

Nanogel-Based Delivery of Phytoconstituents for Enhanced Bioavailability in Osteoarthritis Management

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ABSTRACT

Subchondral bone remodeling, cartilage degradation, synovial inflammation, and reduced joint function are the hallmarks of osteoarthritis (OA), a gradual degenerative joint disease that eventually results in a lower quality of life. There is growing evidence that OA is a complex multifactorial illness involving oxidative stress, inflammatory cytokine signaling, and enzymatic degradation of extracellular matrix components rather than just a mechanical "wear-and-tear" condition. The anti-inflammatory, antioxidant, and chondroprotective qualities of phytoconstituents such as curcumin, resveratrol, quercetin, boswellic acids, and epigallocatechin gallate (EGCG) have drawn a lot of interest. However, their quick metabolic breakdown, low bioavailability, and poor water solubility seriously impede their practical translation. By improving drug stability, permitting targeted distribution, and facilitating controlled release, nanotechnology-based drug delivery systems (NDDS) such as liposomes, nanoparticles, nanoemulsions, and nanogels have emerged as viable approaches to solve these issues. Nanogels are unique among these systems because of their great drug-loading capacity, superior biocompatibility, and physiological stimuli reactivity. This review offers a fresh and promising approach to the management of osteoarthritis by thoroughly discussing the pathophysiology of OA, the therapeutic potential of phytoconstituents, and the role of nanotechnology-driven delivery systems in enhancing their clinical efficacy.

Keywords: Nanoemulsions, and nanogels, biocompatibility, physiological stimuli reactivity, phytoconstituents, nanotechnology-based drug delivery systems

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Introduction

Osteoarthritis (OA) is a degenerative joint disease that manifests as cartilage degradation, synovial inflammation, osteophyte development, and subchondral remodeling of bones. It is one of the most common causes of impairment among the elderly worldwide and has a significant economical burden [1,2]. Osteoarthritis is on the rise due to factors such as inactive lifestyles, obesity, aging, and joint injuries [1]. Clinical manifestations of OA include stiffness, edema, reduced mobility, and joint pain, all of which have a detrimental effect on the affected person's quality of life [2]. Inflammatory mediators and the enzyme-dependent breakdown of both proteoglycans and collagen, two elements of the matrix surrounding cartilage cells, cooperate in a complex way.

Osteoarthritis Pathophysiology

Degenerative joint disease known as arthritis (OA) impacts more than only the joints themselves; it also impacts the surrounding tissues, including the synovium, subchondral bone, ligaments, periarticular

muscles, and cartilage. According to recent studies, OA is a morphological problem that involves metabolic abnormalities, low-level and chronic inflammation, and other inflammatory processes, making it more complex than a straightforward degenerative "wear and tear" condition [10]. Osteoarthritis can eventually develop as a result of biochemical and molecular responses in the joint's microenvironment caused by factors such as mechanical strain, age-related hereditary vulnerability, overweight or obesity, and joint damage [11]. Articular cartilage degradation is a hallmark of OA. Articular cartilage, the only resident cells in cartilage, regulates anabolic and catabolic processes to maintain the equilibrium of its extracellular matrix, or ECM. Because aggrecanases (ADAMTS-4 and ADAMTS-5) and matrix metalloproteinases (MMP-1, MMP-3, and MMP-13) are overexpressed, aggrecan is broken down with type II collagen, causing this balance to swing in favor of metabolism in OA [12]. Erosion and fissuring are brought on by the extracellular matrix's

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slow degradation, which also weakens cartilage's structure and reduces its capacity to absorb damage. Inflammation plays a major role in the development of OA. Increased levels of inflammatory cytokines, including interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α), are seen in the joints of people with OA. These cytokines activate intracellular signaling pathways, such as nuclear factor-kappa B (NF- κ B) and MAPK (mitogen-activated protein kinase), increasing the production of nitric oxide (NO), inflammatory mediators, prostaglandin E2 (PGE2), and other catabolic enzymes [13]. Additionally, this sequence of inflammation accelerates cartilage deterioration and inhibits the formation of extracellular matrix. In pathology, changes to the subchondral bone structure are also important. In early OA, microdamage and increased bone turnover take place beneath the cartilage layer. As the disease progresses, abnormal remodeling of the bone causes osteophyte growth, subchondral sclerosis, and cyst formation, altering joint biomechanics and aggravating pain and stiffness [14]. Synovial inflammation, or synovitis, has a significant impact on the condition's severity. Stimulated synovial neutrophils and fibroblasts emit inflammatory chemicals that penetrate cartilage and exacerbate matrix degradation. Pain perception and inflammatory responses are exacerbated by joint effusion and synovial thickness [15]. As a result, OA is now recognized as a disease affecting the entire joint rather than just the cartilage. The pathophysiology of OA is made worse by the impact of oxidative stress. By encouraging cell aging, mitochondrial malfunction, and chondrocyte mortality, reactive oxygen substances (ROS) impede cartilage repair [16]. Furthermore, inflammatory signaling networks are impacted by metabolic variables such as adipokines linked to obesity. Osteoarthritis (OA) is associated with metabolic syndrome and chronic inflammation [17]. Osteoarthritis causes persistent discomfort and joint deterioration. Mechanical stress, enzyme degradation, oxidative damage, abnormal bone remodeling, and inflammatory substances combine intricately to cause it.

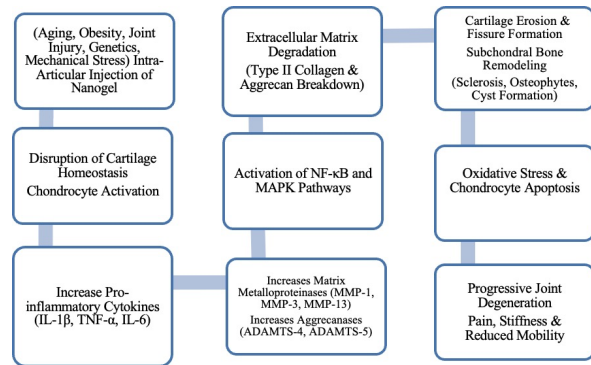


Figure 1: The molecular pathophysiology of osteoarthritis begins with inflammatory signaling and progresses through the degradation of the extracellular matrix and eventual joint degeneration.

Phytoconstituents are bioactive compounds derived from medicinal plants that have a wide range of pharmacological effects, including chondroprotective, anti-inflammatory, anti-catabolic, and antioxidant properties. Over the past 10 years, plant-derived chemicals have gained more interest as potential therapy agents for osteoarthritis (OA) because they can regulate many molecular pathways linked to the disease's pathogenesis with comparatively fewer side effects. Resveratrol, curcumin, quercetin, antioxidants, boswellic acids, and epigallocatechin gallate (EGCG) are among the phytoconstituents that have demonstrated significant promise in both animal and human trials. Many studies have been conducted on the potent anti-inflammatory properties of curcumin, a polyphenolic compound produced from *Curcuma longa*. References [24,25] state that it inhibits nuclear nuclear factor kappa B (NF- κ B) stimulation, suppresses the production of inflammatory cytokines such as tumor necrosis factor-interleukin-1 beta (IL-1 β), alpha (TNF- α), and interleukin-6 (IL-6), and decreases matrix metalloproteinase (MMP) expression to prevent cartilage degradation and inflammation in the synovial cavity. Berries and grapes often contain resveratrol, a stilbene derivative with strong antioxidant and anti-inflammatory qualities. It accomplishes this by collecting reactive oxygen species (ROS), inhibiting the production of inflammatory mediators, and managing autophagy and chondrocyte self-destruction processes, all of which contribute to cartilage preservation [26]. Similarly, quercetin, a naturally occurring flavonoid present in many fruits and vegetables, has been demonstrated to inhibit MMP activity, reduce oxidative stress, and regulate inflammatory pathways, all of which aid in preventing extracellular matrix

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degradation and chondrocyte death [27]. By blocking the 5-lipoxygenase enzyme, boswellic acids, which are derived from the *Boswellia serrata* plant, primarily lessen inflammation and cartilage breakdown [28]. The main catechin in green tea, epigallocatechin gallate (EGCG), has been shown in numerous studies to have antioxidant and anti-inflammatory properties. EGCG inhibits the production of inflammatory cytokines, reduces oxidative stress, and modifies chemical processes like MAPK and NF- κ B to stop cartilage damage and disease progression [29]. All things considered, the therapeutic influence these phytoconstituents have on many cellular processes that lead to the development of osteoarthritis makes them promising candidates for disease-modifying osteoarthritis treatment. Despite their promising pharmacological potential, a number of biopharmaceutical limitations significantly restrict the therapeutic applications of phytoconstituents. Most phytoconstituents are poorly soluble in water and have low membrane permeability, which limits their absorption and systemic availability after ingestion. Their rapid metabolic breakdown and important chemical reactivity during the first phase of metabolism under physiological conditions further limit their therapeutic efficacy. These traits result in varied clinical outcomes, decreased therapeutic level at the targeted location, and inadequate systemic absorption [30, 31]. Therefore, improving the solubility, stability, and preferred circulation of phytoconstituents has become a major area of study in pharmacology. Nanotechnology-based systems like nanogels have shown great potential in overcoming these challenges and enhancing the advantageous effects of plant-based chemicals for the amelioration of osteoarthritis, notably enhanced drug delivery strategies.

Table 1. Major Phytoconstituents in Osteoarthritis Management and Their Mechanisms of Action

Phytoconstituent	Major Molecular Targets	Mechanism of Action in OA	Therapeutic Effects	Ref.
Resveratrol	COX-2, SIRT1, ROS	Inhibits oxidative stress; regulates apoptosis via SIRT1	Anti-inflammatory; antioxidant; protects chondrocytes	[33]
Quercetin	MAPK, NF- κ B, iNOS	Inhibits MAPK/NF- κ B; reduces NO and PGE ₂ production	Reduces inflammation; ECM preservation	[34]
Boswellic Acid	5-LOX, leukotrienes	Inhibits leukotriene synthesis	Reduces joint inflammation	[35]
EGCG	IL-1 β , MMPs	Suppresses IL-1 β -induced MMP expression	Cartilage preservation	[36]
Gingerol	COX pathway, prostaglandins	Reduces inflammatory mediators	Analgesic; anti-inflammatory	[37]
Capsaicin	TRP channels, Substance P	Reduces neurogenic inflammation	Symptomatic pain relief	[38]
Berberine	AMPK, NF- κ B, MMP-13	Activates AMPK; suppresses inflammatory cytokines	Anti-inflammatory; inhibits cartilage degradation	[39]
Curcumin	NF- κ B, IL-1 β , TNF- α , MMPs	Inhibits NF- κ B signaling; suppresses pro-inflammatory cytokine	Anti-inflammatory; chondroprotective	[32]
Icariin	PI3K/Akt, Wnt/ β -	Promotes	Cartilage regeneration	[40]

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	catenin	chondrocyte proliferation; inhibits apoptosis	n; chondroprotective	
Apigenin	NF-κB, MAPK	Suppresses inflammatory signaling pathways	Reduces cartilage degradation	[41]
Kaempferol	ROS, NF-κB	Antioxidant activity; inhibits inflammatory mediators	Protects cartilage matrix	[42]
Genistein	Estrogen receptor, NF-κB	Modulates inflammatory cytokines; reduces oxidative stress	Anti-inflammatory; bone-protective	[43]
Baicalein	MMP-3, MMP-13	Inhibits matrix degradation enzymes	Cartilage preservation	[44]

Nanotechnology-Based Drug Delivery Systems

Nanotechnology has emerged as a crucial instrument in the pharmaceutical industry via the development of nanoscale medication delivery systems. The goal of these systems is to lessen the negative effects on the body while simultaneously making the medicine more bioavailable and effective. Conventional drug delivery techniques frequently result in limited solubility, quick excretion from the body to function properly, non-specific release, and undesirable dosage-related side effects. Nanotechnology based drug delivery systems (NDDS) get around numerous of these restrictions by creating carriers featuring distinct chemical and biological properties compared to their

bigger equivalents, typically falling between 1 and 1000 nm. Particles of lesser size improve medication solubility, surface coverage, and cell membrane adhesion, all of which contribute to improved drug distribution along with absorption. Pharmaceutical applications have led to the development of numerous nanocarrier systems. Numerous materials fall under this

category, including dendrimers, micelles, nanogels, liposomes, nanoemulsions, NLCs and SLNs. By breaking down or diffusing polymers, nanoparticles provide regulated drug release and structural stability. Drugs that are hydrophilic or lipophilic can be encapsulated in liposomes, which are composed of phospholipid layers, enhancing biocompatibility [45]. The hydrophobic medications are improved in their dissolved condition by nanoemulsions. The benefits of lipid-derived systems can be combined with improved loading of drugs or stability in SLNs or NLCs. By modifying their surface characteristics and including certain ligands, these nanocarriers can react to pH, temperature, digestive enzymes, and other environmental conditions. They offer a number of advantages over conventional administration techniques. Their capacity to improve the solubility of medications that are poorly soluble in water, particularly those in Classes II, IV of the BCS, is a significant benefit [46].

Because of their diminutive size, they increase the dissolving rate in accordance with the Noyes-Whitney method, which improves gastrointestinal absorption or systemic availability. Furthermore, by shielding medications from enzymatic and chemical degradation, encapsulating them in nanocarriers increases stability and prolongs recirculation time. The pharmacokinetic properties and pharmacological benefits of tiny carriers can be improved by altering their hydrophilic characteristics and exterior charge such that they dodge rapid elimination by the system of reticuloendothelial cells. A further important benefit of systems based on nanotechnology is their targeted medicine delivery. In inflammatory or sick tissues, increased permeability or retention (EPR) might result in targeted passively. At the location of medical conditions, ligands, peptides or antibodies, can attach to certain receptors, allowing for targeted delivery. A number of processes, including swelling, carrier matrix erosion, dispersion, or degradation, might impact regulated release kinetics. Because of their distinct structure and physical characteristics, nanogels have garnered the most interest among the many nanocarrier

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technologies. Large volumes of water or physiological fluids can be absorbed by nanogels, which are made up of multiple layers of crosslinked nanosized polymers. Because they combine the benefits of hydrogels with nanoparticles, they are especially well-suited for applications for the delivery of medicines. Nanogels provide remarkable high drug capacity, mechanical strength, reactivity to stimuli, and permanence. Nanotechnology-based drug delivery methods for inflammatory diseases like osteoarthritis seek to reduce total exposure, increase resident duration in synovial fluid, and potentially improve deposition of drugs in joint components. Nanocarrier systems present a promising foundation for boosting therapeutic effectiveness, especially for plant-based compounds that face rapid metabolism and low solubility. Therefore, nanotechnology-based drug delivery methods provide a novel and exciting way to tackle the limitations of traditional pharmacotherapy [47].

Through the creation of nanoscale drug delivery systems, nanotechnology has become an essential tool in the pharmaceutical sector. These methods aim to increase the medication's bioavailability and efficacy while reducing its adverse effects on the body. Limited solubility, rapid excretion from the body for proper function, non-specific release, and unfavorable dosage-related adverse effects are common outcomes of conventional drug delivery methods. Many of these limitations are circumvented by nanotechnology-based drug delivery systems (NDDS), which produce carriers with unique chemical and biological characteristics in comparison to their larger counterparts, usually falling between 1 and 1000 nm. Smaller particles enhance drug solubility, surface coverage, and cell membrane adherence, all of which lead to better drug distribution and absorption [48]. Many nanocarrier systems have been developed as a result of pharmaceutical applications. This category includes a wide range of materials, such as dendrimers, micelles, nanogels, liposomes, nanoemulsions, NLCs, and SLNs. Nanoparticles offer controlled medication release and structural stability by dissolving or dispersing polymers. Liposomes, which are made of phospholipid layers, can be used to encapsulate hydrophilic or lipophilic drugs, improving their biocompatibility. Nanoemulsions enhance the dissolved state of hydrophobic drugs. Improved drug loading or stability in SLNs or NLCs can be paired with the advantages of lipid-derived systems. These nanocarriers can respond to pH, temperature, digestive enzymes, and other environmental factors by

altering their surface properties and adding specific ligands. Compared to traditional administration methods, they have several advantages. One major advantage is their ability to increase the solubility of drugs that are poorly soluble in water, especially those in Classes II and IV of BCS [49].

Due to their small size, they promote gastrointestinal absorption or systemic availability by increasing the dissolving rate according to the Noyes-Whitney method. Additionally, encasing drugs in nanocarriers boosts stability and extends recirculation duration by protecting them from enzymatic and chemical destruction. It is possible to enhance the pharmacokinetic characteristics and pharmacological advantages of small carriers by modifying their hydrophilic properties and external charge so that they avoid being quickly eliminated by the reticuloendothelial cell system. Targeted medication administration is another significant advantage of nanotechnology-based systems. Increased permeability or retention (EPR) may lead to passive targeting in inflammatory or diseased tissues. Ligands, peptides, or antibodies can bind to specific receptors at the site of medical disorders, enabling tailored administration [50]. Regulated release kinetics may be impacted by a variety of mechanisms, including as swelling, carrier matrix erosion, dispersion, or degradation. Among the various nanocarrier technologies, nanogels have attracted the greatest attention due to their unique structure and physical properties [51]. Nanogels are composed of several layers of crosslinked nanosized polymers that may absorb large amounts of water or physiological fluids. They are particularly well-suited for drug delivery applications because they combine the advantages of hydrogels and nanoparticles. Nanogels offer very high drug capacity, mechanical robustness, response to stimuli, and durability. For inflammatory conditions like osteoarthritis, nanotechnology-based drug delivery techniques aim to lower overall exposure, lengthen time spent in synovial fluid, and possibly enhance drug deposition in joint components. Particularly for plant-based drugs that have low solubility and fast metabolism, nanocarrier systems offer a viable basis for increasing therapeutic efficacy. Consequently, drug delivery techniques based on nanotechnology offer a fresh and intriguing approach to addressing the drawbacks of conventional pharmacotherapy [52].

Conclusion

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Osteoarthritis is a complicated, multidimensional condition that includes oxidative stress, persistent inflammation, cartilage degradation, and structural alterations in joint components. Conventional treatments can alleviate symptoms, but they frequently have drawbacks including side effects and little ability to change the course of the illness. Because of their anti-inflammatory, antioxidant, and chondroprotective qualities, phytoconstituents have become attractive therapeutic agents; nevertheless, their poor solubility, low bioavailability, and quick metabolic degradation severely limit their clinical use. Drug delivery technologies based on nanotechnology, especially nanogels, provide a practical way to get over these obstacles. Drug stability, bioavailability, targeted distribution, and controlled release of phytoconstituents at the site of action are all improved by nanogels. Their special physicochemical characteristics, such as their high water content, biocompatibility, and stimuli-responsive behavior, make them ideal for treating osteoarthritis. Even if preclinical results are encouraging, more carefully planned clinical trials are required to determine the long-term safety, effectiveness, and scalability of phytoconstituent-loaded nanogel systems. All things considered, combining phytoconstituents with nanogel-based delivery systems is a novel and promising strategy for enhancing treatment results and developing osteoarthritis management.

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