Innovative Nanomedicine Approaches in Osteoarthritis Therapy: A Systematic Review

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Abstract

Osteoarthritis (OA) is a debilitating joint disorder characterized by progressive cartilage degeneration, leading to pain and impaired mobility. Conventional OA treatments have limitations in providing long-lasting relief, necessitating the exploration of advanced therapeutic strategies. In recent years, nanomedicine has emerged as a promising avenue for OA therapy, leveraging various nano-sized carriers to enhance drug delivery and efficacy. This review provides a comprehensive overview of innovative nanomedicine approaches, including liposomes, dendrimers, polymeric nanoparticles (NPs), inorganic NPs, and nanoemulsions, etc. in the context of OA management. Moreover, the review also critically evaluates the current state of research on these innovative nanomedicine approaches, highlighting their advantages, challenges, and potential clinical applications in revolutionizing OA therapy.

Despite the promising potential of these nanomedicine approaches, challenges such as regulatory approval, scale-up production, and long-term safety assessments need to be addressed. Additionally, achieving precise targeting and sustained drug release in the complex joint environment remains a hurdle. Looking ahead, the integration of advanced imaging techniques and personalized medicine approaches holds significant promise for tailoring nanomedicine-based therapies to individual OA patients. Moreover, the development of smart, stimuli-responsive nanocarriers and the exploration of combinatorial approaches with immunomodulatory agents may represent the future frontier in enhancing OA treatment outcomes.

Keywords: Osteoarthritis, Nanomedicine, Liposomes, Dendrimers, Polymeric Nanoparticles, Inorganic Nanoparticles.

Introduction

Osteoarthritis (OA) is a chronic joint disorder characterized by the degeneration of cartilage, the cushioning tissue that covers the ends of bones within a joint. It is one of the most prevalent musculoskeletal conditions worldwide and a leading cause of pain and disability, particularly among the elderly population. Understanding the background of OA is essential for grasping the complexities of this condition and developing effective strategies for prevention and management. The origins of the term "osteoarthritis" can be traced back to the Greek words "osteon," meaning bone, and "arthron," meaning joint. The condition has been recognized for centuries, with early descriptions appearing in medical texts dating back to ancient Greece and Rome. However, it wasn't until the 19th century that significant progress was made in understanding the underlying pathology [Sarzi-Puttini et al., 2005].

OA primarily affects diarthrodial joints, which are synovial joints that allow for a wide range of motion, such as the knees, hips, and hands. The hallmark of OA is the gradual breakdown of articular cartilage, the smooth tissue that covers the ends of bones. This results in joint pain, stiffness, and reduced mobility. As the disease progresses, other joint structures, including ligaments, tendons, and synovial fluid, may become affected. Under normal circumstances, cartilage serves as a shock absorber and facilitates smooth joint movement. In OA, however, a combination of genetic, biochemical, and mechanical factors disrupts the balance between cartilage degradation and repair. This leads to an accelerated breakdown of cartilage, as well as the formation of osteophytes or bone spurs, which are bony outgrowths that develop at the edges of joints [Katz et al., 2021; Ackerman et al., 2017].

Several risk factors contribute to the development and progression of OA. Age is a primary factor, as the incidence of OA increases with advancing years. Joint trauma or injury, either from sports activities or accidents, can also predispose individuals to OA. Additionally, obesity places excessive stress on weight-bearing joints, particularly the knees and hips, making it a significant risk factor. Genetic predisposition, hormonal imbalances, and metabolic disorders also play a role in OA development [Palazzo et al., 2016; Knapik et al., 2018].

Diagnosing OA involves a combination of clinical evaluation, imaging studies (such as X-rays and MRI), and, in some cases, joint aspiration for analysis of synovial fluid. Treatment strategies for OA aim to alleviate pain, improve joint function, and slow down disease progression. Non-pharmacological interventions include exercise, physical therapy, weight management, and the use of assistive devices [Taruc-Uy & Lynch, 2013]. Medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, and intra-articular corticosteroid injections can provide symptomatic relief. In severe cases, surgical interventions like joint replacement may be considered. However, the focus has shifted towards early intervention and lifestyle modifications to prevent or delay the need for surgical intervention [Jang et al., 2021].

The Need for Advanced Therapies in Osteoarthritis (OA)

Osteoarthritis (OA) is a widespread musculoskeletal disorder with a profound impact on individuals' quality of life. As the population ages and the prevalence of OA continues to rise, there is an urgent need for advanced therapeutic approaches to address the complex nature of this condition [Grässel & Muschter, 2020]. Below are some of the factors due to which there is an urgent need of advanced therapies required in OA treatment.

1. Limited Efficacy of Current Treatments: Traditional treatment modalities for OA primarily focus on managing symptoms rather than modifying the underlying disease process. Nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics provide symptomatic relief but do not halt the progression of cartilage degradation. Furthermore, they can be associated with significant side effects, especially when used long-term.

2. Disease Modification: Advanced therapies aim to modify the course of OA by targeting the fundamental biological processes driving cartilage breakdown. Emerging interventions, such as disease-modifying osteoarthritis drugs (DMOADs), hold promise in slowing or halting the degenerative process. These therapies may include agents that stimulate cartilage repair, inhibit enzymes responsible for cartilage breakdown, or modulate inflammation within the joint.

3. Personalized Medicine Approach: Advanced therapies in OA are poised to revolutionize treatment by adopting a personalized medicine approach. By leveraging genetic, molecular, and imaging data, healthcare providers can tailor interventions to individual patients, optimizing efficacy and minimizing potential side effects. This precision medicine approach represents a significant step forward in OA care.

4. Regenerative Medicine and Tissue Engineering: Regenerative medicine holds great potential in the treatment of OA. Techniques such as autologous chondrocyte implantation (ACI) and platelet-rich plasma (PRP) injections aim to stimulate the body's natural healing mechanisms and promote the regeneration of damaged cartilage. Additionally, tissue engineering strategies, including the use of scaffolds and stem cell-based approaches, offer innovative avenues for cartilage repair and regeneration.

5. Minimally Invasive Interventions: Advanced therapies also encompass minimally invasive procedures that can significantly reduce the burden on patients. Arthroscopic techniques, such as microfracture, subchondral drilling, and autologous matrix-induced chondrogenesis (AMIC), allow for targeted treatment of localized cartilage defects, potentially delaying or avoiding the need for joint replacement surgery.

6. Biologics and Novel Pharmacotherapies: Biologic agents, such as monoclonal antibodies and interleukin inhibitors, are being investigated for their potential in modulating the inflammatory pathways implicated in OA. These targeted therapies hold promise in providing more effective and safer alternatives to traditional NSAIDs [Jüni et al., 2006].

Role of Nanomedicine in Addressing Osteoarthritis (OA) Challenges

Innovative OA therapeutics may be facilitated by the multidisciplinary area of nanomedicine, which straddles the fields of medicine and nanotechnology. Nanoparticles (NPs) display a variety of exceptional qualities and novel functions as a result of the particularity of the scale structure, including size effects, interfacial phenomena, and quantum effects, among others [Jeevanandam et al., 2018]. It is more challenging to fully anticipate the behaviour of NPs than microparticles. By exercising control and manipulation over nanostructures, we can harness the unparalleled chemical, physical, and biological properties of NPs to our advantage.

Various NPs used in the treatment of OA are shown in Figure 1.

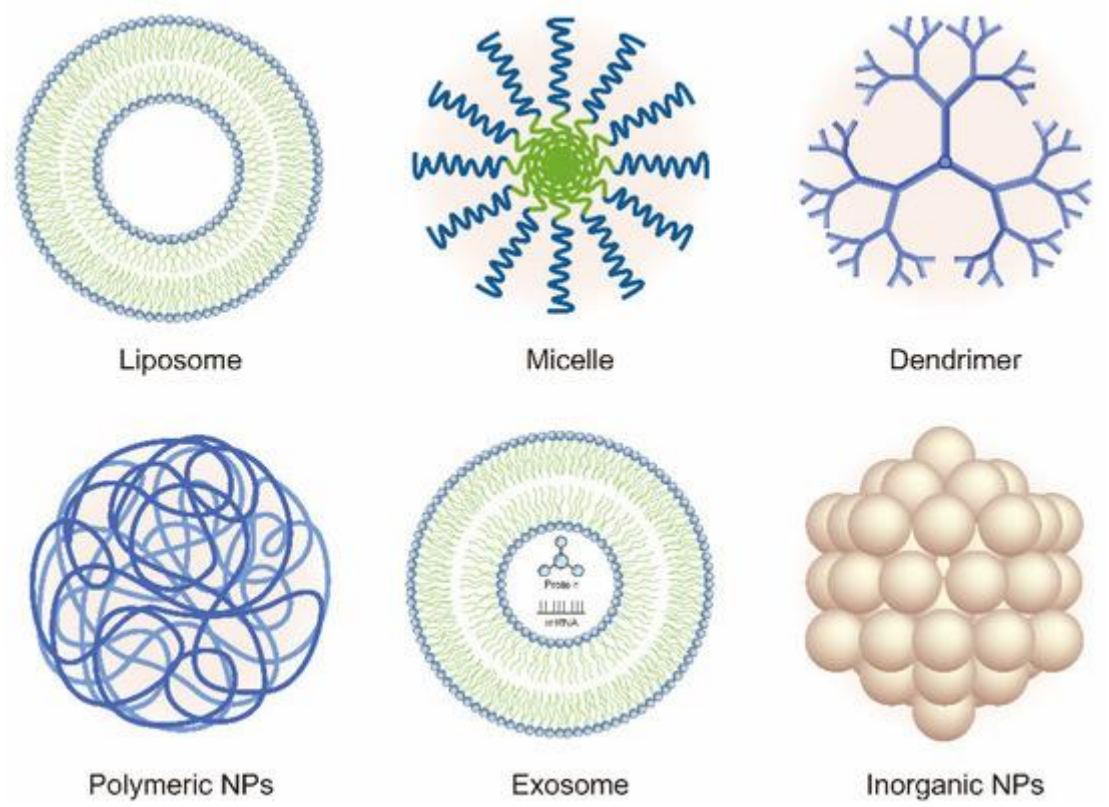

Figure 1. Schematic of the various nanoparticles (NPs) used in the treatment of OA [Jin, 2020].

In general, nanotechnology offers several advantages such as better drug targeting and efficient drug delivery; improved drug solubility and stability; prevention of drug dispersion and degradation in body fluids and extension of drug circulation and retention time in the body; and improved drug efficacy and decreased adverse drug reactions [Gu et al., 2013]. The other associated benefits for the delivery of therapeutics for OA are as follows:

Drug Delivery Enhancement: Nanoparticles, typically in the range of 1-100 nanometers, can be engineered to encapsulate drugs or therapeutic agents. This enables precise targeting of affected joints, improving drug efficacy while minimizing systemic side effects. Controlled release systems allow for sustained therapeutic levels over an extended period, enhancing pain relief and slowing disease progression.

Cartilage Regeneration and Repair: Nanoparticles can serve as carriers for bioactive molecules and growth factors that stimulate chondrocyte (cartilage cells) proliferation and extracellular matrix synthesis. Additionally, nanomaterial-based scaffolds provide a three-dimensional framework for cell attachment, proliferation, and differentiation, promoting cartilage tissue regeneration.

Imaging and Diagnostics: Nanoparticles can be functionalized with contrast agents for advanced imaging techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT). This allows for early detection of OA, precise assessment of cartilage integrity, and monitoring of disease progression over time.

Anti-Inflammatory and Analgesic Effects: Nanoparticles can be engineered to carry anti-inflammatory agents directly to the affected joint. This targeted approach reduces systemic exposure and potential side effects, while increasing the concentration of therapeutic agents at the site of inflammation. Additionally, nanoparticle-based systems can encapsulate analgesic drugs, providing localized pain relief.

Disease-Modifying Therapies: Nanoparticles can serve as carriers for disease-modifying agents, including small molecules, peptides, or nucleic acids. These agents can target specific pathways involved in OA progression, such as inhibiting enzymes responsible for cartilage degradation or modulating inflammatory responses.

Nanoscale Imaging and Monitoring: Advanced nanoscale imaging techniques, such as atomic force microscopy (AFM) and scanning tunneling microscopy (STM), provide unprecedented resolution for studying the nanostructure and biomechanics of cartilage tissue. This enables a deeper understanding of OA at the molecular level, informing the development of more targeted therapies.

Personalized Treatment Approaches: Nanomedicine allows for the customization of treatment strategies based on an individual's genetic and molecular profile. By tailoring nanoparticle formulations and therapies to specific patient characteristics, personalized medicine approaches can optimize treatment outcomes [Liu et al., 2023; Mohammadinejad et al., 2020].

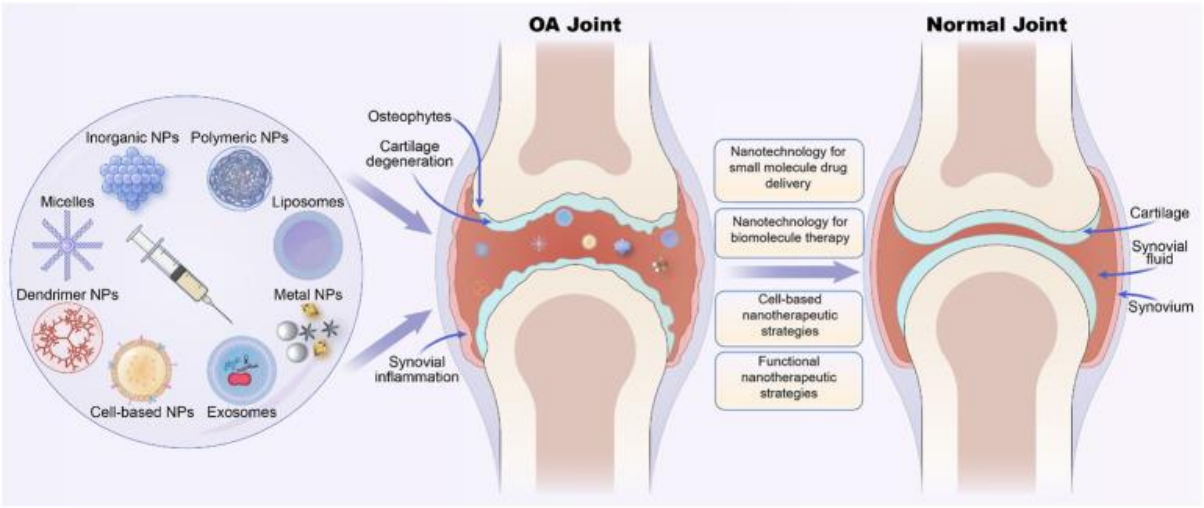

Figure 2: Various nano-therapeutic strategies based on different nanoparticles for osteoarthritis (OA) treatment [Guo et al., 2022].

Figure 2 shows various nano-therapeutic strategies that are based on different types of nanoparticles that may be used in treatment of osteoarthritis (OA). In conclusion, osteoarthritis therapy with nanomedicine has a lot of potential to revolutionise. The application of nanotechnology in clinical settings has the potential to change the way that OA is treated as research in this area develops. Therefore, in this review, we discuss the most recent developments in OA-related novel nanotherapeutic approaches based on various NPs and primarily concentrated on the following areas to summarise, as liposomes, inorganic NPs, micelles, polymeric nanoparticles (PNPs), exosomes, and dendrimers.

Types of Nanomedicine Approaches

Lipid-based Nanoparticles

A flexible and often used subset of nanomedicine are lipid-based nanoparticles. Lipids, which are naturally occurring chemicals that play crucial roles in cellular structure and function, make up these nanoparticles. Lipid-based nanoparticles are very advantageous in the setting of nanomedicine due to their biocompatibility, adaptability, and ability for carrying a variety of therapeutic molecules. With benefits such as long-term circulation following intravenous injection, ease of chemical modification with targeting ligands, and less negative effects because of biocompatibility, lipid-based NPs may be divided into liposomes and lipid NPs [Kraft et al., 2014].

a. Liposomes: Liposomes are spherical vesicles made of a lipid bilayer. They might have a single layer or several concentric layers, or they can be unilamellar. Drugs that are hydrophobic (fat-soluble) or hydrophilic (water-soluble) can both be enclosed in liposomes. Large unilamellar vesicles range in size from 200 to 800 nm, whereas multilamellar vesicles range in size from 500 to 5000 nm. Small unilamellar vesicles are comprised of a single bilayer and are around 100 nm in size. Liposomal characteristics may be easily changed by altering the surface chemistry, coating polymers, or affixing antibodies to form immunoliposomes [Torchilin, 2005].

In osteoarthritis, liposomes have demonstrated promise in the delivery of anti-inflammatory and disease-modifying medications to the afflicted joint. They are a great choice for OA treatment due to their capacity to encapsulate a multitude of medicinal substances. The ability of liposomal formulations to encapsulate both hydrophilic and hydrophobic drug cargos inside the phospholipid bilayer and the aqueous-core as well as their favourable safety profiles make them extensively utilised as drug delivery methods in OA [Barenholz, 2012]. The use of liposomes in OA treatment was demonstrated by Yeh and colleagues, who presented that soybean phosphatidylcholine liposomes loaded with curcumin, a poorly water-soluble compound with therapeutic potential for osteoarthritis (OA), increased the ratio of osteoprotegerin (OPG) to receptor activator of nuclear factor kappa-B ligand (RANKL) in response to interleukin-1 β (IL-1β) stimulation. This increase in OPG/RANKL ratio helped to inhibit the formation of osteoclasts, which in turn slowed down the development of OA.

Moreover, the researchers found that the expression of proinflammatory genes in osteoblasts was reduced after this stimulation, further contributing to the beneficial effects of the liposomes in preventing the progreassion of OA [Yeh et al., 2015]. In another study, Hui et al., (2023) reported the use of dexamethasone liposomes to alleviate osteoarthritis symptoms and reduce inflammation in miR-204/-211-deficient mice. In this study, the effects and mechanisms of Dexamethasone liposome (Dex-Lips) on alleviating destabilization of the medial meniscus (DMM)-induced osteoarthritis (OA) in miR-204/-211-deficient mice were investigated.

Moreover, another study done by Ameya et al., (2023) reported that liposomal Resolvin D1 (lipo-RvD1) was found to be effective in suppressing cartilage damage in obese mice with osteoarthritis. In this research study, the authors have encapsulated Resolvin D1 in liposomes and established its efficacy in the mouse model of osteoarthritis at much lower dosages than freely administered RvD1. To increase the half-life of antioxidant medications in circulation while treating osteoarthritis, liposomes are employed as delivery systems. In order to slow the progression of osteoarthritis by dual antioxidation, Yuzhe et al. (2022) developed an injectable chondroitin sulphate hydrogel (ChsMA) by covalent modification with photo-cross-linkable methacryloyl groups.

Similarly, Xiuling et al., (2019) done a study in which, liposomes loaded with glucosamine sulphate show sustained drug release and improved lubrication for the treatment of osteoarthritis. The experimental results indicated that the GAS-loaded DSPC liposomes could release GAS in a sustained manner while providing good lubrication in pure water (H_2O) and phosphate buffered saline (PBS). Besides, according to a recent research by Chen et al., IA administration of liposome-encapsulated rapamycin significantly reduces inflammation in guinea pigs with spontaneous OA [Chen et al., 2020]. Liposomal formulations provide a number of benefits, including great biocompatibility, minimal toxicity, and the ability to entrap both hydrophilic and lipophilic medicines. However, there are significant drawbacks to liposomes as well, including drug leakage, physical instability, and quick clearance from synovial fluid. Therefore, these shortcomings still present a problem for drug delivery systems based on liposomes.

b. Lipid Nanoparticles & Solid Lipid Nanoparticles (SLNs):

Unlike liposomes, which have a diameter of around 100–200 nm, the core of lipid NPs can produce a number of micelles. Ionizable and cationic lipids that inhibit drug degradation, cholesterol that serves as a stabiliser and promotes membrane fusion, phospholipids that give the particles their shape, and PEG lipids that make lipid nanoparticles more stable when they enter the body [Mitchell et al., 2021; Cheng & Lee, 2016]. Their use in OA was established by various researchers such as, the chondrocytes treated with the lipid NPs-siRNA group were effectively transfected compared to the chondrocytes treated with the free siRNA group in 10-week-old male rats, suggesting that the prepared lipid NPs were effective to transport siRNA. Wang et al. prepared cationic lipid NPs (67± 4.3 nm in diameter) loaded with Indian hedgehog siRNA [Zhang et al., 2014; Wang et al., 2018]. Additionally, this lipid NPs-siRNA system was successful at boosting type II collagen levels and decreasing some pro-inflammatory factors like MMP-13 to delay cartilage deterioration [Wang et al., 2018].

Radiological data showed that rats treated with chloroquine-lipid NPs suffered from less bone and cartilage degeneration than those treated with free chloroquine, according to Bhalekar et al.'s experiments in rat OA models. It was further proven that chloroquine-lipid NPs might lessen synovial inflammation by further inhibiting macrophages' release of the proinflammatory cytokine TNF-α [Bhalekar et al., 2016]. However, lipid-based NPs also have disadvantages that restrict their commercial utilisation, such as the difficult manufacturing process for liposomes that involves injecting organic solvent [Kraft et al., 2014].

On the other hand, SLNs are nanoscale particles with a surfactant-stabilized solid lipid core. They have controlled release qualities and have a crystalline structure. Anti-inflammatory pharmaceuticals and medications that treat diseases can be encapsulated and delivered to the joint via SLNs, giving a sustained release throughout time. It is useful to manage chronic illnesses like OA with this controlled release profile. Additionally, curcumin-loaded solid lipid nanoparticles (Cur-SLNs) are highly effective at reducing arthritis brought on by adjuvants [Wang et al., 2018]. It was reported that Cur-SLNs (10 and 30 mg/kg) could significantly improve mobility score, lowered blood leukocyte count, and significantly reduced oxidative stress, TNF-, and C-reactive protein. They were also found useful in significantly decreasing joint hyperalgesia, joint stiffness, and paw volume [Mohammadinejad et al., 2020].

In conclusion, the treatment of osteoarthritis has a great deal of potential for lipid-based nanoparticles, a promising class of nanomedicine techniques. They are useful tools for creating cutting-edge OA therapeutics because of their biocompatibility, adaptability, and capacity to encapsulate a wide spectrum of therapeutic ingredients. Researchers and medical experts are paving the road for more effective and focused therapies for people with OA by using the benefits of lipid-based nanoparticles.

Polymer-based Nanoparticles

In the field of nanomedicine, polymer-based nanoparticles have become a key category with the potential to entirely transform how osteoarthritis (OA) is treated. These biocompatible polymer-made nanoparticles have special benefits in that they can transport therapeutic drugs directly to the damaged joints, offering a focused and regulated method of treating this painful ailment [Xiao et al., 2022]. PNPs are often employed in the field of nanomedicine because they can be made comparatively easily compared to other NPs. PNPs often serve the following purposes for nano-drug delivery: (1) prolonging drug half-life; and (2) regulating drug release. Nanospheres and nanocapsules are the two different structural shapes that PNPs may take. In contrast to nanocapsules, which are nanostructures with a reservoir core in which the drug is covered by a polymeric membrane, nanospheres are made of a polymer matrix over which the medicine is evenly distributed [Steichen et al., 2013].

Natural biocompatible polymers including chitosan, HA, and sodium alginate as well as synthetic polymers like poly(lactic-co-glycolic acid), poly(ethylene glycol), and poly(-caprolactone) make up the majority of polymeric NPs [Zazo et al., 2016]. The foremost benefit of natural polymers is that they are relatively simple to produce and have great biodegradability, biocompatibility, oxidation resistance, and chemical adaptability [Rozi et al., 2019]. Natural polymers can inhibit an immune response by altering cell adhesion, they

degrade fast through enzymatic or chemical reactions, and their extracellular matrix (ECM) is comparable to that of human tissue, all of which make them biocompatible. However, they are weak mechanically, which makes it challenging to employ them in the medical area [Puertas-Bartolomé et al., 2021]. In comparison with natural polymers, synthetic polymers are made from synthetic macromolecules and may integrate various monomers, allowing for the easy alteration of their biological characteristics [Rahimi et al., 2021]. There use in OA treatment could be evident by the fact is, in order to inhibit the production of VEGF, IL-1, and TNF in mice models of OA, Maudens et al. modified HA through crosslinking with poly (N-isopropylacrylamide) (pNiPAM). Additionally, they also reported that the HA-pNiPAM system was effective in extending the residence time of intra-articular injection materials and dexamethasone when compared to conventional HA [Maudens et al., 2018].

Types of Polymer-based Nanoparticles Used in OA Treatment:

a. PLGA Nanoparticles: Nanoparticles made of poly(lactic-co-glycolic acid) (PLGA) are a popular type of polymer-based delivery method. They are made of biocompatible and biodegradable polymers, which makes them perfect carriers for a variety of medicinal medicines. Anti-inflammatory medications, medications that treat diseases, and substances that promote joint regeneration can all be delivered directly to the joint using PLGA nanoparticles. For the long-term management of OA, their controlled release features allow prolonged medication administration.

Using PLGA as an example, Jung et al. prepared nearly spherical diacerein/PLGA NPs loaded with diacerein, an anthraquinone drug with the ability to slow the progression of OA [Pavelka et al., 2016], which efficiently reduced proinflammatory factors such as IL-1, ADAMTS-5, and MMP-13 in both in vitro study and in vivo OA rat models, demonstrating superior anti-inflammatory effects. This technique also accomplishes continuous drug release over a lengthy period (about two months) without cytotoxicity [Jung et al., 2020]. Bedingfield et al. developed PLGA microtiter plates loaded with MMP-13 siRNA NPs and demonstrated that this nanomicrocarrier technology was capable of releasing siRNA NPs continuously for 5 weeks while maintaining good bioactivity and effectiveness [Bedingfield et al., 2021]. Additionally, this approach was successfully able to limit the production of MMP-13 and proinflammatory cytokines by intra-articular injection in a 28-day research in post-traumatic OA mouse models, as well as further decrease synovial hyperplasia, the growth of osteophytes, and cartilage breakdown [Bedingfield et al., 2021].

Moreover, Zerrillo et al., (2022) reported that PLGA nanoparticles grafted with hyaluronic acid showed increased binding to cartilage cells and tissue, making them a potential treatment for osteoarthritis. In this study, they produced poly(lactide-co-glycolide) (PLGA) nanoparticles (NPs) surfaces decorated with hyaluronic acid (HA), which were used to enhance targeted drug specificity to the osteoarthritic knee joint. In another study, Zerrillo et al., (2021) developed PLGA-PEG-TFA nanoparticles for imaging and drug delivery in osteoarthritis, showing potential for tracking treatments in clinical trials. In this research, they developed an intrinsically fluorinated polymeric NPs modality that can be used in various molecular imaging techniques to visualize and track OA treatments and their potential use in clinical trials.

In addition, Shin et al., (2020) characterizes PLGA nanoparticles loaded with siRNA and their potential therapeutic value in treating osteoarthritis. Their study data suggest that p47phox siRNA NPs may be of therapeutic value in the treatment of osteoarthritis, and significantly attenuated oxidative stress and decreased cartilage damage in mono-iodoacetate (MIA)-induced OA. Liu et al., (2019) reported that PLGA-PEG-PLGA triblock copolymeric nanoparticles loaded with etoricoxib showed chondro-protective effects and alleviated symptoms of osteoarthritis in a rat model. It is found that etoricoxib not only inhibited the expression of inflammation mediators COX-2, prostaglandin E2 (PGE2), and nitric oxide, but also had a similar chondro-protective effect to celecoxib through down-regulating matrix degrading enzymes matrix metalloproteinase-13 (MMP-13).

b. Chitosan Nanoparticles: Chitin, a naturally occurring polysaccharide found in the shells of crustaceans, is the source of chitosan. Its biocompatibility and biodegradability make it a desirable polymer for applications involving medication administration. Chitosan is the only polysaccharide that occurs naturally in its basic form. Chitosan can react with the anionic system to produce physical and chemical changes since it contains a large number of amino groups. For their ability to deliver anti-inflammatory and regenerative medicines to the joint, chitosan nanoparticles have been studied. They are appropriate for intra-articular administration because of their mucoadhesive characteristics, which increase drug retention.

Chitosan and glycosaminoglycan both have structural similarities that may help cartilage formation. In order to successfully stop cartilage deterioration, a tiny chemical called katogenin (KGN) is injected into the joint cavity together with chitosan NPs (KGN conjugated chitosan NPs). KGN induces the differentiation of human bone marrow mesenchymal stem cells into chondrocytes. By lengthening the drug's retention period, this is accomplished [Kang et al., 2014]. A common therapy for OA is intra-articular glucocorticoid injection due to its good anti-inflammatory properties, although after encountering several barriers, the effectiveness of the medications in the joint cavity is reduced. Therefore, it was studies that when dexamethasone is combined with polycationic chitosan [Chitosan-dexamethasone loaded poly (ε-caprolactone) nanofibers], there was production of strong electrostatic effect between the drug and the ECM of cartilage cells, which further allows the drug to continuously enter into the entire layer of cartilage and thereby actively the drug via hydrolysis of ester bond, and thus the therapeutic effect of dexamethasone was observed to be increased [Formica et al., 2019].

c. PEG-based Nanoparticles: A flexible and biocompatible polymer, polyethylene glycol (PEG), is frequently employed in pharmaceutical formulations. Excellent drug loading and controlled release capabilities are provided by PEG-based nanoparticles. It has been investigated to use PEG-based nanoparticles to deliver analgesics, growth hormones, and anti-inflammatory medications right to the joint. They are strong candidates for OA treatment due to their stability and biocompatibility. Their use in treatment of OA could be proved by the study done by Bedingfield et al. as by binding functionalized NPs to type II collagen antibodies, they performed nanotargeted transport in the form of polymeric micelles based on PEG as the shell and RNA cohesive core, also delivering MMP-13 siRNA.

This method was successful in prolonging the residence time of drugs in the joint and inhibiting OA [Bedingfield et al., 2021]. In another study, Xiong et al., (2021) designed PEG nanoparticles (PCFMN) and tested them for the treatment of osteoarthritis, which showed potential therapeutic effects *in vitro* and *in vivo*. In this study, a nanoscaled amphiphilic and cartilage-targeting polymer-drug delivery system by using formononetin (FMN)-poly(ethylene glycol) (PEG) was designed, which was prepared by PEGylation of FMN followed by coupling with cartilage targeting peptide (CollBP). Moreover, in 2019, Liu et al. prepared adenosine-functionalized PLA-b-PEG nanoparticles that showed promising results as a novel approach for achieving prolonged therapeutic effects. The conjugation of adenosine to biodegradable nanoparticles extended the half-life of the adenosine receptor agonists, potentially enhancing their therapeutic utility. In a rat model of post-traumatic osteoarthritis, intra-articular injection of adenosine nanoparticles effectively prevented the development of osteoarthritis, indicating their potential for local treatment of such conditions. There findings suggest that adenosine-functionalized PLA-b-PEG particles could be a promising strategy for developing long-lasting therapies for osteoarthritis and potentially other conditions.

d. Hyaluronic Acid Nanoparticles: In connective tissues, hyaluronic acid (HA), a naturally occurring polysaccharide, can be observed. Excellent biocompatibility and suitability make HA-based nanoparticles ideal for use in drug delivery systems. The ability of HA nanoparticles to transfer painkillers and medications that treat illness to the joint has been researched. They are a desirable choice for treating OA due to their affinity for cartilage tissue. The human body naturally contains hyaluronic acid (HA), which is not species-specific. It has the power to preserve cartilage, lubricate joints, and ease pain. Intra-articular injections of HA can reduce systemic adverse responses while increasing synovial fluid viscoelasticity [Zychowicz, 2014].

HA NPs use in OA treatment was studied by Kamar et al., (2023) in which, they compared hyaluronic acid-chitosan nanoparticle encapsulation to hyaluronic-acid monotherapy in a rat model of knee osteoarthritis. Intra-articular injection of hyaluronic acid-chitosan nanoparticle encapsulation revealed a significant improvement in the knee joint structure compared to hyaluronic-acid in a rat model of osteoarthritis. Hyaluronic acid-chitosan nanoparticle encapsulation significantly improved knee joint structure and reduced inflammatory cytokines compared to hyaluronic acid monotherapy in a rat model of osteoarthritis. Another study done by Zerrillo et al., (2022) was done to develop new poly(lactide-co-glycolide) (PLGA) nanoparticles (NPs) surfaces decorated with hyaluronic acid (HA) to enhance targeted drug specificity to the osteoarthritic knee joint. HA was selected since it binds to specific receptors expressed in many cells, such as the cluster determinant 44 (CD44), a major receptor of chondrocytes, and because of its function in the synovial fluid (SF), such as maintenance of high fluid viscosity. PLGA nanoparticles (NPs) grafted with hyaluronic acid (HA) showed increased binding to cartilage cells and tissue and enhanced accumulation at the target site. The PLGA-HA NPs demonstrated higher affinity towards the chondrocytic C28/I2 cell line compared to control PLGA NPs. The PLGA-HA NPs exhibited no cytotoxicity to chondrocytes. The developed PLGA-HA NPs can serve as a safe drug-delivery system with improved receptor specificity, making them a potential alternative to current nanotherapies for osteoarthritis treatment.

Similarly, Wang et al., (2022) developed hyaluronic acid modified curcumin-loaded chitosan nanoparticles (HA-CUR@CS NPs), which showed superior effects compared to curcumin-loaded chitosan nanoparticles (CUR@CS NPs) in inhibiting inflammation and chondrocyte apoptosis in osteoarthritis (OA) through upregulation of AP-1 and RUNX2. HA-CUR@CS NPs improved the stability and bioavailability of curcumin, and exhibited sustained release and long-lasting effects in the joint cavity. HA-CUR@CS NPs were successfully internalized by chondrocytes and promoted chondrocyte viability while inhibiting chondrocyte apoptosis. HA-CUR@CS NPs upregulated the transcription levels of AP-1 and RUNX2, which activated the Hedgehog pathway and subsequently blocked the Notch pathway. In vivo experiments showed that HA-CUR@CS NPs downregulated the expression of several pro-inflammatory cytokines and exhibited long-term retention in the joint cavity.

Inorganic NPs in OA treatment

With their distinct physical and chemical characteristics, inorganic nanoparticles have emerged as attractive candidates in the search for new OA therapies. These nanoparticles, which are made up of different elements and chemicals, have significant benefits in the delivery of therapeutic agents, the provision of focused treatments, and maybe the reversal of the OA-related degenerative processes. The human body has three primary antioxidant enzymes: peroxidase, catalase, and superoxide dismutase (SOD). By scavenging ROS, they mitigate the harm brought on by oxidative stress [Weydert & Cullen, 2010]. However, due to the impact of the surrounding microenvironment, including proteases, pH, temperature, and other factors, the activity of these endogenous enzymes is readily lost. As a result, the creation of nanozymes is the subject of several investigations. An example of NPs with natural enzyme-like activity is a nanozyme [Wu et al., 2019]. Because of their multi-enzymatic activity, inorganic NPs such as cerium oxide (CeO_2), manganese dioxide (MnO_2), platinum (Pt), and others have garnered a lot of attention in the field of biomedicine among the many nanozymes.

There use in OA treatment could be evident by the studies as in an in vitro model of chronic OA, Ponnurangam et al. employed a commercial CeO_2 NPs with a size of 65 nm × 8 nm to treat the injured chondrocytes brought on by IL-1α. The findings demonstrated that chronic chondrocyte inflammation was significantly reduced by CeO_2 NPs [Ponnurangam et al., 2014]. In order to assess MnO_2 NPs' potential anti-OA properties, Kumar et al. first created MnO_2 NPs by oxidising potassium permanganate with poly (allylamine hydrochloride), which they then administered to a bovine ex vivo model of IL-1β-induced chronic OA. OA might be prevented by MnO_2 NPs by lowering ROS-induced oxidative stress, according to the results [Kumar et al., 2019].

Due to their distinct physical and chemical characteristics, controllability, biocompatibility, and biodegradability, inorganic metal oxides at the nanoscale, particularly iron oxide, are appropriate carriers in magnetically responsive nanodelivery systems [Reddy et al., 2012]. Depending on our various needs for magnetic NPs, common approaches for producing them include coprecipitation, microemulsion techniques, and hydrothermal processes [Wang D, Astruc, 2014]. For example, by using the coprecipitation approach, some researchers produced superparamagnetic iron oxide NPs and coupled them with PLGA matrix to create the appropriate magnetic stimulation system.

The device improved T2 contrast magnetic resonance imaging in in vivo tests [Thirunavukkarasu et al., 2018]. In magnetically stimulated systems, mechanical forces produced by magnetic nanomaterials in dynamic magnetic fields and heat generated by the frequency of high-frequency alternating magnetic fields, which results in phase changes or alterations in the nanocarrier, are potential drug release mechanisms [Wan et al., 2018].

In a similar way, having anti-inflammatory and antioxidant characteristics, gold nanoparticles (GNPs) have anti-arthritis efficacy [Leonavičienė et al., 2012; Khan & Khan, 2018]. Fish oil protein (FP), which possesses anti-inflammatory properties, was used by Sarkar et al. to tag GNPs. The FP-GNPs were then enclosed in dipalmitoyl phosphatidylcholine (DPPC) liposomes. In rat models of OA, the FP-GNP-DPPC was administered by IA injection. The findings demonstrated that FP-GNP was continuously released into the synovial fluid, and that FP-GNP significantly improved antioxidant markers such as glutathione reductase (GSH), superoxide dismutase (SOD), catalase, and apoptotic markers such as Bax, Caspase 3, and p53 compared to the OA control group. Besides, the pro-inflammatory cytokines such as TNF-a, IL-6, NF-κB, etc., were also observed to be decreased as compared with the OA control group. In light of this, the author hypothesised that FP-GNP-DPPC may be a brand-new anti-OA nano-drug [Sarkar et al., 2019]. Teo et al. devised a simple method to increase the effectiveness of nanoparticles made from macrophage membranes [Teo et al., 2022]. They created M2 macrophage membrane-coated gold nanoparticles (Au-M2 NPs) after creating pro-inflammatory M1 and anti-inflammatory M2 macrophages by cell polarisation. The Au-M2 exhibited the most potent pro-inflammatory cytokine sponge capacity and greatly reduced inflammation and matrix breakdown in both IL-1β induced chondrocyte and the explant OA models when compared to the nanoparticles produced from other macrophage subsets. Nitric oxide generation caused by IL-1β stimulation was greatly reduced and Au-M2 eliminated IL-1β-induced MMP13 synthesis. In order to treat OA, Abdel-Aziz et al. biosynthesized, characterised, and assessed the effects of Diacerein® (DIA) and/or AuNPs. The OA rats' metabolic parameters, oestrogen levels, and cartilage joint histology were all improved by the synthesised AuNPs and DIA, which also markedly decreased the serum inflammatory cytokines. They showed that AuNPs are a more potent treatment for OA than DIA, and that the combined therapeutic approach performed better than the solitary approach. This suggests that AuNPs are a potential nanomaterial for OA therapy, both by themselves and in conjunction with DIA. Based on the chemical characteristics of gold nanoparticles (AuNPs), which are being widely researched for the creation of novel multimodal contrast elements or biosensors, another potential method for OA diagnostics with better sensitivity and analysis time is based on these nanoparticles. Target biomarker molecules interact with an AuNP crosslinker or an AuNP-containing antibody in gold nanoparticle biosensing [Elghanian et al., 1997].

Mesoporous silica NPs with strong biocompatibility and porous structure are the most common materials used in inorganic NPs, including metals and metal oxides, for diverse cargo delivery applications [Liu et al., 2021; Wan et al., 2022]. By adding functionalized polyacrylic acid (PAA) to mesoporous silica NPs, He et al. reduced the unintended release of andrographolide, a medication having antioxidant and anti-inflammatory characteristics, in a low-inflammatory environment.

The in vitro study done by them showed better cell viability of chondrocytes by using andrographolide@mesoporous silica NPs-PAA provided, compared with both free andrographolide and andrographolide@mesoporous silica NPs, and in surgery-induced OA rat models. Moreover, the study also revealed that the andrographolide@mesoporous silica NPs-PAA further decreased proinflammatory factors and thereby decrease the pace of cartilage destruction, which was evident by both histological and macroscopic evaluation [He et al., 2021]. In a similar way, Zhao et al. combined mesoporous silica NPs with -cyclodextrin-modified poly(2-methacryloyloxyethyl phosphorylcholine) (CD-PMPC) in addition to PAA modification and azobenzene modification [Zhao et al., 2021]. When azobenzene is exposed to visible light (450 nm) radiation, the azobenzene moiety partially changes from trans to cis isomerization, which causes drug release and enables CD-PMPC to separate from NPs to provide lubrication in the form of a hydrated layer. This device has high biocompatibility and, in an in vitro investigation, showed that light is still engaged in medication release after passing through the dermal tissue of naked mice. It also showed improved anti-inflammatory effects when the anti-inflammatory drug diclofenac was present [Zhao et al., 2021].

Besides, using dexamethasone as an example, Zhao et al. modified chitosan with molybdenum disulfide (MoS_2) as a near-infrared light-responsive nanocarrier. They discovered that this system was able to reduce the levels of TNF- and IL-1 in mice models of OA and extend the residence time of dexamethasone in the joint by IR light action. Additionally, in vivo tests showed that this delivery method did not damage important internal organs including the kidney, spleen, and heart during metabolic processes [Zhao et al., 2019]. Inorganic NPs' especially heavy metal NPs like gold NPs [Sani et al., 2021] and iron oxide NPs [Arias et al., 2018], major problem is their toxicity, which is a result of inadequate toxicological evaluation in the literature. Toxicology research must be strengthened in order to provide trustworthy experimental data for OA therapy.

Nanoemulsions in Osteoarthritis (OA) Treatment

An emulsion having particles in the nano range is referred to as a lipid nanoemulsion. Lipid nanoemulsions are widely employed nowadays as drug carriers to improve the absorption of various medications [Khurana et al., 2013]. Lipid nanoemulsion is a kind of nanocarrier made up of two or more immiscible liquids, with the dispersed phase droplets typically ranging in size from 20 to 500 nm. The system appears to be clear, and the development of turbidity is an indication of instability [Rachmawati et al., 2015]. Because of the Ostwald ripening phenomenon, nanoemulsion systems are particularly prone to stability issues. The solubility of the components of the formula varied depending on the size of the particles. The mobility of tiny droplets and their aggregation into bigger droplets are the typical causes of its occurrence. It is crucial to use the right preparation technique and use the right oils and surfactants for stable formulation [Pople & Singh, 2006].

In addition to enhancing medication retention and bioavailability, lipid base emulsions are a form of nanoemulsion that may dissolve hydrophobic medicines and shield them from cutaneous hydrolysis and enzymatic destruction. In the lab and on a wide scale, high pressure homogenizers have been used to successfully create nanoemulsions [Soliman et al., 2010]. Numerous medications had limited absorption when administered topically, but their inclusion

in the oil core of the nanoemulsion formulation improved their permeability by passive diffusion through the lipid layers of the skin. Additionally, during the course of therapy, the frequency and overall dosage of the medicine were reduced, therefore reducing the negative effects of the drug. Additionally, the enormous surface area of nanoemulsions enhances medication delivery and site-specific targeting [Araújo et al., 2011].

In a study, Gaber et al., (2023) researched about the arthritic disorder, which is a common disease in elderly patients and the most common cause of joint dysfunction. Their study was done with aim to design Piroxicam-loaded nanoemulsion (PXM-NE) formulations to enhance the analgesic and anti-inflammatory activity of the drug for topical use. The results showed good physicochemical properties, higher bioavailability, and a longer analgesic effect of piroxicam from nanoemulsion gel, as compared to the commercial product. Similarly, Ozkan et al., (2022) explored the potential of macrophages as carriers of therapeutic agents into injured joints during post-traumatic osteoarthritis (PTOA). The researchers used a macrophage targeted nanoemulsion (NE) imaging agent to visualize macrophages in PTOA. The study suggests that macrophages could be utilized as a delivery system for therapeutic agents in PTOA, potentially reducing the need for systemic pharmacological treatments with serious side effects. A more recent study done by Leite et al., (2020) evaluated the effects of chondroitin sulfate and glucosamine as structure modifiers to form a nanoemulsion, indicating safety for topical application and enhanced drug permeation through the skin; repair of articular cartilage and pain reduction were observed in some patients after nanoemulsion treatment [89].

Moreover, Mohammadifar et al., (2021) evaluated the effect of nanoemulsion containing peppermint and rosemary essential oils in rats with osteoarthritis (OA). The nanoemulsion containing peppermint and rosemary essential oils did not cause any irritation in rabbit skin and did not show any dermal toxicity or changes in biochemical and hematological parameters in male and female rats. The nanoemulsion reduced mechanical and thermal allodynia, thermal hyperalgesia, and ambulatory-evoked pain in rats with osteoarthritis. The nanoemulsion increased the activity of antioxidant enzymes SOD and GPx and decreased the level of MDA, indicating an improvement in the antioxidant capacity. The nanoemulsion improved the histopathological features of the rats' knee joint with osteoarthritis. The findings suggest that the nanoemulsion formulation can enhance the therapeutic effect of rosemary and peppermint essential oils as a topical treatment for osteoarthritis.

Dendrimers in Osteoarthritis (OA) Treatment

Dendrimers are repeatedly branched macromolecules with topological nanostructures that resemble trees. The core, the branches, and the shell are the three parts that make up dendrimers. The dendrimers' outer surface, which may be utilised for conjugation with drugs or targeting ligands, is provided by the shell. Moreover, the hydrophobic molecule can be carried by the hydrophobic core. The number of generations present in a dendrimer's structure determines its size [Abbasi et al., 2014]. The benefits of dendrimers as a drug delivery method include a well-defined number of surface functional groups, monodispersity, adjustable size, and a high cargo payload efficiency [Abedi-Gaballu et al., 2018]. The two most often utilised dendrimers are polypropylene imine dendrimers and polyamidoamine (PAMAM) dendrimers.

In an ex vivo investigation on bovine cartilage and an in vivo study on rats, Geiger et al. created a dendrimer nanocarrier (≈10 nm) based on polyamidoamine (PAMAM) and changed its amines with terminal PEG, utilising IGF-1 as cargo. They discovered this system exhibited high cartilage penetration. In comparison to the free IGF-1 group, IGF-1 carried by prepared carriers stayed in the joint for up to 30 days longer [Geiger et al., 2018]. In another study, Li et al. created "nanomicrometer" systems by mixing miR-140 with cationic dendrimers to create nanocomplexes, which were then encased in hydrogel microspheres with a diameter of a few micrometres. The findings demonstrate that miR-140 NPs have a greater transfer efficiency than free miR-140, and that off-target effects and drug loss are diminished when miR-140 is enclosed in gel microspheres. In mouse models caused by DMM surgery, intra-articular injection of "nanomicrometer" gel microspheres also shown the capacity to prevent cartilage deterioration and minimise bone flab development [Li et al., 2022]. In another study, it was revealed that the cationic PAMAM dendrimers produced by Geiger et al. and TGFα-NPs prepared by Wei et al. by reducing the surface charge by adding cationic copolymers can both be targeted to treat articular cartilage and have been shown to be effective in treating subchondral osteosclerosis, bone growth, and joint pain [Wei et al., 2021]. Another study showed that PAMAM dendrimers, also known as amine-terminated polyamidoamines (PAMAM), are composed of 64–256 primary cationic amines with dense surface functional groups and terminals functionalized with various PEG molar ratios to control surface charge. The complete layer of bovine cartilage may be penetrated by PAMAN-poly (ethylene glycol)-IGF-1 NPs in 2 days after being coupled with IGF-1, and the residence duration in the rat knee joint is extended by 10 times [Geiger et al., 2018].

Exosomes in Osteoarthritis (OA) Treatment

Exosomes are membrane-bound phospholipid bilayer vesicles with sizes of 50–150 nm that are generated from endosomes. Exosomes carry proteins that can move between cells, bioactive lipids, and nucleic acids (DNAs, mRNAs, microRNAs, and IncRNA) [Mathieu et al., 2019]. Almost all cell types, both diseased and normal cells, have the ability to produce exosomes. In vivo, they are found in bodily fluids such blood, urine, saliva, breast milk, and synovial fluids. In vitro, they are found in the conditioned media of all different kinds of cells [Théry et al, 2002]. mRNAs, miRNAs, and IncRNA are among the nucleic acids found in the majority of exosomes. Additionally, MSCs are the primary source of exosomes utilised to treat OA. Exosomes, which are nanoscale biologically generated vesicles with a variety of regulatory mechanisms, have multifunctional regulatory effects on the treatment of OA in addition to the aforementioned nanocarriers with responsive activities [Ni et al., 2019].

Mesenchymal stem cells (MSCs), which are renowned for their regeneration abilities, are among the cells that produce exosomes, which are tiny, membrane-bound vesicles. They include genetic material (RNA and DNA), proteins, lipids, and other bioactive substances. Exosomes have drawn a lot of attention in the context of treating osteoarthritis (OA) because of their ability to reduce inflammation, encourage tissue repair, and promote regeneration [Xiao et al., 2022]. Multivesicular structures that merge with the cytoplasmic side of the plasma membrane release exosomes, a subtype of secretory vesicles, into the ECM. According to van Niel et al. (2018), they are disc-shaped and range in diameter from 30-150 nm. Exosomes'

pathophysiological roles in the development of OA have also been studied recently. Exosomes may be crucial to the treatment of OA when mesenchymal stem cells (MSCs) are employed extensively [Bobis-Wozowicz et al., 2015]. A unique kind of exosome released by bone marrow-derived mesenchymal stem cells (BMSCs) from tissue with congenital polydactyly was described by Zhou et al. By encouraging chondrocyte growth, these exosomes may reduce the symptoms of osteoarthritis [Zhou et al., 2020]. The findings demonstrated that polydactyly bone marrow-derived MSCs (pBMSCs) were more capable than BMSCs of differentiating into chondrocytes, and that exosomes released by pBMSC (pBMSC-EXOs) induced chondrocyte migration and proliferation. Additionally, injecting pBMSC-EXOs and BMSC-EXOs reduced OA in a rat model of the disease. Besides, the ability of exosomes produced from synovial mesenchymal stem cells to penetrate and target cartilage in chondrocytes is anticipated to make them a suitable carrier for nucleotide medicines [Bao & He, 2021]. Extracellular vesicles (PDLLA-PEG-PDLLA) were initially suggested by Tao et al. as nanoscale carriers for the treatment of OA [Tao et al., 2021]. Synovial mesenchymal stem cell-derived exosomes can transfer nucleic acids to chondrocytes to encourage chondrocyte proliferation.

Exosomes are unique in that they can be used as nanocarriers with high biocompatibility and strong transmembrane penetration as well as modified for highly targeted drug delivery to treat OA at various stages. For example, MSCs [Kim et al., 2020], chondrocytes [Ni et al., 2019], and osteocytes[Sato et al., 2017] in joint-derived exosomes are directly involved in OA regulation. By fusing the chondrocyte affinity peptide with the exosome surface protein, Liang et al. created a chondrocyte affinity peptide-Exosome vector that was loaded with microRNA-140 (miR-14), a miRNA that has the potential to block the enzymes responsible for degrading cartilage [Liang et al., 2020]. The studies also showed in vitro studies that demonstrated the ability of the chondrocyte affinity peptide-Exosome system to target and deliver miR-140 to chondrocytes, and in vivo studies in rat models of OA have demonstrated the superiority of this system over unmodified exosomes for inhibiting ADAMTS-5 and MMP-13 and promoting cartilage repair [Liang et al., 2020]. In addition, Li et al. found that using extracellular vesicles made from human bone marrow MSCs as nanocarriers for curcumin was able to further inhibit proinflammatory cellular pathways, such as the reduced phosphorylation of p38MARK when compared to free curcumin, which inhibited this pathway, increased cell viability, and decreased apoptosis in vitro [Li et al., 2021].

Yang et al. also demonstrated that intra-articular injection of umbilical cord blood MSCs with highly expressed long-stranded non-coding RNA H19 in their secreted exosomes can modify particular signalling pathways, modulating the sensitivity of the central nervous system in advanced OA and subsequently relieving pain [Yang et al., 2021]. Ma et al. collected secreted small-cell exosome vesicles from human bone MSCs in relation to bone regeneration by cultivating them on titanium plates with various morphologies. Based on in vitro cellular studies and in vivo studies carried out on mouse models, it was revealed that there was positive bone regenerative effect of small-cell exosomes vesicles, which were collected after 21 days of culture. Such effect was observed due to the ability of particular miRNAs from small-cell exosomes vesicles to regulate osteogenic signalling pathways like TGF- β, AMP-activated protein kinase, and Forkhead box O to promote osteogenesis [Ma et al., 2022].

Additionally, it has been demonstrated that exosomes released by endothelial cells can improve bone and joint conditions such osteoporosis and arthritis by promoting bone resorption and showing greater bone targeting than exosomes produced by bone marrow MSCs or osteoblasts [Song et al., 2019]. Recent research has demonstrated that exosomal miRNAs and IncRNAs are essential for the anti-OA effectiveness [Jin et al., 2020; Liu et al., 2018; Wu et al., 2019]. For instance, it is still exceedingly difficult to transport drugs through the thick cartilage matrix. To get around this problem, Liang et al. employed the lysosome-associated membrane glycoprotein 2b to fuse a chondrocyte-affinity peptide (CAP) to the surface of exosomes generated from chondrocytes. The in vivo investigation demonstrated that IA injection of miR-140 delivered by CAP-exosomes greatly slowed the progression of OA in rat models [Liang et al., 2020]. There have been several research on the function of natural exosomes, but in contrast, studies on designing exosomes as efficient vectors, particularly for OA, have received less attention. This is because the traditional centrifugation method, ultracentrifugation, takes more time to extract exosomes while also raising the danger of infection [Ni et al., 2020]. Additionally, there are no well-defined pathways for enhancing the generation of exosomes with therapeutic benefits specifically for the treatment of OA.

Natural exosomes can act as drug delivery vehicles in addition to carrying therapeutic moeity itself [Sato et al., 2017]. The limited quantities of exosomes that MSCs release, however, are insufficient for clinical studies. Consequently, it is now technically difficult to acquire enough exosomes for usage in vivo. Some research is investigating and employing hypoxic three-dimensional spheroid culture, microvesicles, and cellular-nanoporation approaches to increase exosomes production [Ni et al., 2020]. We anticipate a new era in the treatment of OA with the understanding of the mechanism of action and the maturation of exosome production technologies.

Challenges and Future Directions

Osteoarthritis (OA) is a challenging condition to treat effectively, with current clinical approaches primarily focused on symptom management and disease progression delay. However, recent research in the field of nanomedicine offers promising avenues for more effective OA treatment. This review delves into the potential of Nanoparticles (NPs)-based drug delivery systems as a game-changing approach. Current clinical treatments for OA primarily aim to delay disease progression, alleviate pain, and improve mobility. Unfortunately, there is no definitive curative method available. However, NPs-based drug delivery systems show tremendous promise in OA treatment due to their ability to achieve targeted drug distribution, extend drug release, and enhance drug retention within the affected joints.

One significant breakthrough in OA research revolves around anabolic-catabolic balance strategies. A standout player in this domain is Kartogenin (KGN), which gained attention in 2012 when a study published in Science showcased its potential for promoting cartilage repair by stimulating chondrogenesis of endogenous Mesenchymal Stem Cells (MSCs). Subsequent studies have consistently supported these findings.

Notably, KGN not only drives chondrogenic differentiation of MSCs but also enhances the proliferation and survival of chondrocytes. This positions KGN as one of the leading candidates among therapeutic agents for OA [Johnson et al., 2012].

Another exciting avenue lies in the use of nanozymes, such as CeO2, MnO2, and Pt NPs, which mimic natural antioxidant enzymes. These nanozymes exhibit robust reactive oxygen species (ROS)-scavenging activities. Delivering KGN using nanozymes as carriers presents a promising strategy for OA treatment, potentially augmenting its therapeutic efficacy. MicroRNAs (miRNAs) have emerged as another potent tool for OA treatment. These small RNA molecules play crucial roles in both cartilage development and homeostasis as individuals age [Jin, 2020]. While the exact mechanism of miRNAs in OA treatment requires further exploration, they represent an excellent candidate for therapeutic agents. The integration of novel nanotechnology with miRNAs in appropriate OA models holds great promise for achieving optimal therapeutic outcomes in the near future.

However, it's essential to acknowledge the challenges in the application of nanomedicine for OA. Most NPs lack specificity towards the various cell types implicated in OA. While surface functionalization of NPs with proteins is a common approach to target specific cell receptors, many receptors are not uniquely expressed by a single cell type. This can lead to off-target effects. Surface functionalization also tends to be a low-throughput process, heavily reliant on the discovery of novel cell receptors. A potential solution lies in the use of DNA barcoding technology, where a segment of nucleotide sequence (DNA barcode) can be incorporated into NPs for high-throughput screening of cell-NP interactions [Wang & Wagner, 2020]. For OA treatment, this approach holds promise in screening interactions with macrophages, chondrocytes, and osteoblasts in the joints.

Exploring innovative combinations of NPs with other materials for more targeted tissue delivery is another avenue of interest. While nanomedicine holds promise for selective interactions with cells, the conventional route of administration through intravenous injection can lead to lower drug concentrations at the targeted joint area and potential systemic side effects. Intra-articular injection, the most common route for OA administration, can overcome these disadvantages but involves invasive needle injection, associated with pain and needle phobia. Microneedles integrated with NPs offer a potential solution to this problem [Kim et al., 2012].

Nevertheless, it's crucial to recognize that nanotechnology is currently costly and unfamiliar to most OA patients, limiting its widespread therapeutic use. Addressing these challenges is paramount, and continued efforts are required to overcome these limitations. Improving the efficiency of nano drug delivery systems to transition from intra-articular injection to oral or external drugs for ultra-early OA treatment is a priority. Blocking OA progression at the genetic level is another critical avenue, as is the development of improved implant materials to accelerate bone healing and extend joint replacement prosthesis lifespan. With the emergence of new therapeutic procedures, selecting the optimal clinical treatment plan for individual patients becomes increasingly complex, necessitating careful consideration of their specific conditions. Moreover, the field of nanotherapeutics for OA treatment is still in its early stages, presenting room for growth and refinement.

Many existing nanocarriers face limitations, particularly in terms of drug loading and sustained-release systems. Additionally, the construction of functional nanoparticles remains a challenge, as synthesized nanomaterials are prone to interactions with proteins expressed on various cell membranes after entering the body. To enhance their efficacy, some researchers turn to polymer materials for nanoparticle surface functionalization, although these may trigger immune reactions and form a "protein corona" [Corbo et al., 2017]. Besides, the natural cell membrane-modified biomimetic nanocarriers offer a more biocompatible alternative. They have demonstrated excellent therapeutic effects in OA treatment. However, their preparation currently involves cell lysis and membrane purification, which can lead to product contamination and damage to key proteins. Furthermore, the advantages of cell membranes derived from single cells are limited, prompting researchers to explore nanotherapeutic strategies based on hybrid cell membranes. As nanomaterials, synthetic techniques, and relative ligands continue to evolve, common issues such as nanocarrier stability, retention time, minimal side effects in non-target tissues, and systemic biosafety can be addressed, further enhancing the potential of nanotherapeutic strategies for OA.

Conclusions

In conclusion, the future of OA treatment looks promising with the continuous advancements in nanotechnology and our growing understanding of OA's pathological mechanisms. Different nanoparticles have been extensively explored in the therapy of OA and other diseases. The main benefits of these drug delivery systems based on different nanoparticles are their ability to release drugs over extended periods, increase drug retention in the joints, and enhance therapeutic efficacy through functional regulatory strategies. This allows for lower therapeutic doses, reduced administration frequency, increased pharmacological efficacy, and decreased off-target toxicity. Additionally, novel fields like chondroprotective treatment, nanomaterial-based scaffolds for cartilage regeneration, and immunotherapy strategies are being developed. While challenges remain, ongoing multidisciplinary collaboration is expected to drive the progress of nanotherapy in OA treatment.

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References

Abbasi, E.; Aval, S.F.; Akbarzadeh, A.; Milani, M.; Nasrabadi, H.T.; Joo, S.W.; Hanifehpour, Y.; Nejati-Koshki, K.; Pashaei-Asl, R. Dendrimers: Synthesis, applications, and properties. *Nanoscale Res. Lett.* 2014, *9*, 247.

Abdel-Aziz M. A., Ahmed H. M. S., El-Nekeety A. A., Sharaf H. A., Abdel-Aziem S. H., Abdel-Wahhab M. A. (2021). Biosynthesis of Gold Nanoparticles for the Treatment of Osteoarthritis Alone or in Combination with Diacerein® in a Rat Model. *Inflammopharmacology* 29 (3), 705–719. 10.1007/s10787-021-00833-8

Abedi-Gaballu, F.; Dehghan, G.; Ghaffari, M.; Yekta, R.; Abbaspour-Ravasjani, S.; Baradaran, B.; Dolatabadi, J.E.N.; Hamblin, M.R. PAMAM dendrimers as efficient drug and gene delivery nanosystems for cancer therapy. *Appl. Mater. Today* 2018, *12*, 177–190.

Ackerman IN, Kemp JL, Crossley KM, Culvenor AG, Hinman RS. Hip and Knee Osteoarthritis Affects Younger People, Too. J Orthop Sports Phys Ther. 2017 Feb;47(2):67-79.

Ameya, A., Dravid., Kaamini, M., Dhanabalan., Soumya, Naskar., Akshi, Vashistha., Smriti, Agarwal., Bhagyashree, Padhan., Mahima, Dewani., Rachit, Agarwal. (2023). Sustained release Resolvin D1 liposomes are effective in the treatment of osteoarthritis in obese mice. bioRxiv, doi: 10.1101/2023.01.21.525015

Araújo FA, Kelmann RG, Araújo BV, Finatto RB, Teixeira HF, Koester LS. European journal of pharmaceutical sciences development and characterization of parenteral nanoemulsions containing thalidomide. *Eur J Pharm Sci*. 2011;42:238–245.

Arias, L. S., Pessan, J. P., Vieira, A. P. M., Lima, T. M. T. D., Delbem, A. C. B., & Monteiro, D. R. (2018). Iron oxide nanoparticles for biomedical applications: A perspective on synthesis, drugs, antimicrobial activity, and toxicity. *Antibiotics*, *7*(2), 46.

Bao C., He C. (2021). The role and therapeutic potential of MSC-derived exosomes in osteoarthritis. *Arch. Biochem. Biophys.* 710, 109002.

Barenholz Y. Doxil®--the first FDA-approved nano-drug: lessons learned. J Control Release. 2012 Jun 10;160(2):117-34.

Bedingfield SK, Colazo JM, Di Francesco M, Yu F, Liu DD, Di Francesco V, Himmel LE, Gupta MK, Cho H, Hasty KA, Decuzzi P, Duvall CL. Top-Down Fabricated microPlates for Prolonged, Intra-articular Matrix Metalloproteinase 13 siRNA Nanocarrier Delivery to Reduce Post-traumatic Osteoarthritis. ACS Nano. 2021 Sep 28;15(9):14475-14491.

Bedingfield SK, Colazo JM, Yu F, Liu DD, Jackson MA, Himmel LE, Cho H, Crofford LJ, Hasty KA, Duvall CL. Amelioration of post-traumatic osteoarthritis via nanoparticle depots delivering small interfering RNA to damaged cartilage. Nat Biomed Eng. 2021 Sep;5(9):1069-1083.

Bhalekar MR, Upadhaya PG, Madgulkar AR. Fabrication and efficacy evaluation of chloroquine nanoparticles in CFA-induced arthritic rats using TNF-α ELISA. Eur J Pharm Sci. 2016 Mar 10;84:1-8.

Bobis-Wozowicz S., Kmiotek K., Sekula M., Kedracka-Krok S., Kamycka E., Adamiak M., et al. (2015). Human Induced Pluripotent Stem Cell-Derived Microvesicles Transmit RNAs and Proteins to Recipient Mature Heart Cells Modulating Cell Fate and Behavior. *Stem Cells* 33 (9), 2748–2761.

Chen CH, Kuo SM, Tien YC, Shen PC, Kuo YW, Huang HH. Steady Augmentation of Anti-Osteoarthritic Actions of Rapamycin by Liposome-Encapsulation in Collaboration with Low-Intensity Pulsed Ultrasound. Int J Nanomedicine. 2020 May 28;15:3771-3790.

Cheng X, Lee RJ. The role of helper lipids in lipid nanoparticles (LNPs) designed for oligonucleotide delivery. Adv Drug Deliv Rev. 2016 Apr 1;99(Pt A):129-137.

Corbo C., Molinaro R., Taraballi F., Toledano Furman N. E., Hartman K. A., Sherman M. B., et al. (2017). Unveiling the In Vivo Protein Corona of Circulating Leukocyte-like Carriers. ACS Nano 11 (3), 3262–3273.

Elghanian R, Storhoff JJ, Mucic RC, Letsinger RL, Mirkin CA. Selective colorimetric detection of polynucleotides based on the distance-dependent optical properties of gold nanoparticles. Science. 1997 Aug 22;277(5329):1078-81.

Formica F. A., Barreto G., Zenobi-Wong M. (2019). Cartilage-targeting dexamethasone prodrugs increase the efficacy of dexamethasone. *J. Control. Release* 295, 118–129.

Gaber DA, Alsubaiyel AM, Alabdulrahim AK, Alharbi HZ, Aldubaikhy RM, Alharbi RS, Albishr WK, Mohamed HA. Nano-Emulsion Based Gel for Topical Delivery of an Anti-Inflammatory Drug: In vitro and in vivo Evaluation. Drug Des Devel Ther. 2023 May 15;17:1435-1451.

Geiger, B. C., Wang, S., Padera Jr, R. F., Grodzinsky, A. J., & Hammond, P. T. (2018). Cartilage-penetrating nanocarriers improve delivery and efficacy of growth factor treatment of osteoarthritis. *Science translational medicine*, *10*(469), eaat8800.

Grässel S, Muschter D. Recent advances in the treatment of osteoarthritis. F1000Res. 2020 May 4;9:F1000 Faculty Rev-325.

Gu, W.; Wu, C.; Chen, J.; Xiao, Y. Nanotechnology in the targeted drug delivery for bone diseases and bone regeneration. *Int. J. Nanomed.* 2013, *8*, 2305–2317.

Guo X, Lou J, Wang F, Fan D, Qin Z. Recent Advances in Nano-Therapeutic Strategies for Osteoarthritis. Front Pharmacol. 2022 Jun 21;13:924387.

He M, Qin Z, Liang X, He X, Zhu B, Lu Z, Wei Q, Zheng L. A pH-responsive mesoporous silica nanoparticles-based drug delivery system with controlled release of andrographolide for OA treatment. Regen Biomater. 2021 Jun 30;8(4):rbab020.

Hui, Teng., Kai-Jian, Fan., Qi-Shan, Wang., Bin, Xu., Di, Chen., Futao, Zhao., Tingyu, Wang. (2023). Dexamethasone Liposomes Alleviate Osteoarthritis in miR-204/-211-Deficient Mice by Repolarizing Synovial Macrophages to M2 Phenotypes.. Molecular Pharmaceutics, doi: 10.1021/acs.molpharmaceut.2c00979

Jang S, Lee K, Ju JH. Recent Updates of Diagnosis, Pathophysiology, and Treatment on Osteoarthritis of the Knee. Int J Mol Sci. 2021 Mar 5;22(5):2619.

Jeevanandam, J.; Barhoum, A.; Chan, Y.S.; Dufresne, A.; Danquah, M.K. Review on nanoparticles and nanostructured materials: History, sources, toxicity and regulations. *Beilstein J. Nanotechnol.* 2018, *9*, 1050–1074.

Jin G-Z. Current Nanoparticle-Based Technologies for Osteoarthritis Therapy. *Nanomaterials*. 2020; 10(12):2368.

Jin, Z.; Ren, J.; Qi, S. Exosomal miR-9-5p secreted by bone marrow-derived mesenchymal stem cells alleviates osteoarthritis by inhibiting syndecan-1. *Cell Tissue Res.* 2020, *381*, 99–114.

Johnson, K.; Zhu, S.; Tremblay, M.S.; Payette, J.N.; Wang, J.; Bouchez, L.C.; Meeusen, S.; Althage, A.; Cho, C.Y.; Wu, X.; et al. A stem cell-based approach to cartilage repair. *Science* 2012, *336*, 717–721.

Jung JH, Kim SE, Kim HJ, Park K, Song GG, Choi SJ. A comparative pilot study of oral diacerein and locally treated diacerein-loaded nanoparticles in a model of osteoarthritis. Int J Pharm. 2020 May 15;581:119249.

Jüni P, Reichenbach S, Dieppe P. Osteoarthritis: rational approach to treating the individual. Best Pract Res Clin Rheumatol. 2006 Aug;20(4):721-40.

Kamar SS, ShamsEldeen AM, Hosny SA, El-Shafei AA, Rashid L, Hassanein RT, Hassan R. (2023). Comparing Effectiveness of Hyaluronic Acid-Chitosan Nanoparticles Encapsulation Versus Hyaluronic Acid Monotherapy in Osteoarthritis Rat Model: Microarray Screening for miR-140. Microscopy and Microanalysis, 29(2):686-697. doi: 10.1093/micmic/ozac048

Kang M. L., Ko J. Y., Kim J. E., Im G. I. (2014). Intra-articular delivery of kartogenin-conjugated chitosan nano/microparticles for cartilage regeneration. *Biomaterials* 35, 9984–9994.

Katz JN, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. JAMA. 2021 Feb 9;325(6):568-578.

Khan, M.A.; Khan, M.J. Nano-gold displayed anti-inflammatory property via NF-kB pathways by suppressing COX-2 activity. *Artif. Cells Nanomed. Biotechnol.* 2018, *46*, 1149–1158.

Khurana S, Jain NK, Bedi PMS. Nanoemulsion based gel for transdermal delivery of meloxicam: physico-chemical, mechanistic investigation. *Life Sci*. 2013;92:383–392.

Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev. 2012 Nov;64(14):1547-68.

Kim, Y. G., Choi, J., & Kim, K. (2020). Mesenchymal Stem Cell-Derived Exosomes for Effective Cartilage tissue repair and treatment of osteoarthritis. *Biotechnology journal*, *15*(12), 2000082.

Knapik JJ, Pope R, Orr R, Schram B. Osteoarthritis: Pathophysiology, Prevalence, Risk Factors, and Exercise for Reducing Pain and Disability. J Spec Oper Med. 2018 Fall;18(3):94-102.

Kraft JC, Freeling JP, Wang Z, Ho RJ. Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems. J Pharm Sci. 2014 Jan;103(1):29-52.

Kumar, S.; Adjei, I.M.; Brown, S.B.; Liseth, O.; Sharma, B. Manganese dioxide nanoparticles protect cartilage from inflammation-induced oxidative stress. *Biomaterials* 2019, *224*, 119467.

Leite C.B., Coelho J.M., Ferreira-Nunes R., Gelfuso G.M., Durigan J.L., Azevedo R.B., Muehlmann L.A., Sousa M.H. Phonophoretic application of a glucosamine and chondroitin nanoemulsion for treatment of knee chondropathies. *Nanomedicine.* 2020;15:647–659.

Leonavičienė, L.; Kirdaitė, G.; Bradūnaitė, R.; Vaitkienė, D.; Vasiliauskas, A.; Zabulytė, D.; Ramanavičienė, A.; Ramanavičius, A.; Ašmenavičius, T.; Mackiewicz, Z. Effect of gold nanoparticles in the treatment of established collagen arthritis in rats. *Medicina* 2012, *48*, 91–101.

Li S, Stöckl S, Lukas C, Herrmann M, Brochhausen C, König MA, Johnstone B, Grässel S. Curcumin-primed human BMSC-derived extracellular vesicles reverse IL-1β-induced catabolic responses of OA chondrocytes by upregulating miR-126-3p. Stem Cell Res Ther. 2021 Apr 29;12(1):252.

Li, B., Wang, F., Hu, F., Ding, T., Huang, P., Xu, X., Liang, J., Li, C., Zhou, Q., Lu, M. and Deng, L., 2022. Injectable “nano-micron” combined gene-hydrogel microspheres for local treatment of osteoarthritis. *NPG Asia Materials*, *14*(1), p.1.

Liang Y, Xu X, Li X, Xiong J, Li B, Duan L, Wang D, Xia J. Chondrocyte-Targeted MicroRNA Delivery by Engineered Exosomes toward a Cell-Free Osteoarthritis Therapy. ACS Appl Mater Interfaces. 2020 Aug 19;12(33):36938-36947.

Liu L, Tang H, Wang Y. Nanotechnology-Boosted Biomaterials for Osteoarthritis Treatment: Current Status and Future Perspectives. Int J Nanomedicine. 2023 Sep 4;18:4969-4983.

Liu P, Gu L, Ren L, Chen J, Li T, Wang X, Yang J, Chen C, Sun L. Intra-articular injection of etoricoxib-loaded PLGA-PEG-PLGA triblock copolymeric nanoparticles attenuates osteoarthritis progression. Am J Transl Res. 2019 Nov 15;11(11):6775-6789.

Liu X, Corciulo C, Arabagian S, Ulman A, Cronstein BN. Adenosine-Functionalized Biodegradable PLA-b-PEG Nanoparticles Ameliorate Osteoarthritis in Rats. Sci Rep. 2019 May 15;9(1):7430.

Liu, K., Zhang, D., & Wang, W. (2021). Nanoparticle-Based Drug Delivery System—A Target Strategy for Osteoarthritis Treatment. *Journal of Nanomaterials*, *2021*, 1-15.

Liu, Y.; Lin, L.; Zou, R.; Wen, C.; Wang, Z.; Lin, F. MSC-derived exosomes promote proliferation and inhibit apoptosis of chondrocytes via lncRNA-KLF3-AS1/miR-206/GIT1 axis in osteoarthritis. *Cell Cycle* 2018, *17*, 2411–2422.

Ma L, Li G, Lei J, Song Y, Feng X, Tan L, Luo R, Liao Z, Shi Y, Zhang W, Liu X, Sheng W, Wu S, Yang C. Nanotopography Sequentially Mediates Human Mesenchymal Stem Cell-Derived Small Extracellular Vesicles for Enhancing Osteogenesis. ACS Nano. 2022 Jan 25;16(1):415-430.

Mathieu, M.; Martin-Jaular, L.; Lavieu, G.; Théry, C. Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication. *Nat. Cell Biol.* 2019, *21*, 9–17.

Maudens P, Meyer S, Seemayer CA, Jordan O, Allémann E. Self-assembled thermoresponsive nanostructures of hyaluronic acid conjugates for osteoarthritis therapy. Nanoscale. 2018 Jan 25;10(4):1845-1854.

Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov. 2021 Feb;20(2):101-124.

Mohammadifar M, Aarabi MH, Aghighi F, Kazemi M, Vakili Z, Memarzadeh MR, Talaei SA. Anti-osteoarthritis potential of peppermint and rosemary essential oils in a nanoemulsion form: behavioral, biochemical, and histopathological evidence. BMC Complement Med Ther. 2021 Feb 9;21(1):57.

Mohammadinejad R, Ashrafizadeh M, Pardakhty A, Uzieliene I, Denkovskij J, Bernotiene E, Janssen L, Lorite GS, Saarakkala S, Mobasheri A. Nanotechnological Strategies for Osteoarthritis Diagnosis, Monitoring, Clinical Management, and Regenerative Medicine: Recent Advances and Future Opportunities. Curr Rheumatol Rep. 2020 Apr 4;22(4):12.

Ni Z, Zhou S, Li S, Kuang L, Chen H, Luo X, Ouyang J, He M, Du X, Chen L. Exosomes: roles and therapeutic potential in osteoarthritis. Bone Res. 2020 Jun 19;8:25.

Ni Z., Kuang L., Chen H., Xie Y., Zhang B., Ouyang J., et al. (2019). The Exosome-like Vesicles from Osteoarthritic Chondrocyte Enhanced Mature IL-1β Production of Macrophages and Aggravated Synovitis in Osteoarthritis. *Cell. Death Dis.* 10 (7), 522.

Ozkan H, Valdés-Fernández J, Willcockson HH, Livingston EW, Frank JE, Yuan H, Krelli C, Janjic j, Longobardi l. (2022). Imaging macrophages during post-traumatic

osteoarthritis with nirf labeled nanoemulsion. Osteoarthritis and Cartilage, 30:S293-S294. doi: 10.1016/j.joca.2022.02.393

Palazzo C, Nguyen C, Lefevre-Colau MM, Rannou F, Poiraudeau S. Risk factors and burden of osteoarthritis. Ann Phys Rehabil Med. 2016 Jun;59(3):134-138.

Pavelka K, Bruyère O, Cooper C, Kanis JA, Leeb BF, Maheu E, Martel-Pelletier J, Monfort J, Pelletier JP, Rizzoli R, Reginster JY. Diacerein: Benefits, Risks and Place in the Management of Osteoarthritis. An Opinion-Based Report from the ESCEO. Drugs Aging. 2016 Feb;33(2):75-85.

Ponnurangam, S.; O'Connell, G.D.; Chernyshova, I.V.; Wood, K.; Hung, C.T.; Somasundaran, P. Beneficial effects of cerium oxide nanoparticles in development of chondrocyte-seeded hydrogel constructs and cellular response to interleukin insults. *Tissue Eng. Part A* 2014, *20*, 2908–2919.

Pople PV, Singh KK. Development and evaluation of topical formulation containing solid lipid nanoparticles of vitamin A. *AAPS PharmSciTech*. 2006;7:E63–E69.

Puertas-Bartolomé M, Mora-Boza A, García-Fernández L. Emerging Biofabrication Techniques: A Review on Natural Polymers for Biomedical Applications. Polymers (Basel). 2021 Apr 8;13(8):1209.

Rachmawati H, Budiputra DK, Mauludin R. Curcumin nanoemulsion for transdermal application: formulation and evaluation. *Drug Dev Ind Pharm*. 2015;41:560–566.

Rahimi M, Charmi G, Matyjaszewski K, Banquy X, Pietrasik J. Recent developments in natural and synthetic polymeric drug delivery systems used for the treatment of osteoarthritis. Acta Biomater. 2021 Mar 15;123:31-50.

Reddy LH, Arias JL, Nicolas J, Couvreur P. Magnetic nanoparticles: design and characterization, toxicity and biocompatibility, pharmaceutical and biomedical applications. Chem Rev. 2012 Nov 14;112(11):5818-78.

Rozi P, Abuduwaili A, Mutailifu P, Gao Y, Rakhmanberdieva R, Aisa HA, Yili A. Sequential extraction, characterization and antioxidant activity of polysaccharides from Fritillaria pallidiflora Schrenk. Int J Biol Macromol. 2019 Jun 15;131:97-106.

Sani A, Cao C, Cui D. Toxicity of gold nanoparticles (AuNPs): A review. Biochem Biophys Rep. 2021 Apr 10;26:100991.

Sarkar, A.; Carvalho, E.; D'souza, A.A.; Banerjee, R. Liposome-encapsulated fish oil protein-tagged gold nanoparticles for intra-articular therapy in osteoarthritis. *Nanomedicine* 2019, *14*, 871–887.

Sarzi-Puttini P, Cimmino MA, Scarpa R, Caporali R, Parazzini F, Zaninelli A, Atzeni F, Canesi B. Osteoarthritis: an overview of the disease and its treatment strategies. Semin Arthritis Rheum. 2005 Aug;35(1 Suppl 1):1-10.

Sato M, Suzuki T, Kawano M, Tamura M. Circulating osteocyte-derived exosomes contain miRNAs which are enriched in exosomes from MLO-Y4 cells. Biomed Rep. 2017 Feb;6(2):223-231.

Shin HJ, Park H, Shin N, Kwon HH, Yin Y, Hwang J-A, Kim SI, Kim SR, Kim S, Joo Y, et al. p47phox siRNA-Loaded PLGA Nanoparticles Suppress ROS/Oxidative Stress-Induced Chondrocyte Damage in Osteoarthritis. *Polymers*. 2020; 12(2):443.

Soliman SM, Abdel Malak NS, El-Gazayerly ON, Abdel Rehim AA. Formulation of microemulsion gel systems for transdermal delivery of celecoxib: in vitro permeation, anti-inflammatory activity and skin irritation tests. *Drug Discov Ther*. 2010;4:459–471.

Song H, Li X, Zhao Z, Qian J, Wang Y, Cui J, Weng W, Cao L, Chen X, Hu Y, Su J. Reversal of Osteoporotic Activity by Endothelial Cell-Secreted Bone Targeting and Biocompatible Exosomes. Nano Lett. 2019 May 8;19(5):3040-3048.

Steichen SD, Caldorera-Moore M, Peppas NA. A review of current nanoparticle and targeting moieties for the delivery of cancer therapeutics. Eur J Pharm Sci. 2013 Feb 14;48(3):416-27.

Tao S. C., Huang J. Y., Gao Y., Li Z. X., Wei Z. Y., Dawes H., et al. (2021). Small extracellular vesicles in combination with sleep-related circRNA3503: A targeted therapeutic agent with injectable thermosensitive hydrogel to prevent osteoarthritis. *Bioact. Mater.* 6, 4455–4469.

Taruc-Uy RL, Lynch SA. Diagnosis and treatment of osteoarthritis. Prim Care. 2013 Dec;40(4):821-36, vii.

Teo K. Y. W., Sevencan C., Cheow Y. A., Zhang S., Leong D. T., Toh W. S. (2022). Macrophage Polarization as a Facile Strategy to Enhance Efficacy of Macrophage Membrane-Coated Nanoparticles in Osteoarthritis. *Small Sci.* 2 (4), 2100116. 10.1002/smsc.202100116

Théry, C.; Zitvogel, L.; Amigorena, S. Exosomes: Composition, biogenesis and function. *Nat. Rev. Immunol.* 2002, *2*, 569–579.

Thirunavukkarasu GK, Cherukula K, Lee H, Jeong YY, Park IK, Lee JY. Magnetic field-inducible drug-eluting nanoparticles for image-guided thermo-chemotherapy. Biomaterials. 2018 Oct;180:240-252.

Torchilin, V.P. Recent advances with liposomes as pharmaceutical carriers. *Nat. Rev. Drug Discov.* 2005, *4*, 145–160.

van Niel G., D'Angelo G., Raposo G. (2018). Shedding Light on the Cell Biology of Extracellular Vesicles. *Nat. Rev. Mol. Cell. Biol.* 19 (4), 213–228.

Wan, L., Song, H., Chen, X., Zhang, Y., Yue, Q., Pan, P., Su, J., Elzatahry, A.A. and Deng, Y., 2018. A magnetic-field guided interface coassembly approach to magnetic mesoporous silica nanochains for osteoclast-targeted inhibition and heterogeneous nanocatalysis. *Advanced materials*, *30*(25), p.1707515.

Wan, L., Wang, Y., Tan, X., Sun, Y., Luo, J., & Zhang, H. (2022). Biodegradable lubricating mesoporous silica nanoparticles for osteoarthritis therapy. *Friction*, *10*, 68-79.

Wang D, Astruc D. Fast-growing field of magnetically recyclable nanocatalysts. Chem Rev. 2014 Jul 23;114(14):6949-85.

Wang J, Wang X, Cao Y, Huang T, Song D, Tao H. Therapeutic potential of hyaluronic acid/chitosan nanoparticles for the delivery of curcuminoid in knee osteoarthritis and an in vitro evaluation in chondrocytes. Int J Mol Med. 2018;42(5):2604–14.

Wang J, Zhang L, Zhu J, Gu J, Wang X, Tao H. Hyaluronic Acid Modified Curcumin-Loaded Chitosan Nanoparticles Inhibit Chondrocyte Apoptosis to Attenuate Osteoarthritis via Upregulation of Activator Protein 1 and RUNX Family Transcription Factor 2. J Biomed Nanotechnol. 2022 Jan 1;18(1):144-157.

Wang S, Wei X, Sun X, Chen C, Zhou J, Zhang G, Wu H, Guo B, Wei L. A novel therapeutic strategy for cartilage diseases based on lipid nanoparticle-RNAi delivery system. Int J Nanomedicine. 2018 Jan 31;13:617-631.

Wang Y, Wagner E. Non-Viral Targeted Nucleic Acid Delivery: Apply Sequences for Optimization. Pharmaceutics. 2020 Sep 18;12(9):888.

Wei, Y., Luo, L., Gui, T., Yu, F., Yan, L., Yao, L., Zhong, L., Yu, W., Han, B., Patel, J.M. and Liu, J.F., 2021. Targeting cartilage EGFR pathway for osteoarthritis treatment. *Science translational medicine*, *13*(576), p.eabb3946.

Weydert, C.J.; Cullen, J.J. Measurement of superoxide dismutase, catalase and glutathione peroxidase in cultured cells and tissue. *Nat. Protoc.* 2010, *5*, 51–66.

Wu, J.; Wang, X.; Wang, Q.; Lou, Z.; Li, S.; Zhu, Y.; Qin, L.; Wei, H. Nanomaterials with enzyme-like characteristics (nanozymes): Next-generation artificial enzymes (II). *Chem. Soc. Rev.* 2019, *48*, 1004–1076.

Wu, Y.; Lu, X.; Shen, B.; Zeng, Y. The Therapeutic Potential and Role of miRNA, lncRNA, and circRNA in Osteoarthritis. *Curr. Gene Ther.* 2019, *19*, 255–263.

Xiao L, Cui J, Sun Z, Liu Y, Zheng J, Dong Y. Therapeutic potential of nanotechnology-based approaches in osteoarthritis. Front Pharmacol. 2022 Aug 8;13:920824.

Xiong W, Lan Q, Liang X, Zhao J, Huang H, Zhan Y, Qin Z, Jiang X, Zheng L. Cartilage-targeting poly(ethylene glycol) (PEG)-formononetin (FMN) nanodrug for the treatment of osteoarthritis. J Nanobiotechnology. 2021 Jul 3;19(1):197.

Xiuling, Ji., Yufei, Yan., Tao, Sun., Qiang, Zhang., Yixin, Wang., Ming, Zhang., Hongyu, Zhang., Xin, Zhao. (2019). Glucosamine sulphate-loaded distearoyl phosphocholine liposomes for osteoarthritis treatment: combination of sustained drug release and improved lubrication.. Biomaterials Science, doi: 10.1039/C9BM00201D

Yang Q, Yao Y, Zhao D, Zou H, Lai C, Xiang G, Wang G, Luo L, Shi Y, Li Y, Yang M, Huang X. LncRNA H19 secreted by umbilical cord blood mesenchymal stem cells

through microRNA-29a-3p/FOS axis for central sensitization of pain in advanced osteoarthritis. Am J Transl Res. 2021 Mar 15;13(3):1245-1256.

Yeh CC, Su YH, Lin YJ, Chen PJ, Shi CS, Chen CN, Chang HI. Evaluation of the protective effects of curcuminoid (curcumin and bisdemethoxycurcumin)-loaded liposomes against bone turnover in a cell-based model of osteoarthritis. Drug Des Devel Ther. 2015 Apr 20;9:2285-300.

Yuzhe, He., Miao, Sun., Jirong, Wang., Xiaofu, Yang., Changjian, Lin., Lujie, Ge., Chenting, Ying., Kailun, Xu., An, Liu., Lidong, Wu. (2022). Chondroitin sulfate microspheres anchored with drug-loaded liposomes play a dual antioxidant role in the treatment of osteoarthritis.. Acta Biomaterialia, doi: 10.1016/j.actbio.2022.07.052

Zazo H, Colino CI, Lanao JM. Current applications of nanoparticles in infectious diseases. J Control Release. 2016 Feb 28;224:86-102.

Zerrillo L, Gigliobianco MR, D'Atri D, Garcia JP, Baldazzi F, Ridwan Y, Fuentes G, Chan A, Creemers LB, Censi R, et al. PLGA Nanoparticles Grafted with Hyaluronic Acid to Improve Site-Specificity and Drug Dose Delivery in Osteoarthritis Nanotherapy. *Nanomaterials*. 2022; 12(13):2248.

Zerrillo L, Gupta KBSS, Lefeber FAWM, Da Silva CG, Galli F, Chan A, Veltien A, Dou W, Censi R, Di Martino P, et al. Novel Fluorinated Poly (Lactic-Co-Glycolic acid) (PLGA) and Polyethylene Glycol (PEG) Nanoparticles for Monitoring and Imaging in Osteoarthritis. *Pharmaceutics*. 2021; 13(2):235.

Zhang C, Wei X, Chen C, Cao K, Li Y, Jiao Q, Ding J, Zhou J, Fleming BC, Chen Q, Shang X, Wei L. Indian hedgehog in synovial fluid is a novel marker for early cartilage lesions in human knee joint. Int J Mol Sci. 2014 Apr 28;15(5):7250-65.

Zhao W, Wang H , Wang H , Han Y , Zheng Z , Liu X , Feng B , Zhang H . Light-responsive dual-functional biodegradable mesoporous silica nanoparticles with drug delivery and lubrication enhancement for the treatment of osteoarthritis. Nanoscale. 2021 Apr 7;13(13):6394-6399.

Zhao Y, Wei C, Chen X, Liu J, Yu Q, Liu Y, Liu J. Drug Delivery System Based on Near-Infrared Light-Responsive Molybdenum Disulfide Nanosheets Controls the High-Efficiency Release of Dexamethasone To Inhibit Inflammation and Treat Osteoarthritis. ACS Appl Mater Interfaces. 2019 Mar 27;11(12):11587-11601.

Zhou X., Liang H., Hu X., An J., Ding S., Yu S., et al. (2020). BMSC-derived Exosomes from Congenital Polydactyly Tissue Alleviate Osteoarthritis by Promoting Chondrocyte Proliferation. *Cell. Death Discov.* 6 (1), 142.

Zychowicz M. E. (2014). Viscosupplementation for knee osteoarthritis. *J. Am. Assoc. Nurse Pract.* 26, 163–175.