory activity

Betulin exerts potent anti-inflammatory effects by modulating multiple molecular pathways. It suppresses the activation of nuclear factor kappa B (NF-κB), a central regulator of inflammatory responses, thereby reducing the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). This leads to decreased synthesis of prostaglandin E2 (PGE2) and nitric oxide (NO), both of which are implicated in joint inflammation. In addition, betulin downregulates pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), contributing to the attenuation of synovial inflammation and joint swelling [32].

Antioxidant and chondroprotective roles

Oxidative stress plays a pivotal role in cartilage degeneration and progression of arthritis. Betulin demonstrates strong antioxidant properties through free radical scavenging, inhibition of lipid peroxidation, and upregulation of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase. These effects reduce reactive oxygen species

(ROS)-mediated cartilage damage. Furthermore, betulin and its derivatives promote chondroprotection by preserving glycosaminoglycan (GAG) content, preventing matrix metalloproteinase (MMP)-mediated cartilage degradation, and maintaining the structural integrity of articular cartilage [33].

In vitro studies on arthritis models

Cell culture studies have confirmed the protective effects of betulin in arthritis-related conditions. In human chondrocyte and synoviocyte models, betulin reduces IL-1β-induced inflammatory mediator release, decreases MMP activity, and protects against oxidative stress-induced apoptosis. Similar findings have been reported in macrophage models, where betulin significantly inhibits lipopolysaccharide (LPS)-induced cytokine expression and NO production, supporting its anti-inflammatory potential at the cellular level [34].

In vivo animal studies (anti-arthritic efficacy)

Betulin has shown promising anti-arthritic effects in several preclinical models. In carrageenan-induced paw edema and Freund's complete adjuvant (FCA)-induced arthritis models, betulin reduced paw swelling, joint stiffness, and histopathological signs of inflammation. In collagen-induced arthritis, treatment with betulin significantly decreased arthritis scores, preserved cartilage integrity, and reduced systemic inflammatory markers. These in vivo studies provide strong evidence for its potential role as a disease-modifying anti-arthritic agent [35].

Potential synergism with other phytochemicals/drugs

Synergistic effects of betulin have been observed when combined with other natural triterpenoids (such as lupeol, ursolic acid) and conventional drugs (NSAIDs). Such combinations not only enhance therapeutic efficacy but also allow dose-sparing of synthetic drugs, thereby reducing systemic toxicity [36]. The possibility of integrating betulin with nanocarrier-based delivery systems further improves its bioavailability and enhances therapeutic outcomes in arthritis management. A mechanistic summary of the pharmacological activities of betulin in arthritis is presented in Table 3.

Table 3. Pharmacological activities of betulin in arthritis and their mechanistic pathways

Activity	Molecular mechanism	Experimental evidence	Relevance to arthritis	References
Anti-inflammatory	Inhibition of NF-κB, suppression of COX-2 and iNOS, downregulation of TNF-α, IL-1β, IL-6	In vitro (synoviocytes, macrophages); In vivo (adjuvant-induced arthritis)	Reduces joint inflammation and synovial hyperplasia	[37]
Antioxidant	Free radical scavenging, inhibition of lipid peroxidation, upregulation of SOD and catalase	In vitro oxidative stress models; animal arthritis models	Prevents ROS-mediated cartilage damage	[38]
Chondroprotective	Inhibition of MMPs, preservation of glycosaminoglycans, prevention of chondrocyte apoptosis	Chondrocyte culture studies, collagen-induced arthritis models	Protects cartilage integrity and delays disease progression	[39]
Analgesic	Modulation of nociceptive mediators, reduction of hyperalgesia	Paw edema and pain threshold models	Relieves joint pain and improves mobility	[40]
Synergistic activity	Combination with triterpenoids (lupeol, ursolic acid) or NSAIDs enhances efficacy	Preclinical combination therapy studies	Dose-sparing effect, reduced toxicity	[41]

Formulation Approaches for Betulin Topical Gels

Polymers used in gel formulations

Polymers form the structural backbone of topical gels and are selected based on viscosity, bioadhesion, and compatibility with lipophilic drugs such as betulin. Carbopol is among the most widely employed polymers due to its excellent rheological properties, ease of neutralization, and ability to form stable gels [42]. Hydroxypropyl methylcellulose (HPMC)

serves as a thickening and stabilizing agent that improves spreadability and drug dispersion. Natural biopolymers such as chitosan, sodium alginate, and guar gum have also been explored, offering the advantage of biodegradability, biocompatibility, and synergistic wound-healing activity [43].

Role of penetration enhancers

Given the lipophilic nature of betulin, the use of penetration enhancers is critical to improve its dermal absorption. Chemical enhancers such as propylene glycol, ethanol, dimethyl sulfoxide (DMSO), and surfactants disrupt the stratum corneum, facilitating drug permeation. Natural enhancers such as essential oils (eucalyptus, clove, or peppermint oil) have been increasingly investigated due to their dual benefits of improving skin permeation and offering intrinsic anti-inflammatory properties, thus complementing the therapeutic activity of botulin [44].

Nanocarrier-based gels

Recent advances in formulation science have highlighted the incorporation of nanocarriers into gel matrices to further enhance betulin delivery. Nanoemulgels combine the advantages of emulsions (increased solubility of lipophilic drugs) with the consistency of gels, ensuring better skin retention and controlled release [45]. Liposomal gels encapsulate betulin within phospholipid vesicles, improving drug stability, permeability, and bioavailability. Other approaches include solid lipid nanoparticle (SLN) gels and nanostructured lipid carrier (NLC)-based gels, which provide sustained release, improved dermal penetration, and reduced systemic toxicity. These nanocarrier-based formulations hold significant promise in enhancing the therapeutic efficacy of betulin in arthritis [46].

Comparative advantages of topical vs oral delivery

Unlike oral administration, which subjects betulin to first-pass metabolism and poor absorption, topical gels provide localized drug action at the inflamed site, thereby reducing systemic exposure and associated adverse effects. Additionally, topical gels ensure patient-friendly administration, avoid gastrointestinal irritation, and maintain sustained drug release at the site of pathology [47]. These advantages position betulin-loaded gels as a superior alternative for long-term arthritis management. In Table 4 and Figure 2, while conventional gels remain widely used due to simplicity, the integration of nanocarrier systems and natural penetration enhancers represents the most promising direction for achieving enhanced therapeutic outcomes in arthritis. These formulation approaches address the solubility and permeability limitations of betulin, ultimately supporting its development as a clinically relevant topical therapy [48].

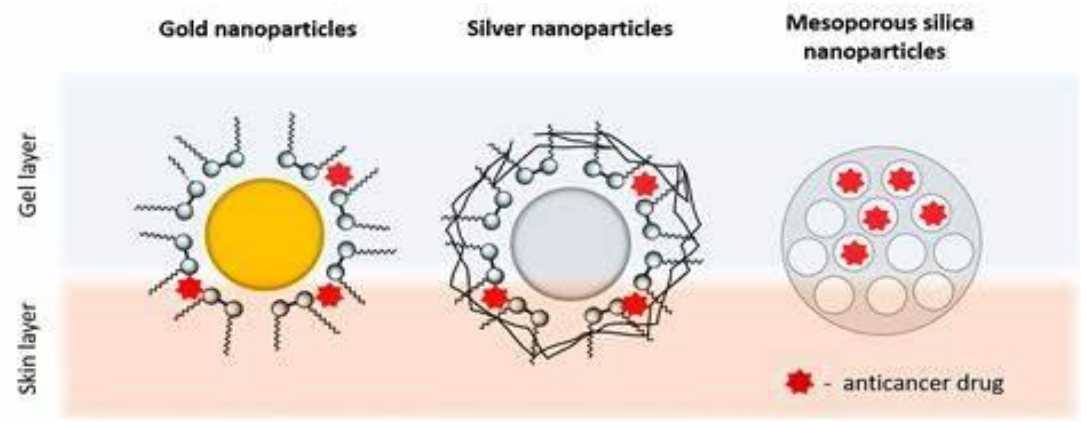

Figure 2. Schematic Representation of Betulin Topical Gel Formulation.

Table 4. Formulation approaches for betulin topical gels [49, 50, 51]

Formulation approach	excipients/polymers	Advantages	Limitations	Relevance in arthritis therapy
Conventional gels	Carbopol, HPMC, sodium alginate, guar gum	Easy preparation, good stability, cost-effective	Limited penetration of betulin	Suitable for mild arthritis and superficial application

Gels with chemical penetration enhancers	Propylene glycol, ethanol, DMSO, surfactants	Improved dermal absorption, enhanced drug release	Risk of skin irritation with prolonged use	Effective for localized inflammation relief
Herbal-enhanced gels	Essential oils (eucalyptus, peppermint, clove)	Dual effect (permeation + anti-inflammatory activity), safer than synthetic enhancers	Possible variability in potency	Enhances efficacy through synergism
Nanoemulgels	Oil phase + surfactants in gel matrix	Solubilizes lipophilic betulin, controlled release, high permeation	Stability depends on surfactant system	Promising for chronic arthritis therapy
Liposomal/nanolipid gels	Phospholipids, SLNs, NLCs incorporated into gel	High stability, enhanced skin penetration, sustained release	Complex manufacturing, higher cost	Strong potential for long-term arthritis management

Evaluation Parameters of Betulin Topical Gels

Physicochemical and Content Evaluation

Fundamental physicochemical parameters such as appearance, homogeneity, pH, viscosity, and spreadability are essential for ensuring formulation consistency and patient acceptability. These factors determine ease of application and residence time on the skin, which directly influence therapeutic effectiveness. In addition, drug content uniformity, typically assessed using validated analytical methods such as HPLC or UV–Vis spectrophotometry, guarantees reproducible dosing and uniform distribution of betulin across the gel matrix [52].

In vitro and Ex vivo Performance Studies

In vitro release studies, often conducted using Franz diffusion cells or dialysis membranes, provide insights into the diffusion kinetics of betulin from the gel matrix. Release data are further interpreted through mathematical models (e.g., zero-order, first-order, Higuchi, or Korsmeyer–Peppas) to predict mechanisms of drug diffusion. Complementary to this, ex vivo permeation studies using excised animal or human skin evaluate the dermal penetration and drug retention profiles. These investigations are particularly important in confirming the role of penetration enhancers or nanocarrier systems in improving betulin delivery [53].

Stability Assessment

Stability studies conducted under accelerated and real-time conditions, as per ICH guidelines, help determine the robustness of formulations during storage. Parameters such as pH, viscosity, drug content, and phase integrity are monitored to ensure prolonged shelf life and reliability. Stability evaluation ensures that the therapeutic and physicochemical properties of betulin gels remain uncompromised throughout their intended shelf life [54].

In vivo Anti-Arthritic Evaluation

The ultimate validation of betulin-loaded gels requires in vivo testing in established arthritis models, such as adjuvant-induced, collagen-induced, or carrageenan-induced arthritis. These studies assess clinical and biochemical endpoints including paw edema, joint diameter, histopathology of synovial tissue, and systemic levels of inflammatory mediators (e.g., TNF-α, IL-6, CRP). Positive outcomes in such models confirm the translational relevance of betulin gels and substantiate their development as plant-derived anti-arthritic therapeutics [55].

Comparative Insights with Conventional Anti-Arthritic Therapies

The therapeutic management of arthritis has traditionally relied on nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs). While effective in providing symptomatic relief, NSAIDs are associated with significant limitations such as gastrointestinal irritation, cardiovascular risks, renal dysfunction, and systemic toxicity, especially with prolonged use. In contrast, betulin offers a natural alternative with a favorable safety profile, acting through multi-targeted mechanisms including NF-κB inhibition, COX-2 suppression, cytokine modulation, and antioxidant activity. The delivery platform further distinguishes betulin formulations from conventional therapies. Oral and systemic administration of NSAIDs provide generalized distribution, which contributes to adverse effects and reduced patient compliance [56]. Betulin-loaded topical gels, on the other hand, enable localized delivery at inflamed joints,

minimizing systemic exposure and reducing the risk of toxicity. Moreover, topical formulations provide sustained drug release, easier administration, and improved adherence, making them particularly suitable for long-term therapy in chronic conditions like arthritis. A comparative overview of betulin topical gels and conventional anti-arthritic therapies is summarized in Table 5.

Table 5. Comparative overview of betulin-loaded topical gels versus conventional NSAID-based therapies [57, 58]

Parameter	Betulin-loaded topical gels	Conventional NSAIDs (oral/systemic)
Primary mechanism	Multi-targeted: NF-κB inhibition, suppression of COX-2, cytokine modulation, antioxidant and chondroprotective roles	Primarily COX-1 and COX-2 inhibition, prostaglandin suppression
Site of action	Localized delivery at inflamed joints with sustained release	Systemic circulation following oral or parenteral administration
Onset of action	Moderate, depends on dermal penetration and release kinetics	Rapid systemic absorption, faster pain relief
Safety profile	Plant-derived, minimal systemic exposure, low risk of GI, renal, or cardiac toxicity	Significant risk of gastric ulceration, renal impairment, cardiovascular events
Efficacy in arthritis	Addresses inflammation, oxidative stress, and cartilage degeneration simultaneously	Mainly symptomatic relief through anti-inflammatory and analgesic effects
Mode of administration	Topical application, non-invasive, patient-friendly	Oral tablets/capsules, injections, transdermal patches
Patient compliance	High, due to ease of use, minimal side effects, and suitability for chronic therapy	Moderate to low in chronic users due to adverse drug reactions and dependency
Suitability for long-term therapy	Strong, because of safety and localized action with reduced systemic risks	Limited, as prolonged use causes GI and renal complications
Formulation flexibility	Can be designed as gels, nanoemulgels, liposomal gels, or herbal-enhanced gels	Mainly restricted to tablets, capsules, and parenteral formulations
Cost-effectiveness	Moderate; use of natural raw materials but advanced formulations (nanogels) may increase cost	Widely available and low cost, though long-term side effects increase healthcare expenses
Regulatory acceptance	Currently under preclinical/experimental evaluation; potential for herbal drug recognition (AYUSH, EMA herbal monographs)	Fully approved with standardized regulatory pathways but with boxed warnings for toxicity

Safety, Toxicity, and Regulatory Aspects

The therapeutic development of betulin-based topical gels requires a careful assessment of safety, toxicological parameters, and regulatory considerations to ensure clinical acceptability. Being a plant-derived triterpenoid, betulin has traditionally been considered safe, but systematic studies are essential for modern pharmaceutical validation. Toxicological evaluations of betulin and its derivatives have consistently demonstrated a favorable safety profile. Preclinical investigations reveal that betulin possesses very low acute oral toxicity, with an LD50 value exceeding 2 g/kg in rodents, indicating minimal systemic risk. Subchronic and chronic toxicity studies further suggest the absence of significant adverse effects on vital organs such as the liver, kidney, and heart. In dermal applications, betulin gels have not shown signs of irritation, erythema, or sensitization, supporting their suitability for long-term topical use. However, certain derivatives of betulin (e.g., betulinic acid) may exhibit cytotoxic activity at higher concentrations, which necessitates dose optimization in formulations. Evidence from preclinical and limited clinical studies also reinforces the safety of betulin. Birch bark extracts containing

high concentrations of betulin have been traditionally consumed as teas, decoctions, and topical poultices without major safety concerns. Clinical studies on birch bark ointments, primarily for skin disorders and wound healing, have reported excellent tolerability with negligible adverse reactions [59]. The antioxidant and anti-inflammatory activities of betulin further suggest a protective pharmacological profile, reducing the likelihood of long-term toxicity. While specific clinical studies in arthritis are limited, the cumulative evidence from ethnomedicine, toxicology, and initial clinical applications supports its safe use in humans. From a regulatory perspective, betulin and birch-derived preparations currently occupy an intermediate position between traditional herbal remedies and modern phytopharmaceuticals. In Europe, the European Medicines Agency (EMA) recognizes birch bark extracts in herbal monographs, primarily for dermatological applications. In India, betula-based products are acknowledged under the AYUSH system of medicine, highlighting their ethnopharmacological heritage. However, no specific betulin-based topical gel has yet received formal approval from major regulatory bodies such as the FDA or EMA for arthritis treatment. For successful translation, issues such as standardization of raw materials, Good Manufacturing Practices (GMP), and comprehensive toxicological evaluations will be critical [60].

Future Perspectives

Translating betulin-loaded topical gels from bench to bedside will require coordinated advances across clinical development, formulation science, and commercialization pathways. Early-phase clinical trials should prioritize safety, dermal tolerability, and proof-of-mechanism at inflamed joints using imaging and biomarker endpoints. Combination therapy represents a rational strategy to achieve dose-sparing of conventional NSAIDs while leveraging the multi-targeted anti-inflammatory and chondroprotective actions of betulin. In parallel, advanced dermal delivery platforms—such as nanogels, liposomal/nanolipid gels, and hydrogel patches—can enhance local bioavailability and residence time at the site of pathology. Market adoption will be strengthened by robust intellectual property, GMP-compliant manufacturing, and partnerships that bridge phytopharmaceutical innovation with rheumatology practice. A concise development roadmap is presented in Table 6, and each priority area is discussed below with emphasis on feasibility and impact. Clinical trial needs should begin with a carefully staged Phase I program focused on dermal tolerability, followed by Phase II studies powered for pain and function outcomes (for example, WOMAC and responder analyses). Incorporating imaging endpoints, such as ultrasound synovitis scores or MRI cartilage biomarkers where feasible, will strengthen mechanistic claims. Combination therapy trials can be designed to demonstrate non-inferiority at reduced NSAID doses, providing a clinically meaningful safety advantage while preserving symptom control; such outcomes would be highly persuasive for guideline adoption and payer acceptance, as indicated in Table 6.

Advanced delivery systems are likely to determine clinical differentiation. Nanogels and liposomal or nanostructured lipid carrier hydrogels can improve solubilization, penetration, and retention of betulin within periarticular tissues, while hydrogel patches and microneedle-facilitated application can address onset of action and adherence challenges. As summarized in Table 6, a quality-by-design scale-up strategy, coupled with dermatological safety testing, will be essential to translate these platforms into consistent, clinic-ready products. Market and commercialization opportunities will depend on credible intellectual property around composition and process, a standardized and traceable botanical active pharmaceutical ingredient, and GMP-compliant manufacturing. Real-world evidence programs and pragmatic post-marketing registries can generate the adherence and safety data favored by payers and rheumatology stakeholders. With these elements in place, betulin-loaded topical gels can progress from an experimental phytopharmaceutical to a differentiated, patient-centered therapy for chronic arthritis, aligning scientific novelty with regulatory and market expectations [58, 59].

Table 6. Development roadmap for betulin-loaded topical gels: clinical, technological, and commercialization priorities [60]

Priority area	Specific objective	Proposed design/approach	Primary endpoints	Anticipated challenges	Mitigation strategies	Expected impact
Phase I clinical study	Establish safety, skin tolerability, and pharmacodynamic signal	Randomized, vehicle-controlled, ascending-dose dermal study in mild–moderate OA	Local AEs, dermal irritation index, pain VAS change, inflammatory cytokines in synovial fluid (optional)	Variability in pain outcomes; limited synovial sampling	Use microdialysis/dermal biomarkers; enrich with target joint involvement	Safety validation and early mechanistic confirmation

Phase II proof-of-concept	Demonstrate efficacy vs. standard care	Multicenter, double-blind trial: betulin gel ± low-dose NSAID vs NSAID alone	Pain VAS, WOMAC, rescue medication use, ultrasound synovitis score	Placebo response; adherence to topical regimen	Electronic adherence caps; run-in period; objective use markers	Dose-sparing and additive efficacy evidence
Combination therapy (phytopharm + NSAID)	Reduce NSAID dose while maintaining outcomes	Factorial design comparing full-dose NSAID, reduced-dose NSAID + betulin gel, and betulin gel alone	Non-inferiority on pain/function; GI/renal safety labs	Regulatory clarity on combo claims	Pre-IND meetings; define add-on vs fixed-dose strategy	Safety advantage with comparable symptom control
Advanced delivery: nanogels	Enhance dermal penetration and joint residence	Betulin nanogel (100–200 nm), thermoresponsive matrix	Ex vivo skin flux; in vivo joint targeting via imaging	Scale-up reproducibility; surfactant irritation	QbD scale-up; biocompatible surfactants; patch testing	Higher local bioavailability with controlled release
Liposomal/NLC hydrogel patches	Prolonged residence and steady release	Occlusive hydrogel patch with liposomal/NLC reservoir	24–72 h release kinetics; user convenience scores	Patch adhesion and sweat interference	Optimized polymers; wearability studies	Improved adherence and weekend dosing options
Microneedle-assisted delivery	Bypass stratum corneum barrier	Dissolvable microneedle array pre-loaded or co-applied with gel	Rapid onset of pain relief; reduced lag time	User acceptability; cost	Short-wear, low-pain arrays; health-economic modeling	Faster onset without systemic exposure
Real-world evidence and PV	Confirm effectiveness and safety at scale	Post-marketing registry, ePROs, passive AE surveillance	Adherence, flare frequency, AE rate	Under-reporting; data heterogeneity	App-based tracking; standardized outcome sets	Credible effectiveness profile for payers and clinicians
IP, GMP, and market access	Secure differentiation and supply integrity	Patents on composition/process; validated botanical APIs; payer dossiers	Freedom-to-operate; cost of goods; formulary status	Raw material variability; pricing pressure	Biomarker-based standardization; multi-sourcing birch bark; value dossiers	Sustainable commercial pathway and competitive moat

2. CONCLUSION

Betulin, a naturally occurring pentacyclic triterpenoid predominantly sourced from birch bark, has emerged as a promising candidate in the management of arthritis owing to its multi-targeted pharmacological profile. Preclinical evidence highlights its potent anti-inflammatory, antioxidant, and chondroprotective activities, all of which directly address the pathological hallmarks of arthritis progression. Unlike conventional NSAIDs that provide only symptomatic relief while posing significant risks of systemic toxicity, betulin offers a safer phytopharmaceutical alternative with a broad mechanistic spectrum. The development of betulin-loaded topical gels further enhances its therapeutic relevance by enabling localized delivery at inflamed joints, minimizing systemic exposure, and improving patient compliance in chronic therapy. Advances

in formulation science, particularly nanogels, liposomal gels, and hydrogel patches, provide novel platforms to overcome solubility and permeability challenges, ensuring sustained release and superior therapeutic outcomes. Taken together, betulin-based topical gels represent a next-generation phytopharmaceutical approach with the potential to bridge traditional herbal wisdom and modern clinical practice. With continued efforts in standardization, regulatory validation, and clinical trial evaluation, these formulations hold significant promise for integration into mainstream arthritis management as safe, effective, and patient-friendly therapeutic solutions.

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