ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

NANO-BASED DRUG DELIVERY SYSTEMS FOR OSTEOARTHRITIS: FOCUS ON INTRA-ARTICULAR AND HYDROGEL-BASED APPROACHES

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ARTICLE INFO

Key words:

Osteoarthritis; Chondroprotective agents; Pomegranate peel extract; Nanogel; *In-vitro* diffusion; Controlled release

Access this article online
Website: https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Osteoarthritis (OA) is a chronic degenerative joint disease marked by cartilage deterioration, inflammation, and compromised joint function. Natural bioactive compounds, particularly pomegranate peel extract (PPE), have gained attention for their potent antioxidant, anti-inflammatory, and chondroprotective properties, positioning them as promising candidates for OA management. Incorporation of PPE into advanced drug delivery systems—including nanogels, emulsions, and polymeric nanoparticles—enhances bioavailability, targeted localization, and sustained release within articular tissues, thereby maximizing therapeutic efficacy while minimizing systemic side effects. This review provides a comprehensive analysis of formulation strategies, mechanistic pathways, and therapeutic potential of PPE-based delivery platforms in OA. Emphasis is placed on how these systems can protect cartilage, modulate inflammatory responses, and support tissue regeneration. The evidence suggests that PPE-integrated drug delivery systems offer a novel and effective approach to OA treatment, bridging natural therapeutics with cutting-edge pharmaceutical technologies. Future research should focus on clinical validation, optimization of formulation parameters, and in-depth mechanistic studies to translate these promising findings into practical therapeutic applications.

INTRODUCTION:

Osteoarthritis (OA) is a long-term, progressive joint disorder characterized by gradual degradation of articular cartilage, structural changes in the subchondral bone, and varying levels of synovial inflammation. It is the most common type of arthritis and a major cause of pain, physical impairment, and reduced mobility worldwide[1]. The condition predominantly involves weight-bearing joints, particularly the knees and hips, and commonly affects the hands, spine, and feet of the patient[2].The pathogenesis of osteoarthritis is multifactorial, involving mechanical stress, aging-related changes, genetic predisposition, obesity, and prior

joint injury. Excessive or abnormal mechanical loading leads to an imbalance between cartilage matrix synthesis and degradation, resulting in progressive cartilage loss and OA. Low-grade inflammatory mediators, including cytokines and matrix-degrading enzymes, contribute to disease progression[3]. Unlike inflammatory arthritic conditions such as rheumatoid arthritis, osteoarthritis is largely confined to the joints and does not involve systemic organ damage[4]. Clinically, osteoarthritis presents with joint pain that worsens with activity and improves with rest, morning stiffness of short duration, reduced range of motion, crepitus, and occasional swelling. In advanced stages, structural joint changes can lead to deformities and significant functional impairment[5].Frequently used treatments, including analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and intra-articular corticosteroids, offer only short-term pain relief and do not halt the ongoing degradation of the cartilage[6].Articular cartilage has a poor regenerative ability because it lacks blood vessels and exhibits minimal cellular turnover. Following injury, chondrocytes show diminished anabolic activity and increased expression of catabolic enzymes, including matrix metallo-proteinases and aggrecanases, leading to the accelerated breakdown of the extracellular matrix[7]. Chondroprotective therapies aim to retard the progression of cartilage degradation by safeguarding chondrocyte viability, suppressing inflammatory mediators, and preserving the equilibrium between extracellular matrix synthesis and degradation. Various agents, such as glucosamine sulfate, chondroitin sulfate, diacerein, and hyaluronic acid, have been reported to exhibit potential chondro-protective properties by influencing cartilage metabolic processes and inflammatory signaling pathways [8].

NOVELTY OF THE WORK

This review integrates nanocarrier-based intra-articular delivery systems with pomegranate peel extract for osteoarthritis therapy. It emphasizes hydrogel and nanogel platforms for targeted and sustained drug delivery. The manuscript addresses key limitations of conventional therapies, including poor bioavailability and rapid clearance. It also highlights formulation challenges and future translational prospects.

METHODS AND MATERIALS

This review article was prepared through a systematic collection and analysis of published literature related to osteoarthritis, chondroprotective therapies, nanocarrier-based intra-articular drug delivery systems, hydrogel formulations, and pomegranate peel extract (PPE). Relevant scientific articles were collected from electronic databases including PubMed, Scopus, Google Scholar, and Web of Science using keywords such as "osteoarthritis," "pomegranate peel extract," "hydrogel systems," "nanocarriers," "nanogels," "intra-articular drug delivery," "controlled release," and "chondroprotective agents."

The literature search was focused on articles published between 2012 and 2025 in the English language. Original research articles, review articles, clinical studies, and systematic reviews relevant to osteoarthritis treatment and advanced drug delivery systems were included. Studies unrelated to osteoarthritis, duplicate publications, conference abstracts, patents, and articles without full-text availability were excluded from the review. The selected studies were analyzed based on the formulation design, mechanism of drug release, cartilage targeting ability, therapeutic outcomes, and the role of PPE in reducing inflammation, oxidative stress, and cartilage degradation. Special emphasis was given to hydrogel-based delivery systems due to their sustained release properties and improved intra-articular retention. The collected data were critically evaluated to identify current advancements, formulation challenges, and future opportunities in the development of PPE-based nanocarrier systems for osteoarthritis management.

Innovative drug delivery systems that enhance cartilage penetration and provide prolonged therapeutic residence

Targeted delivery is often achieved through strategies such as cartilage-specific binding motifs, electrostatic interactions with negatively charged glycosaminoglycans and

enzyme-responsive release systems. By increasing local drug concentration and maintaining therapeutic levels over time, these innovative delivery approaches not only improve symptom management but also hold the potential to slow cartilage degradation and modify disease progression, making them highly promising for the treatment of osteoarthritis[9]. Articular cartilage has a limited regenerative capacity, and systemic administration of drugs often fails to achieve therapeutic concentrations at the site of cartilage damage. Repeated intra-articular injections, while directly delivering drugs to the joint, are invasive and carry risks such as infection and tissue injury[10]. These challenges have led to the development of advanced drug delivery systems designed to enhance cartilage penetration and prolong the residence time of therapeutic agents in the joint. Nanoparticles, liposomes, micelles, hydrogels, and polymer-based scaffolds are promising platforms for targeted osteoarthritis therapy. Nanoparticles can encapsulate chondro-protective or anti-inflammatory drugs, protecting them from premature degradation while enabling their sustained release directly within the cartilage tissue[11]. Injectable hydrogels and thermo responsive nanogels can form localized drug depots in the joint, providing extended therapeutic exposure &reducing systemic side effects [12].

Natural compounds like pomegranate peel extract as promising chondroprotective agents due to their anti-inflammatory and antioxidant properties, highlighting its bioactive metabolites

Pomegranate (Punica granatum L.) is a medicinal fruit, and its peel and pulp are rich in bioactive compounds, including soluble polyphenols, organic acids, and tannins. Multiple studies have highlighted the antioxidant and anti-inflammatory potentials of these components. The peel contains high levels of phenolic compounds, such as hydrolyzable tannins (punicalin, punicalagin, gallic acid, pedunculagin, and ellagic acid) and flavonoids (anthocyanins, catechins, and other complex flavonoids)[13,14]. Pomegranate peel extract (PPE) exhibits up to ten times higher antioxidant activity and total phenolic and flavonoid content than pulp extract[15]. Furthermore, evidence suggests that PPE can stimulate type I procollagen synthesis while inhibiting the production of matrix metalloproteinase-1 (MMP-1) and monocyte chemoattractant protein-1 (MCP-1) in dermal fibroblasts[16]. MMP-1 plays a key role in extracellular matrix turnover, accelerating cartilage degradation, whereas MCP-1, a beta chemokine, is associated with chondrocyte degradation and the progression of knee osteoarthritis [17,18]. These properties highlight the potential of PPE as a natural chondroprotective agent for osteoarthritis management[19].

Need for novel formulations to enhance drug delivery and efficacy

Achieving optimal therapeutic outcomes in osteoarthritis largely depends on the localized delivery of bioactive compounds to the affected joints. Current research highlights that nanocarrier systems provide a versatile platform for this purpose, as their surfaces can be engineered to confer enhanced biocompatibility, targeted tissue delivery, and improved cellular uptake 20. An accurate spatial distribution of therapeutic agents within pathological regions is essential for effective OA intervention. Evidence indicates that nanomaterials can be designed using different targeting strategies, including passive, active, and stimulus-responsive mechanisms, to selectively reach specific cells, tissues, or organs[21]. Passive targeting relies on the natural accumulation of nanoparticles in inflamed joints, facilitated by the enhanced permeability and retention (EPR) effect. This process exploits the compromised vascular integrity of inflamed tissues, allowing nanoparticles to preferentially accumulate in these regions and enhance their cellular uptake[22]. In contrast, active targeting involves functionalization of the nanoparticle surface with ligands that specifically bind to receptors on target cells, improving the precision of drug delivery to diseased cartilage[23].

This review highlights future prospects and formulation opportunities for developing novel, effective, and patient-compliant

chondroprotective drug delivery systems.

Osteoarthritis: Pathophysiology and Current Treatment

Pathophysiology of Osteoarthritis

Osteoarthritis (OA) is a long-term degenerative joint disease characterized by the gradual breakdown of articular cartilage and pathological alterations in the subchondral bone, synovial tissue, ligaments, and periarticular muscles. Contemporary evidence identifies OA as a complex, whole-joint disorder arising from the interplay of mechanical overload, metabolic dysfunction, and inflammatory signaling, rather than being solely attributable to age-related cartilage wear [24].

Cartilage Matrix Degradation and Chondrocyte Dysregulation

Under normal physiological conditions, chondrocytes maintain cartilage integrity by balancing the synthesis and degradation of extracellular matrix components, such as type II collagen and proteoglycans. In OA, this homeostatic balance is disrupted, leading to enhanced catabolic activity and reduced matrix production. The upregulation of matrix-degrading enzymes, including matrix metalloproteinases and aggrecanases, accelerates cartilage breakdown and compromises tissue structure [25].

Inflammatory and Immune-Related Mechanisms

Although OA is not traditionally categorized as inflammatory arthritis, persistent low-grade inflammation plays a significant role in its progression. Activated chondrocytes and synovial macrophages secrete pro-inflammatory cytokines and chemokines that intensify cartilage destruction and suppress reparative pathways [26]. These inflammatory mediators also induce the production of prostaglandins and nitric oxide, which are closely associated with joint pain, swelling, and functional impairment in OA.

Subchondral Bone Remodeling and Osteophyte Development

Structural changes in the subchondral bone occur in the early stages of OA and substantially influence disease progression. Enhanced bone turnover results in subchondral sclerosis, bone marrow lesions, and osteophyte formation, leading to abnormal load transmission across the joint and further cartilage damage[27]. Ongoing biochemical interactions between bone and cartilage perpetuate joint degeneration and structural instability.

Synovial Alterations and Pain Pathways

Synovial involvement is frequently observed in OA and is closely associated with symptom severity. Synovial membrane thickening and immune cell infiltration increase the release of inflammatory mediators, which sensitize nociceptive nerve endings and stimulate angiogenesis and nerve ingrowth into regions that are normally non-innervated[28]. These processes play a central role in the development of chronic pain and reduced joint mobility.

Oxidative Stress and Cellular Aging

Oxidative stress has been increasingly recognized as a key factor in the pathogenesis of OA. Excessive generation of reactive oxygen species disrupts mitochondrial activity, promotes chondrocyte apoptosis, and accelerates cellular senescence, thereby diminishing the regenerative capacity of the cartilage 29. This pro-oxidant environment further amplifies the inflammatory cascades and matrix degradation. Collectively, these interconnected pathological processes drive the progressive deterioration of joint structure and function in OA, underscoring the importance of disease-modifying and chondroprotective therapeutic approaches aimed at preserving cartilage integrity, controlling inflammation, and restoring joint homeostasis.

Current Treatments in Osteoarthritis

The management of osteoarthritis (OA) primarily focuses on alleviating pain, restoring joint function, and improving the quality of life of patients, as curative therapies are currently unavailable. Treatment approaches typically involve a combination of non-pharmacological, pharmacological, and surgical strategies implemented in a stepwise and individualized manner based on disease severity and patient-specific factors[30].

Non-Pharmacological Interventions

Non-pharmacological strategies are the cornerstone of OA management and are

recommended for all disease stages. These approaches include patient education, weight control, physiotherapy, structured exercise regimens, and the use of supportive or assistive devices. Low-impact physical activities, such as walking, cycling, and aquatic exercises, have been shown to enhance joint flexibility, increase muscle strength, and reduce pain and disability[31].

Pharmacological Therapies

Analgesics and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Analgesics, such as acetaminophen (paracetamol), are commonly prescribed for mild OA-related pain, although their analgesic benefits are limited. NSAIDs, including ibuprofen, naproxen, and diclofenac, are more effective in controlling pain and inflammation; however, their prolonged use is constrained by the risk of gastrointestinal and cardiovascular adverse effects, especially in elderly patients[32].

Topical Agents

Topical formulations, including NSAID gels and capsaicin creams, offer a safer alternative for patients with localized joint pain or those at a higher risk of systemic side effects. These preparations provide targeted pain relief with minimal systemic absorption, thereby improving tolerability and safety[33].

Intra-Articular Therapies

In patients with moderate to severe symptoms unresponsive to oral therapy, intra-articular injections are frequently used. Corticosteroid injections can provide short-term analgesic effects by suppressing local inflammation, although repeated administration may be associated with limited duration of benefit and potential adverse effects on cartilage 34. Intra-articular hyaluronic acid injections aim to restore joint lubrication and viscoelasticity, offering modest symptom improvement in some patients, although clinical outcomes remain variable[35].

Symptomatic Slow-Acting Drugs for OA (SYSADOAs)

Compounds such as glucosamine sulfate and chondroitin sulfate are widely used as symptomatic slow-acting agents with proposed chondroprotective properties in OA treatment. While certain clinical studies have reported improvements in pain and joint function, the overall evidence regarding their efficacy remains inconsistent and controversial[36].

Regenerative Medicine Approaches

Regenerative strategies, including platelet-rich plasma (PRP) and mesenchymal stem cell (MSC) therapies, are being actively investigated for their potential to reduce pain and support tissue repair. Although the early results are encouraging, standardized treatment protocols and robust long-term safety and efficacy data are still required [37].

Pomegranate Peel Extract: Bioactive Compounds and Chondroprotective Properties

Pomegranate peels are rich in bioactive compounds such as polyphenols, flavonoids, hydrolyzable tannins, and polysaccharides, which contribute to their strong antioxidant, anti-inflammatory, and therapeutic properties. Among these, pectin is the major polysaccharide and is widely studied for its pharmaceutical importance. It is mainly composed of galacturonic acid residues and is classified into homogalacturonan (HG), rhamnogalacturonan-I (RG-I), and rhamnogalacturonan-II (RG-II). These polysaccharides contain significant amounts of uronic acids and neutral sugars, supporting their potential use in functional foods and drug delivery systems. Recent techniques like ultrasonic-assisted extraction have improved the recovery and preservation of these bioactive compounds, making pomegranate peel a promising natural source for therapeutic applications. Overall, the complex mixture of polyphenols, flavonoids, tannins, fatty acids, and minor constituents underlies the broad pharmacological and health-promoting potential of pomegranate peel, making it a promising candidate for functional foods, nutraceuticals, and therapeutic applications [38].

Nanocarriers for Intra-Articular Drug Delivery

The limitations of conventional intra-articular (IA) drug administration, such as rapid clearance, poor cartilage penetration, and enzymatic degradation, have driven the development of nanocarrier-based delivery systems. Nanocarriers can enhance drug

retention, protect labile compounds, and facilitate targeted delivery to the articular cartilage and synovial tissues.

1. Polymeric Nanoparticles

Polymeric nanoparticles (NPs), composed of biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, and polylactic acid (PLA), are widely used for IA delivery. They provide controlled and sustained drug release, protect drugs from enzymatic degradation, and can be surface-functionalized with ligands to target chondrocytes or ECM components. Positively charged polymeric NPs can also exploit electrostatic interactions with the negatively charged cartilage matrix to enhance retention and penetration [40,42.]

Advantages:

•Sustained release over weeks to months
•Biodegradable and biocompatible
•Amenable to surface modifications for targeting

2. Liposomes

Liposomes are vesicular systems composed of phospholipid bilayers that encapsulate hydrophilic or hydrophobic drugs. In OA therapy, liposomes improve drug solubility and retention within the synovial cavity, reduce systemic exposure, and minimize toxicity. Liposomal formulations can also be functionalized with targeting ligands for cartilage-specific delivery [41].

Advantages:

•Can carry both hydrophilic and hydrophobic drugs
•Enhanced biocompatibility and low toxicity
•Potential cartilage- targeting modifications

3. Hydrogels

Hydrogels are three-dimensional, water-swollen polymer networks capable of encapsulating drugs or nanoparticles for IA delivery. They provide a localized depot effect, maintaining drugs in the joint space for prolonged periods. Hydrogels can be injectable, shear-thinning, or stimulus-responsive, allowing minimally invasive administration and sustained release [42].

Advantages:

•Injectable and minimally invasive
•Provides sustained, localized drug release
•Can incorporate nanoparticles or bioactive molecules

4. Micelles

Polymeric micelles are nanosized self-assembled structures with a hydrophobic core and hydrophilic shell. They are particularly useful for poorly water-soluble drugs, improving solubility and stability in the joint environment. Micelles can penetrate cartilage due to their small size (<100 nm) and can be engineered to release drugs in a stimulus-responsive manner, such as pH or enzyme-triggered release [43].

Advantages:

•High drug loading for hydrophobic drugs
•Small size allows better tissue penetration
•Potential for responsive release mechanisms

Overcoming Challenges in Intra-Articular Drug Delivery Using Nanocarriers

Nanocarrier-based delivery systems, such as polymeric nanoparticles, liposomes, micelles, and hydrogels, are designed to address the key barriers that limit the efficacy of conventional intra-articular (IA) therapies for osteoarthritis (OA).

1. Targeted Delivery

One of the major challenges in IA therapy is delivering drugs specifically to chondrocytes embedded within the dense cartilage ECM while minimizing off-target effects on synoviocytes or surrounding tissues. Nanocarriers can be engineered for active targeting by conjugating ligands (peptides, antibodies, or small molecules) that bind to receptors expressed on chondrocytes or components of the ECM, such as collagen II or cartilage proteoglycans. This ensures preferential accumulation in pathological regions of the joint, increasing local drug concentration and efficacy [40,43.]

Mechanisms:

•Ligand-receptor binding for cell-specific uptake
•Surface charge manipulation (positively charged NPs interact with negatively charged cartilage matrix)

2. Sustained and Controlled Release

Rapid clearance from synovial fluid is a key limitation of conventional IA injections. Nanocarriers can encapsulate drugs within biodegradable polymers or hydrogels, allowing controlled and sustained release over days to weeks. This reduces the frequency of injections, minimizes systemic

exposure, and maintains therapeutic levels of the drug within the joint. For example, PLGA nanoparticles slowly degrade to release encapsulated compounds, while hydrogel depots can gradually release incorporated drugs in response to joint movement or enzymatic activity [41,42.]

Mechanisms:

•Biodegradation-mediated drug release

•Diffusion-controlled release through hydrogel matrices

3. Enhanced Cartilage Penetration and Permeability

Cartilage is dense and avascular, limiting drug diffusion. Nanocarriers overcome this by reducing particle size (typically <100 nm) and using surface modifications to improve interaction with ECM components. Positively charged nanocarriers interact with the negatively charged glycosaminoglycans in cartilage, facilitating deep penetration into the tissue. Additionally, stimulus-responsive systems can release the drug in response to environmental triggers (pH, enzymatic activity), improving site-specific delivery to degenerated cartilage [40,43.]

4. Reduced Systemic Side Effects

Targeted, localized delivery allows drugs to act within the joint without significant systemic absorption. This reduces adverse effects associated with oral or systemic administration, such as gastrointestinal, cardiovascular, or renal toxicity from NSAIDs, making nanocarriers safer for long-term OA management [41].

5.Protection Against Enzymatic Degradation

Many therapeutic agents, particularly biologics and natural compounds, are susceptible to degradation by enzymes in the synovial fluid. Encapsulation within liposomes, polymeric nanoparticles, or micelles shields these drugs from enzymatic activity, preserving their stability and bioactivity until they reach target sites [42].

Formulation Perspectives of PPE-Incorporated Drug Delivery Systems.

1. Polymeric Nanoparticles

Biodegradable polymers such as PLGA, chitosan, and PLA can encapsulate PPE, protecting it from enzymatic degradation and enabling controlled, sustained release. Nanoparticles can also be surface-modified to target cartilage by exploiting electrostatic interactions with negatively charged glycosaminoglycans in the extracellular matrix. These systems allow enhanced cartilage penetration and retention, which is crucial for chondroprotective activity [40,42].

Potential Advantages:

•Sustained drug release

•Possibility of targeted delivery to cartilage

•Small particle size for ECM penetration

2. Lipid-Based Systems

Liposomes and solid lipid nanoparticles (SLNs) are lipid-based carriers that can encapsulate both hydrophilic and hydrophobic PPE components. These carriers enhance solubility, biocompatibility, and stability while reducing systemic toxicity. Functionalized liposomes may achieve targeted delivery to inflamed joints, and SLNs can provide controlled release of bioactive compounds over time [41,44].

Potential Advantages:

•Encapsulation of bioactive molecules

•Biocompatible and low immunogenicity

•Improved drug retention in the joint

3. Hydrogels

Injectable hydrogels can serve as localized depots for PPE, allowing sustained intra-articular release. Hydrogels can be formulated to mimic cartilage ECM, providing a protective environment for bioactive compounds and improving joint retention. They can also be combined with nanoparticles or micelles for dual delivery systems [42].

Potential Advantages:

•Prolonged retention in joint space

•Injectable and minimally invasive

•Can encapsulate multiple bioactive molecules

4. Micelles

Polymeric micelles are self-assembling nanosystems suitable for poorly water-soluble components of PPE. Their small size (<100 nm) facilitates penetration into cartilage ECM, and they can be engineered for stimulus-responsive release (e.g., pH or enzyme-triggered) in inflamed joints. Micelles enhance the stability and bioavailability of PPE compounds [43].

Potential Advantages:

•High solubilization capacity for hydrophobic molecules

•Enhanced cartilage penetration

RESULT AND DISCUSSIONS:

Key Formulation Factors for PPE-Based Drug Delivery Systems

Designing effective drug delivery systems for pomegranate peel extract (PPE) requires careful consideration of multiple formulation factors to ensure therapeutic efficacy, safety, and cartilage targeting.

1. Biocompatibility

Materials used for PPE delivery must be non-toxic, non-immunogenic, and safe in the joint microenvironment. Polymers, lipids, and crosslinkers should not induce inflammation or cytotoxicity, which could worsen cartilage damage. Biocompatibility testing in cell culture and animal models is essential before clinical translation [40].

2. Loading Efficiency

The proportion of PPE successfully encapsulated within a delivery system—known as loading efficiency—is influenced by polymer/lipid selection, solvent system, and encapsulation technique. Low loading can result in insufficient therapeutic doses, while high loading may cause aggregation or destabilization of the carrier. Optimizing these parameters is essential to ensure maximum payload retention and controlled release [42,44].

4. Release Kinetics

Controlled release is a key goal for intra-articular therapy. The rate and duration of PPE release depend on carrier composition, particle size, polymer crosslinking, and degradation rate. Ideal systems should avoid burst release, maintain therapeutic levels for extended periods, and allow site-specific delivery to inflamed cartilage. Improper release profiles can reduce efficacy or increase systemic exposure [41,43].

5. Biodegradability

For intra-articular applications, carriers should degrade safely and predictably without producing toxic by-products. Biodegradable polymers such as PLGA, PLA, and chitosan are commonly used. The degradation rate should match the desired release kinetics, ensuring PPE remains available for cartilage protection over an extended period without accumulation of carrier material [42,44].

Research Evidence Supporting PPE Effects

Anti-Inflammatory Modulation of Cytokines by PPE Comparative chemical analysis of pomegranate peel extracts demonstrated significant *in vitro* reduction in proinflammatory cytokines such as IL1β and IL6 in LPS stimulated macrophage cultures, underscoring the extract's capacity to modulate key inflammatory mediators relevant to cartilage pathology [45]. Matrix Metalloproteinase (MMP) Inhibition by Pomegranate Extract Although not PPE specific, pomegranate fruit extract has been shown in human cartilage explant and chondrocyte models to inhibit IL1βinduced expression of MMPs (MMP1, MMP3, MMP13) by suppressing MAP kinase and NFκB signalling, a key anticatabolic mechanism relevant for cartilage protection in OA [47].

In Vivo and Preclinical Models

Animal Osteoarthritis Models: Systematic reviews of pomegranate peel studies in collagenase-induced OA rat models reported that oral administration of Punica granatum peel extract significantly reduced cartilage erosion, lowered histopathological cartilage damage scores, and preserved proteoglycan and collagen content compared with untreated arthritic controls, indicating in vivo chondroprotective efficacy [46].

PPE Delivery Systems versus Conventional OA Treatments

PPE delivered through advanced systems mechanistically differs by targeting the underlying pathogenic pathways, including oxidative stress, inflammatory signalling (NF-κB and MAPK pathways), and catabolic enzyme expression. Clinical and preclinical studies report that pomegranate peel–derived formulations reduce inflammatory biomarkers such as IL-1β and MMP-1, markers that are not directly addressed by conventional analgesics [47].

Conclusion

Chondroprotective therapy plays an essential role in limiting cartilage degeneration in osteoarthritis, yet conventional treatments are often constrained by inadequate targeting, limited bioavailability, and safety concerns associated with long-term use. These

challenges emphasize the need for improved drug delivery approaches.

Pomegranate peel extract has gained attention as a natural chondroprotective candidate due to its antioxidant and anti-inflammatory properties. However, its therapeutic application is restricted by stability and permeability limitations. Advanced formulation strategies, including topical and nanotechnology-based delivery systems, offer effective solutions by enhancing stability, localized delivery, and controlled release of both pomegranate peel extract and chondroprotective agents.

Although current findings are promising, further in vivo studies, clinical validation, and standardization are required to support successful translation. Overall, incorporating pomegranate peel extract into advanced chondroprotective drug delivery systems represents a viable and innovative direction in pharmaceutics for improving cartilage-protective therapies.

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