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Review Article

An Approach to New Treatments for Osteoarthritis: Advancing Phenotype-Specific Treatments and the Promise of Nanotechnology in Drug Delivery

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Abstract

Osteoarthritis (OA) is a prevalent joint disease causing substantial physical disability among adults, with no available therapy effectively halting structural deterioration or reversing existing defects. To address this, efforts have focused on tailoring treatment options through subgroup classification based on common characteristics.

These subgroups encompass structural types primarily driven by degenerative events affecting cartilage and bone, alongside inflammatory, pain-driven, senescence, and metabolic syndrome phenotypes. While classifying individuals into specific subtypes may prove challenging, it could aid in identifying patient groups most likely to benefit from specific therapies. Current clinical trials predominantly aim to regenerate or repair defects in cartilage and bone or target inflammatory mediators through intra-articular injections. However, this approach faces limitations due to low retention time and reduced efficacy, mainly attributed to rapid clearance from the joint.

Nanotechnology-based drug delivery systems offer promising solutions to these limitations. Advanced delivery platforms, including liposomes, natural polymers and their derivatives, and inorganic nanoparticles, have demonstrated superior retention and targeted delivery capabilities within the joint, potentially improving therapeutic outcomes and demonstrated promise in enhancing drug retention within the joint area. They provide solutions to current intra-articular medication delivery problems. Intra-articular drug delivery systems offer a significant improvement in drug efficacy by targeting specific cells or components. However, research in this field is still in its early stages and requires further investigation. This review article investigates recent developments in treatment options tailored to specific phenotypes of OA. In the following section, nanotechnology and its application in drug delivery for OA are explained.

Keywords: Drug delivery systems, Intra-articular therapy, Nanomaterial, Osteoarthritis, Pain therapy

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Introduction

Osteoarthritis (OA) is a complex chronic disorder that primarily impacts the knee, with the hand and hip being affected subsequently (1), and it affects about 80% of people over the age of 55 years (2). The development of OA involves various joint components, including cartilage, subchondral bone, the joint capsule, synovial membrane, and surrounding muscles. It is characterized by cartilage damage, subchondral bone hardening, and inflammation of the synovial membrane (3).

While articular cartilage breakdown and synovial membrane inflammation are key features of OA, the precise mechanisms initiating degradation remain elusive (4). Subchondral bone, the tissue beneath the calcified cartilage, includes both the subchondral cortical plate and the subchondral trabecular bone, though the distinction between these structures is not precisely defined (5). During OA initiation and progression, subchondral bone undergoes dynamic morphological transformations driven by altered osteoblast metabolism—osteoblasts being the bone-building cells of mesenchymal origin that differentiate from mesenchymal progenitors, either directly or via osteochondroprogenitors (6). These changes lead to pathological remodeling, in which subchondral bone transitions from increased resorption to bone accretion, ultimately result in tissue sclerosis (4).

Complementary therapies like diacerein and nutraceutical agents such as Avocado and Soybean Unsaponifiables (ASU), glucosamine, and Chondroitin Sulfate (CS) are also utilized, showing efficacy in symptom alleviation and sometimes joint structure modification (4).

ASU is a complex mixture of compounds, including fat-soluble vitamins, sterols, triterpene alcohols, and potentially furan fatty acids, though the specific active components remain unknown. The sterol content in ASU preparations is a primary contributor to its biological activity in articular chondrocytes. ASU modulates OA pathogenesis by inhibiting multiple molecules and pathways implicated in OA. Additionally, it inhibits fibrinolysis by stimulating plasminogen activator inhibitor expression.

ASU exhibits chondroprotective, anabolic, and anticatabolic properties. It prevents cartilage breakdown and promotes cartilage repair by stimulating the synthesis of collagen and aggrecan. This is achieved through the inhibition of inflammatory cytokines such as IL-1, IL-6, IL-8, TNF, and PGE2, mediated by modulation of the NF-kappaB pathway (7).

Similarly, glucosamine has demonstrated favorable effects on cartilage. It promotes anabolic processes by stimulating cartilage synthesis and inhibits catabolic reactions associated with OA through anti-inflammatory and antioxidant mechanisms. These effects help delay cartilage degeneration, resulting in reduced pain and swelling, along with improved joint mobility in OA patients (8).

Although many of routine treatments mainly offer symptomatic relief, they lack efficacy in halting disease progression, a primary cause of disability (3). Frequently prescribed treatments include pain relievers, Nonsteroidal Anti-inflammatory Drugs (NSAIDs), corticosteroids, and viscosupplementation. Viscosupplementation involves injecting Hyaluronic Acid (HA) into affected joints to restore the physiologic viscoelasticity of Synovial Fluid (SF) in the absence of inflammation (9). While traditionally regarded as a safe and effective therapy for knee OA, recent guidelines have refrained from recommending its use.

One study compared viscosupplementation to NSAIDs, reporting similar efficacy but with more prolonged effects than corticosteroids. However, it also concluded that the clinical benefits of viscosupplementation are minimal and associated with an increased risk of adverse events (9).

As a result, many aspects of viscosupplementation remain uncertain and controversial. Current guidelines neither fully advocate for nor oppose its routine use in managing OA symptoms.

Moreover, although intra-articular therapy has a number of advantages, it faces some limitations, such as low retention time and high clearance rates from the joint (10). Intra-articular drug delivery systems have focused on prolonging drug retention throughout the entire joint (11). They provide solutions to current intra-articular medication delivery problems. Nanotechnology-based drug delivery systems offer promising solutions to these limitations. Advanced delivery platforms, including liposomes, natural polymers and their derivatives, and inorganic nanoparticles, have demonstrated superior retention and targeted delivery capabilities within the joint, potentially improving therapeutic outcomes and demonstrated promise in enhancing drug retention

within the joint area.

Due to the growing trend of OA in Iran (12) and the importance of effective disease-modifying drugs, this review article investigates recent developments in treatment options tailored to specific phenotypes.

These phenotypes represent distinct subgroups of the disease characterized by underlying biological or clinical features, such as articular cartilage degradation, chronic pain mechanisms, metabolic syndrome, abnormal bone remodeling, and inflammation. In the following section, drug carriers, including liposomes, nanoparticles, and synthetic polymers, and their application in drug delivery for OA are thoroughly explained.

Liposomes can enhance drug delivery by concentrating therapeutic agents at the lesion site, thereby improving efficacy, reducing toxicity, and enhancing drug stability. Additionally, their lubricating properties help minimize bone wear in OA joints, making them a preferred drug carrier (13).

Similarly, nanoparticles improve the effectiveness of intra-articular injections by enabling controlled drug release, extending retention time, and enhancing penetration into joint tissues (14).

Targeting joint cartilage

Articular cartilage is a delicate connective tissue that covers the surfaces within diarthrodial joints. For example, in a normal human adult knee, the thickness of articular cartilage typically ranges from 1.5 to 3 *mm*. Cartilage primarily consists of chondrocytes and an Extracellular Matrix (ECM). The ECM is mainly made up of water, glycosaminoglycans, type II collagen, and proteoglycans. It is highly susceptible to damage from overloading, inflammation, trauma, and other factors, making articular cartilage damage a significant feature of OA.

However, articular cartilage possesses limited self-repair capabilities due to its poor blood supply and low metabolism. Without timely repair of cartilage injuries in OA, the condition can worsen, potentially involving surrounding tissues (15).

Anabolism-enhancing compound

Sprifermin: Sprifermin, a recombinant form of human fibroblast growth factor 18 (16), substantially enhances articular chondrocyte proliferation and ECM synthesis, resulting in a dose-dependent increase in cartilage thickness. Additionally, it significantly inhibits the activity of proteolytic enzymes such as Matrix Metalloproteinase-13 (MMP-13) and ADAMTS-5, leading to a marked reduction in the degeneration of articular cartilage (17). Currently undergoing phase III clinical trials, Sprifermin has shown no reported local or systemic safety issues (18).

BMP-7

Bone Morphogenetic Protein-7 (BMP-7) is a potent anti-inflammatory growth factor (19) with a pro-anabolic effect (18). BMP-7, significantly influences chondrocyte metabolism. It promotes the production (20,21) arrangement and preservation of matrix components. With aging and the progression of articular cartilage degeneration, the natural expression of BMP-7 decreases (22), suggesting its possible role in the advancement of cartilage degeneration (20).

Insulin-like Growth Factor 1 (IGF1)

Insulin-like Growth Factor 1 (IGF-1), a member of the growth factor family, is structurally very similar to pro-insulin (23). It is as the key anabolic growth factor within cartilage, essential for structural upkeep by stimulating the production of cartilage matrix molecules. Its significance in articular cartilage lies in overseeing the synthesis of type II collagen and proteoglycans, crucial for sustaining chondrocyte activity. Recent research indicates that IGF-1 also serves to shield chondrocytes from apoptosis (24).

Ozone

Ozone (a solution of O_2–O_3) is recognized as a potent antioxidant compound. Numerous studies have illustrated ozone's effectiveness in modulating inflammation and triggering the release of stem cells and growth factors, thereby facilitating cartilage growth and mechanisms for joint repair. A recent study suggests that ozone can impact the progression of OA by reducing inflammatory cytokines, diminishing catabolic chemokines, boosting anti-inflammatory cytokines, and fostering anabolic chemokines (IGF-1, TGF-β) (25,26). Furthermore, ozone stimulates chondrocyte and fibroblast proliferation; thus, synthesis of articular cartilage and repair of tissue defects are anticipated outcomes. Consequently, based

on these findings, ozone emerges as a viable option for managing knee OA owing to its anti-inflammatory, metabolic, and anabolic properties (25).

Regeneration based medical compounds

Gene therapy: Gene therapy holds promise as a clinical strategy for delivering genes that encode cartilage growth factors, pro-regenerative agents, and anti-inflammatory substances directly to damaged sites. This approach seeks to minimize invasive delivery methods, providing sustained therapeutic effects as an alternative to daily injections of recombinant proteins or chemical compounds. In phase I and II trials, cell-mediated gene treatments that use allogeneic chondrocytes modified to produce Transforming Growth Factor beta (TGF-β1) have demonstrated significant improvements in joint function and symptoms in patients with severe late-stage OA (24). The most recent phase III trial showed significant improvements in International Knee Documentation Committee (IKDC), Visual Analogue Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the Knee Injury and Osteoarthritis Outcome Score (KOOS scores) after a single dose of chondrocytes that had been retrovirally transduced with TGF-β (27,28).

Cell therapy and intra-articular Mesenchymal Stem/Stromal Cell (MSC) therapy

One approach that shows promise for improving damaged joint cartilage and treating hypocellularity brought on by chondrocyte depletion is cell therapy (18,29) directed towards chondrocyte replenishment.

Mesenchymal Stem/Stromal Cells (MSCs) have gained attention as a possible osteoarthritis treatment. The ability of Bone Marrow Mesenchymal Stem Cells (BM-MSCs) to differentiate into many cell lineages, such as type II chondrocytes, adipocytes, and osteoblasts/osteocytes, is known as their multipotency. In comparison to existing translational OA therapeutic therapies, MSCs have several advantages. First, since they are autologous, the chance of autoimmune rejection is reduced. Second, MSCs have a high degree of purity and may be extracted in relatively large quantities, which maximizes their ability to differentiate into target tissues inside the injured joint area. Third, MSCs have potent anti-inflammatory qualities similar to other products used in regenerative therapy; they express IL-1Ra and can directly combat resident macrophages in the joint region, preventing the release of pro-inflammatory cytokines. Fourth, Good Manufacturing Practices (GMP) can be used to cultivate and expand human MSCs *ex vivo*, enabling further pharmacological treatments to improve cell proliferation, maturation, and repair capability (29).

Platelet Rich Plasma (PRP) Therapy

Another product from regenerative medicine, Platelet-Rich Plasma (PRP), has become the focus of current clinical trials for the treatment of OA in the knee. PRP contains significantly higher quantities of platelets and related growth factors compared to regular plasma. PRP solutions often have platelet concentrations that are four to six times higher than the patient's baseline values (29).

Since PRP is derived from autologous blood and may be utilized in outpatient clinics, it is safe from immune responses and blood-borne diseases. Furthermore, it is affordable, effective, and does not require any further procedures (30). Studies regarding the role of PRP in OA were controversial. Additionally, platelet-derived growth factors control various biological processes involved in tissue repair (31).

Targeting pain

While pain is frequently reported by individuals with OA (32-41), healthcare professionals have a limited understanding of its origin, mechanism, and treatment (32). In recent years, the scientific literature has begun to publish classification schemes based on pain mechanisms (33-35). This classification system theoretically facilitates the identification of the most suitable treatment approach and enhances outcomes (36). One benefit of these classifications is their ability to offer a more thorough comprehension of the differences observed in the character and intensity of clinical presentations in musculoskeletal pain syndromes such as OA (37,38). Although there are various classifications, the most important classifications are explained in this section.

Targeting nerve growth factor

Significant efforts have been made to develop therapies targeting Nerve Growth Factor (NGF). NGF

can be released through mechanical stimulation or by inflammatory mediators from various cell types, including osteoclasts, osteocytes, chondrocytes, synovial fibroblasts, and macrophages, in both pre-clinical and human studies OA (18). Research suggests that anti-NGF therapy holds promise in alleviating pain and improving function for patients with severely symptomatic OA unresponsive to conventional analgesics. However, given the evident risks of significant adverse effects, it is crucial to pinpoint patients most likely to benefit from this therapy and identify those at the highest risk of toxicity. Ongoing safety studies and post-marketing surveillance are essential for defining these patient groups (39).

Targeting peripheral opioid receptors

Opioids are potent analgesics; however, their usage is restricted due to significant adverse effects such as constipation, respiratory depression, tolerance, and dependence. Presently, there is ongoing development of new Opioid Receptor (OR) agonists targeting the μ, δ, and κ subtypes, aimed at improving safety profiles (18).

Targeting central sensitization

Chronic pain in OA patients is partly due to a biological process known as central sensitization, which is triggered by painful stimuli from damaged bone and joint tissue (42). This phenomenon was observed in both animal and human OA models (43-45). In addition to chronic pain and disability, around 21% of adults with OA also suffer from depression (10).

Targeting metabolic Syndrome (MetS)

Metabolic OA is now recognized as a distinct subtype of OA, and there is an association between this phenotype and MetS, encompassing both individual MetS components and MetS as a whole. The discussion below outlines various presentations of these cases.

- Hypertension is linked to OA *via* subchondral ischemia, which can hinder the exchange of nutrients into the articular cartilage and prompt bone remodeling (46). The management of osteoarthritis in individuals with hypertension presents a therapeutic challenge since many analgesics, particularly non-steroidal anti-inflammatory drugs (NSAIDs), negatively impact blood pressure. When used over an extended period, even modest drug-induced increases in blood pressure can significantly raise the risk of patients with cardiovascular disease (47).
- In addition, two major ways that T2DM affects OA are persistent hyperglycemia, which is linked to oxidative stress, abnormal pro-inflammatory cytokine production, the formation of Advanced Glycation End products (AGEs) in joint tissues, and insulin resistance, which can both sustain a systemic low-grade inflammatory condition and have local effects (18).
- Furthermore, metabolic factors associated with obesity, particularly changes in adipokine levels, play a role in the development of OA by promoting the expression of pro-inflammatory factors and degradative enzymes. This results in the suppression of cartilage matrix synthesis and the stimulation of subchondral bone remodeling (46).
- Additionally, the development of OA may be sped up by dyslipidemia-induced ectopic lipid deposition in chondrocytes, which is then made worse by abnormal cellular lipid metabolism in joint tissues (46).

Therapy

Statin: Statins are competitive inhibitors of hydroxymethyl-glutaryl-coenzyme A reductase (HMG-CoA), an enzyme crucial in cholesterol biosynthesis, and are commonly prescribed for managing hypercholesterolemia (47). Statins have been proposed as potential disease-modifying drugs for OA (48) due to their ability to target various underlying mechanisms. However, their use is controversial due to reported adverse musculoskeletal and metabolic effects (49). Statins like atorvastatin and simvastatin may offer preventive benefits for deteriorating joint cartilage by lowering serum cholesterol levels. Atorvastatin has shown a protective effect against cartilage degradation induced by interleukin-1β stimulation, mediated through the STAT1-caspase-3 signaling pathway. Similarly, simvastatin demonstrated chondroprotective effects *in vitro* by reducing matrix metalloproteinase expression (50).

Curcuminoid

Curcuminoids, natural polyphenols known for their potent antioxidant properties, may offer therapeutic benefits in osteoarthritis treatment (51). Typically, curcuminoids consist of three main components:

curcumin (75%), dimethoxy curcumin (10–20%), and bisdemethoxycurcumin (5–10%). The diverse actions of curcuminoids in various diseases may be attributed to their potent antioxidant effects. These compounds act as chain-breaking antioxidants, effectively reducing lipid peroxidation. Additionally, curcuminoids have the ability to scavenge free radicals like superoxide, hydroxyl, and nitrite, enhance the activity of several antioxidant enzymes, and suppress the generation of Reactive Oxygen Species (ROS) (51). Curcumin is considered to have good clinical efficacy and safety in Knee OA treatment (52).

Metformin

Metformin, as the primary medication for treating type 2 diabetes, is increasingly recognized for its hypoglycemic, anti-aging, and anti-inflammatory properties. In recent years, there has been a growing focus on exploring its potential in treating OA. As an anti-diabetic agent, metformin may indirectly mitigate the negative impact of obesity on OA development. Clinical research has indicated favorable outcomes of metformin on the long-term knee health of obese individuals. Furthermore, metformin can activate AMPK, a key enzyme involved in pain signaling and chondrocyte metabolism (53). In addition, another study supported a favorable effect of metformin on chondroprotection, immunomodulation and pain reduction in knee OA (54).

Targeting aging

Age is a significant risk factor for OA development, and age-related changes within the joint may present therapeutic targets. Hallmarks of aging, including cellular senescence, mitochondrial dysfunction, and mitochondrial genetics, contribute to OA progression. The mitochondrion serves as a crucial source of Reactive Oxygen Species (ROS). As individuals age, mitochondrial function tends to decline and a causal relationship between age-related mitochondrial dysfunction, oxidative stress, and disease has been proposed (55).

In addition, elevated levels of cytokines like IL-6 in OA patient's synovial fluid suggest a role in OA progression. IL-6 can induce senescence in neighboring cells, perpetuating a cycle of cellular aging. Chondrocytes further propagate senescence through Extracellular Vesicles (EVs), which are increased in OA patients and can induce senescence in nearby cells. Cytokines can also upregulate Matrix Metalloproteinases (MMPs) and ADAMTS, enzymes that degrade ECM proteins in cartilage. This catabolic activity contributes to ECM loss, a hallmark of OA (56).

Aging therapy

Coenzyme Q10 (CoQ10), and methylene blue are the antioxidants, playing a role in mitigating senescence induced by oxidative stress, with CoQ10 being the most extensively researched.

Methylene Blue (MB)

It is a widely recognized mitochondria-targeted antioxidant that has demonstrated potential in combating aging, especially skin aging. Methylene blue is noted for its effectiveness in delaying cellular senescence in the skin and prolonging fibroblast lifespan *in vitro*, along with enhancing mitochondrial functions. In addition, MB effectively treats OA-associated pain by increasing the levels of lncRNA MEG3. Furthermore, in a rabbit model of OA, lncRNA MEG3 alleviates pain and inflammation by suppressing the expression of P2X3 (57).

CoQ10

Lipid-soluble CoQ10 contributes, either directly or indirectly, to metabolism, mitochondrial permeability, antioxidant defense, and oxidative phosphorylation. Aging and neurological diseases are among the ailments that have been associated to CoQ10 deficiency (58-63). For example, it has been demonstrated that pharmacologically suppressing the production of CoQ10 causes accelerated aging, oxidative stress, apoptosis, and mitochondrial dysfunction in human dermal fibroblasts (58).

Coenzyme Q10 (CoQ10) has shown varied biological impacts on bone and cartilage. Observational studies hint at its potential to decelerate OA progression and alleviate inflammation. Yet, the precise influence of CoQ10 on OA remains uncertain (64).

Targeting inflammatory process

It is now widely recognized that OA includes an inflammatory component, which may be more

prominent in certain patient subgroups and specific joint tissues (18). Cytokines play multifaceted roles in OA, contributing to primary cartilage damage and the observed synovial activation in osteoarthritic joints. In laboratory experiments and animal studies focused on OA, various cytokines have emerged as possible targets for therapeutic interventions (65). In addition, pro-inflammatory cytokines may disrupt articular cartilage homeostasis through metabolic changes and significantly hasten joint damage.

Throughout the progression of the disease, these compounds impact most cells in the joints and the production of cytokines. Chemokines, including CCL2, CCl3, CCL4, CCL5, and IL8 play a main role in OA changes (66). Figure 1 illustrates the central inflammatory mechanisms and factors involved in OA development.

In OA, anti-inflammatory cytokines play a crucial role by inhibiting at least one of the primary pro-inflammatory cytokines responsible for OA development and progression. The most important of these therapies are explained.

Anti-IL-1 therapy

The potential effectiveness of IL-1 receptor antagonists (IL-1Ra) in reducing OA severity was initially demonstrated in *in vitro* studies, which showed a decrease in cartilage degradation with this treatment. Further evidence from animal models of OA supported these findings. For example, administering IL-1Ra locally in dogs reduced both macroscopic and microscopic knee OA lesions in a dose-dependent manner, underscoring the therapeutic potential of the drug (67).

Anti-TNF-alpha therapy

While the role of TNF-alpha in the pathophysiology of OA is well-established, only a limited number of experimental trials have explored the effectiveness of blocking this pro-inflammatory cytokine in OA treatment. A human case report revealed that adalimumab effectively treated inflammatory knee OA, leading to significant symptom improvement and positive changes in MRI results. This included a substantial decrease in synovitis and synovial effusion, as well as the complete resolution of bone marrow edema (67).

Hydroxychloroquine

Hydroxychloroquine, a derivative of chloroquine primarily employed in treating malaria and inflammatory autoimmune conditions such as rheumatoid arthritis (RA), purportedly operates through Toll-like receptor (TLR) 7/9 (18). Multiple studies investigating Hydroxychloroquine for hand OA have yielded inconclusive results (68,69), while data from knee OA studies are currently unavailable (18).

Targeting bone remodeling

Recent developments in bone cell biology have identified new targets for treating bone loss. These targets focus on preventing bone resorption by osteoclasts or promoting bone formation by osteoblasts (70).

Bisphosphonates (BPs)

BPs are a group of synthetic drugs that have been extensively utilized for several decades. The first documentation of BPs dates back to 1969, and they have profoundly influenced the clinical administration of bone-targeting medications (71-73). For a considerable period, BPs were regarded as the benchmark in drug delivery to skeletal tissues.

Bisphosphonates have a well-understood structure and mechanism (74,75). They are defined by two terminal phosphate groups (P-C-P) and a central carbon with accessible side chains, or R groups, that can influence binding interactions and drug release.

In addition, BPs have a strong affinity for Hydroxyapatite (HA), a major component of hard bone, resulting in preferential binding to this tissue (76). When used alone, BPs hinder bone resorption by osteoclasts and can also promote osteoblast differentiation (77), thereby facilitating bone formation. As a result, they have been widely employed in the treatment of OA.

Nevertheless, there are drawbacks to utilizing bisphosphonates as targeted agents, such as their low absorption, requirement for high dosages, and accompanying side effects, including mouth ulcers, osteonecrosis, and musculoskeletal pain (71).

Strontium ranelate

A recently developed drug known as strontium ranelate is known to improve bone architecture and

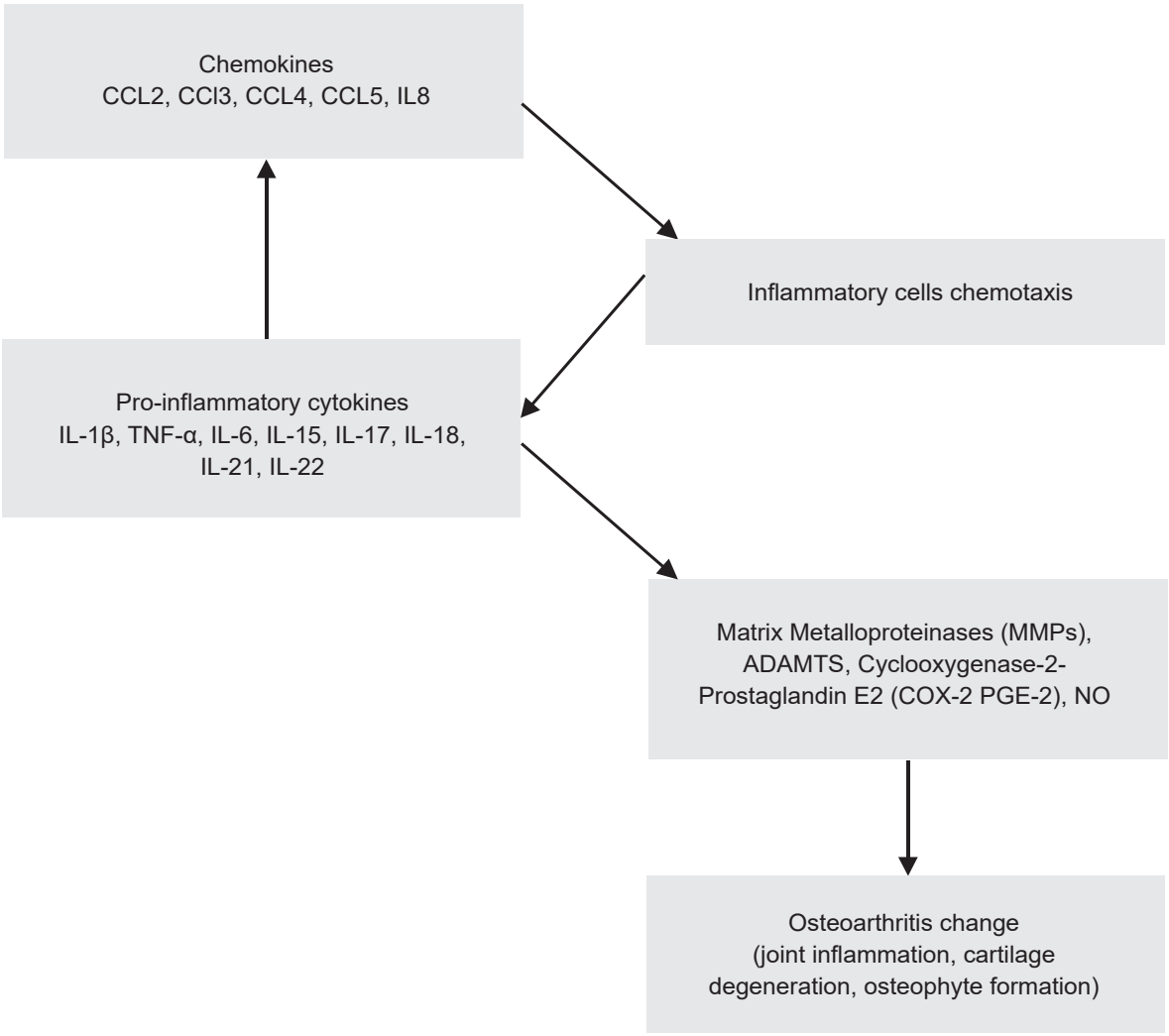

Figure 1. The central inflammatory mechanisms and factors involved in OA development [66].

increase bone mass. It is approved to treat osteoporosis and successfully lowers the risk of hip and vertebral fractures. In animal models such as ovariectomized rats or rats with hindlimb immobility, strontium ranelate acts on both bone production and resorption, preventing trabecular bone loss, reducing bone resorption, and either increasing or maintaining bone formation (78). In mice, rat, and monkey, it has also been demonstrated to reduce bone resorption, increase bone mass, and strengthen bones (79-81). According to *in vitro* research, strontium ranelate directly promotes pre-osteoblast replication and development while suppressing osteoclast differentiation and resorption (82-84).

Preclinical studies in both normal and osteopenic animals suggest that strontium ranelate positively impacts bone quantity and quality, including microarchitecture, geometry, and intrinsic properties, resulting in a favorable bone balance. Its properties imply a potentially major involvement in maintaining subchondral bone tissue homeostasis in individuals with OA, even though its role in other skeletal disorders is still unknown. A phase III clinical trial is currently being conducted to evaluate the drug's ability to change the structure of patients' knee OA joints (4).

Cathepsin K inhibitors

Cathepsin K, a cysteine endoproteinase found in osteoclasts, is crucial for degrading the type I collagen-rich bone matrix. Additionally, this protease is involved in the breakdown of cartilage in OA and changes in subchondral bone (85).

While the majority of clinical trials focused on phase II investigations and primarily explored the effects on Bone Mineral Density (BMD), only one phase II study targeting OA patients was initiated. Nevertheless, these clinical trials were stopped due to adverse events, notably

skin alterations. Despite this setback, the inhibition of cathepsin K emerges as a promising intervention for OA, as it has the potential to target both cartilage and subchondral bone remodeling. Ensuring safety remains paramount for future phase II and III studies (4).

Vitamin D

It is widely recognized that circulating vitamin D levels decrease with age, which may contribute to heightened bone remodeling. Vitamin D deficiency in adults can lead to elevated bone turnover, increased bone loss, and a higher risk of fragility fractures. While vitamin D is acknowledged as a vital hormonal regulator of cartilage and chondrocyte equilibrium, and chondrocytes do possess vitamin D receptors (86), its precise role in OA remains somewhat elusive and subject to debate. Although some clinical investigations have indicated a link between vitamin D deficiency and an elevated risk of knee OA progression and hip OA incidence (87,88), others have failed to establish a correlation between serum vitamin D levels and joint space reduction or deteriorating cartilage scores in knee OA (89,90). Many of these studies relied on radiographic evaluations of OA, with one utilizing MRI. However, in the MRI study (89), the entire knee or cartilage volume was not assessed.

Notably a recent investigation (91) examined knee OA structural alterations through both radiographic and quantitative MRI methods and revealed a positive correlation between changes in serum vitamin D levels and alterations in cartilage volume. Despite the uncertain mechanisms through which vitamin D influences cartilage, it may exert a direct impact on cartilage *via* specific vitamin D receptors.

Tetracyclines (TCs)

Tetracyclines (TCs) are small molecular compounds primarily recognized for their antibiotic properties used in treating bacterial infections. However, they have also shown promise in developing targeting moieties to address diseases with skeletal manifestations, particularly alveolar bone loss. TCs inhibit bone resorption through various mechanisms. Apart from their action on bone, TCs act as inhibitors of collagenases, targeting MMPs by chelating Ca^{2+} and Zn^{2+}. Zn^{2+} sequestration prevents procollagenase from being activated into its active form and consequently reduces the expression of the collagenase gene. TCs also reduce acid production and the secretion of lysosomal cysteine proteinases while promoting the expression of procollagen mRNA, thereby increasing the ratio of active to inactive osteoblasts (71).

Moreover, findings from basic science mechanistic studies suggest three main mechanisms through which TCs may benefit the progression of OA: inhibition of matrix metalloproteinases, immunomodulation, and inhibition of nitric oxide synthase (92).

Denosumab

The RANK/RANKL/OPG pathway plays a crucial role in regulating the equilibrium between osteoblasts and osteoclasts, which is vital for preventing bone loss and maintaining healthy bone turnover (71). Denosumab (monoclonal antibody) (93) stands out as the only therapy directed at RANKL, presenting a new avenue in osteoporosis treatment. Numerous studies have showcased denosumab's efficacy in diminishing the presence of specific bone resorption markers among postmenopausal women (71).

Nanotechnology and drug delivery systems

Joints present significant challenges for drug administration, such as the quick removal of medicines after intra-articular injection and the medication's low bioavailability (94).

Bioavailability refers to the proportion of an administered drug dose that reaches the bloodstream as the active ingredient, becoming available to exert a therapeutic effect. Several factors influence bioavailability, including the drug's physicochemical properties, mode of administration, interactions with other substances, absorption, hepatic metabolism, and excretion (95).

In comparison to medications that are administered freely, nanomaterials have consistently demonstrated promise in enhancing drug retention within the joint area. They provide solutions to current intra-articular medication delivery problems.

First of all, their size can be adjusted to promote slower clearance, which will increase the drug's biodistribution in the joint and extend its residence time. Furthermore, drugs can be released intracellularly or within the ECM of tissues due to the capacity of nanoscale materials

to cross cellular and extracellular matrix barriers. In the joint, the ability of nanomaterials to penetrate cells and tissues must be carefully balanced with lymphatic clearance, as smaller materials may be more readily cleared from the joint. Therefore, precise control over nanomaterial size during design may offer improved management of drug biodistribution and efficacy compared to macro-scale delivery systems (94).

Joint as a target for drug delivery

Engineered drug carriers for intra-articular delivery have historically focused on prolonging drug retention throughout the entire joint, suitable for drugs targeting multiple tissues. This approach, exemplified by IL-1 receptor antagonists, aims to mitigate cytokine-induced damage by distributing drugs throughout the synovium, cartilage, and other tissues (96). However, if drugs have poor uptake in specific tissues, this approach may be ineffective (97).

Efforts have shifted towards incorporating drugs into carriers too large to be quickly cleared, such as large microparticles, which accumulate in the synovium. However, this may lead to off-target drug uptake if the drug is needed in other tissues like cartilage. Thus, drug delivery strategies should be guided by therapeutic targets, potentially incorporating targeting strategies for specific tissues. Nanomaterial targeting can enhance joint retention and precise tissue delivery, using the localized site of nanomaterials as a reservoir for controlled drug release over time. Moreover, both active and passive tissue-specific targeting methods, such as ionic cross-linking with hyaluronic acid in synovial fluid, are designed to increase the residence time in specific joint tissues (94).

Cartilage as a tissue target for intra-articular drug delivery

In the context of intra-articular drug delivery, the focus on cartilage becomes paramount due to its central role in disease progression. As one of the primary tissues to degrade within the joint, cartilage releases substances that fuel the inflammatory milieu, worsening the condition (98). Additionally, preserving or regenerating the compromised cartilage extracellular matrix is crucial for reinstating mechanical and metabolic balance within the joint. Therefore, targeting cartilage for therapeutic delivery is essential, prompting the development of nanomaterials tailored to optimize payload delivery to this specific site (94).

Synovium as a tissue target for intra-articular drug delivery

Nanomaterials are now being engineered to target not just cartilage but also other crucial joint tissues like the synovium, addressing the complex progression of osteoarthritis (OA). The synovium, a thin connective tissue in joints, plays a significant role in OA inflammation and serves as a pathway for molecules entering and exiting the joint (99). Recent focus has turned towards recognizing synovitis as a treatment target, prompting the development of nanomaterials customized for delivery to specific synoviocyte types (94).

Classification of drug delivery system

The following are the most important drug delivery systems used in the treatment of OA.

Liposome

A liposome is an artificial membrane composed of phospholipid molecules. It forms when the hydrophilic heads of the phospholipid molecules interact with water, while the hydrophobic tails orient away from water, often extending into the air or forming a bilayer structure (100,101). Liposomes serve as effective carriers for delivering genetically modified or prepared medications, capable of merging with the cell membrane to facilitate drug delivery into the cell. They are recognized as one of the best medication delivery methods and were the first nanodrug carriers to receive FDA approval. Since liposome formulations have excellent biocompatibility and can transport both hydrophilic and hydrophobic medicines, they have been extensively investigated as drug carriers in OA (100).

Synthetic polymers-based nanoparticles (NPs)

Polymeric nanoparticles are solid colloidal particles with a size in the range of 10–1000 *nm*, and are made of biodegradable and biocompatible polymers or copolymers, in which the drug can be entrapped or encapsulated within the carrier, physically adsorbed on the surface of the carrier, or chemically linked to

the surface (102).

- Polymeric nanoparticles, like Poly Lactic Acid (PLA) and its derivative Poly(lactic-co-glycolic) Acid (PLGA), provide controlled drug release and are biocompatible.
- Studies show that PLGA nanoparticles loaded with TNF-α siRNA can significantly reduce inflammation and disease activity in arthritis models (99).
- Modifying the surface of PLA/PLGA with PEG enhances drug loading, delivery efficiency, circulation time, and prevents aggregation (103).

Natural polymers and their derivates based NPs

Natural polymers and their derivatives, such as chitosan, alginate, and cellulose derivatives, hold promise for intra-articular drug delivery (104,105).

- Chitosan nanoparticles are biocompatible and mimic natural cartilage glycosaminoglycans, supporting cartilage formation and reducing systemic drug exposure (106,107).
- These nanoparticles extend drug presence in synovial fluid and show efficacy in gene and drug delivery for OA treatment (99).

Inorganic nanoparticles

Inorganic nanoparticles are emerging as novel drug delivery system due to their unique physical properties that mainly include size dependent optical, magnetic, electronic, and catalytic properties (108).

Inorganic nanoparticles like Mesoporous Silica Nanoparticles (MSNs) have been utilized for delivering drugs and genes intra-articularly for arthritis treatment, capitalizing on their extensive surface area, large pore volume, capacity for morphology and pore structure modification, controlled surface functionality, and excellent biocompatibility (103,109). Mesoporous silica nanoparticles (MSNs) enable high-capacity drug loading and sustained release of target drugs in arthritis therapy (110,111).

- Specific MSN formulations can deliver hyaluronan synthase, reducing inflammation for up to three weeks after a single injection by enhancing HA synthesis in joints.

Nanoparticles

Nanoparticles are tiny materials having size ranges from 1 to 100 *nm*. They can be classified into different classes based on their properties, shapes or sizes (112). Nanoparticles offer a substantial improvement in drug efficiency by targeting specific cells or components within joint tissue.

- Nanoparticles improve drug efficiency through active and passive targeting (113).
- Active targeting uses ligands for receptor-specific binding, enhancing uptake (113).
- Passive targeting relies on nanoparticle properties like size and charge, increasing interaction with joint tissues (99).

Examples of OA drug targets addressing several OA phenotypes are shown in table 1.

Conclusion

OA significantly impacts adult mobility, with existing therapies unable to stop or reverse joint damage. Tailoring treatments based on subgroups—structural, inflammatory, pain-driven, senescence, and metabolic syndrome phenotypes show promise but is challenging due to patient categorization. Current clinical trials focus on cartilage and bone regeneration or targeting pro-inflammatory mediators *via* intra-articular injections, which suffer from low retention and efficacy. However, these strategies are limited by low retention times and reduced efficacy, primarily due to the rapid clearance from the joint. Nanomaterials offer a promising solution by improving drug retention and targeted delivery within joint tissues, potentially enhancing OA treatment effectiveness.

Various nanotechnology platforms, including liposomes, synthetic and natural polymer-based nanoparticles, and inorganic nanoparticles, have demonstrated potential in improving the outcomes of osteoarthritis therapies. From prolonging drug activity in synovial fluid to enabling intracellular and extracellular matrix penetration, these systems provide tailored solutions to meet the complex demands of joint treatment.

Looking ahead, continued progress in the development of nanotechnology-based drug delivery systems holds the promise of revolutionizing the treatment landscape for OA. As research continues to refine these platforms, overcoming challenges such as nanoparticle stability, biocompatibility, and scalability, there is substantial potential for improving the clinical

Table 1. Examples of Current OA drug targets addressing several OA phenotypes

Category	Therapy	Type of study	Explanation	Ref
Targeting articular cartilage (Anabolic drug)	PRP	Systematic review	This study, which included 10 trials, found that intra-articular PRP injections were more effective in reducing pain compared to a placebo at 6 months post-injection. Additionally, compared to hyaluronic acid, PRP demonstrated a significant reduction in pain on visual analogue and numeric rating scales at 6 months. However, nearly all trials had a high risk of bias	31
	PRP	Systematic review and meta-analysis	From 1452 records, 14 studies (1099 patients) were included. The PRP preparation process and treatment protocols varied (follow-up 6–12 months). Meta-analysis showed that PRP treatment did not significantly increase cartilage thickness (4 studies, 187 patients). Additionally, 3 RCTs (112 patients) found no significant difference in overall knee cartilage content change with PRP injections than no PRP	114
	PRP	Systematic review and meta-analysis	This study found that PRP resulted in a lower VAS score, a higher IKDC subjective score at 6 months, and significantly lower WOMAC scores during follow-up compared to a placebo. PRP also had a lower WOMAC score at 6 months compared to oral NSAIDs. Compared to HA, PRP showed better VAS, WOMAC, and IKDC scores. Adverse event rates were similar between PRP, placebo, and HA, with no significant differences. Additionally, different PRP applications indicated no significant differences in VAS scores at 1 month or WOMAC scores at 3 months. PRP was more effective in relieving symptoms compared to conservative treatments, with no significant difference between triple and single PRP applications in the short term	115
	Sprifermin	A meta-analysis	Eight studies were analyzed, revealing that patients treated with sprifermin experienced significantly less improvement in WOMAC total scores compared to those receiving a placebo. However, sprifermin-treated patients exhibited greater gains in cartilage thickness and volume in the femorotibial joint, along with less cartilage loss	116
	BMP-7	Clinical trial	This phase 1, double-blind, randomized study with 33 knee OA participants across 4 dosing cohorts found that the 1 *mg* BMP-7 group had more injection site pain but no ectopic bone formation. By week 12, both BMP-7 and placebo groups demonstrated a 20% pain improvement, with similar results. Participants on 0.1 *mg* and 0.3 *mg* BMP-7 showed a trend toward greater improvement. Secondary endpoints, including the OARSI criteria, indicated more responders in the BMP-7 groups. No dose-limiting toxicity was identified	117
	Ozone	A Meta-Analysis	Ozone treatment exhibited a therapeutic effect compared to other noninvasive treatments. However, when compared to hyaluronic acid or platelet-rich plasma, no significant advantages were observed for ozone treatment. Nonetheless, ozone demonstrated a notable short-term benefit in alleviating knee pain, with pain relief lasting between 3 and 6 months	118
Targeting articular cartilage (Cell therapy)	Ozone	Systematic review and meta-analysis	In five RCTs with 428 patients, 53% received ozone and 47% received control injections (HA, dextrose, air). The VAS mean difference favored ozone in the first month (MD= -0.23, p=0.71) but favored controls in the third and sixth months (MD=1.04 and 1.31). Control injections provided more prolonged pain relief. WOMAC scores also favored ozone initially but shifted to favor control injections at later follow-ups. Adverse events were similar between groups. The meta-analysis concluded that ozone injection is effective and durable for 3-6 months in managing mild to moderate knee OA	119
	IGF-1	Systematic review	This meta-analysis comprised 11 studies involving over 3000 primary OA cases. Observational data revealed no link between serum IGF-1 levels and the occurrence of radiographic OA	120

Contd. table 1.

Targeting Pain process	Intra-articular injection of infrapatellar fat pad–derived Mesenchymal Stem (MSC) Cells	Open-label, non-comparative clinical trial (Phase 1)	Patients with knee OA underwent 25 stem cell injections alongside arthroscopic debridement. The trial group received an average of 1.89 × 10^6 stem cells with 3.0 *mL* of platelet-rich plasma (PRP). Short-term results indicate that intra-articular MSC treatment from infrapatellar fat pads is safe and reduces pain while enhancing functionality for knee OA patients	121
	Mesenchymal stem cells injection	Systematic review and meta-analysis	The assessment of seven randomized controlled and controlled clinical trials indicates that, overall, mesenchymal stem cells injection does not yield a significant effect on pain but does show a tendency to enhance self-reported physical function at the final follow-up. However, findings from two high-quality trials involving 94 patients demonstrate a positive impact of MSCs injection on pain	122
	Pan Trk inhibitor GZ389988(its target: NGF receptor tropomyosin-related kinase A (TrkA)	Clinical trial	The short-term moderate pain reduction was seen compared to control group	123
	NSAIDs	Review article	NSAIDs have historically been the cornerstone of pharmacologic treatment for OA, offering analgesic effects by inhibiting the cyclooxygenase (COX) family of enzymes. These enzymes play a role in prostaglandin formation within both the peripheral and central nervous systems (CNS)	124
	NSAIDs and opioid	Systematic analytic review	The analysis included 27 treatment arms from 17 studies, covering various medications like celecoxib, NSAIDs (diclofenac, naproxen, piroxicam), and opioids (tramadol, hydromorphone, oxycodone). All drug classes led to comparable pain reductions when efficacy-related withdrawals were considered. Meta-regression indicated that studies with more male subjects and worse baseline pain experienced greater pain reduction. Network meta-analysis did not reveal significant differences in WOMAC pain reduction among the three analgesic classes	125
	Opioids	Cross-sectional	The study compared OA patients on prescription opioids (n=471) to those on nonopioid medications (n=185), revealing that opioid users had more prior treatments, higher pain intensity, and lower quality of life. Through regression analysis adjusting for demographics and pain intensity, it was found that opioid users were less satisfied with their treatment regimen, had lower confidence in medication effectiveness, and expressed greater concerns about treatment quality and addiction compared to nonopioid users	126
	Mavatrep	Clinical trial (phase 1b)	Patients were treated with a single-dose of mavatrep (50 *mg*), naproxen twice-daily (500 *mg*), and placebo. The findings showed that mavatrep significantly reduced pain, stiffness, and improved physical function compared to placebo in knee osteoarthritis patients. Its safety profile aligned with its mechanism of action as a TRPV1 antagonist	127
	Amitriptyline	Clinical trial	The efficacy of low dose amitriptyline (25*mg*/day), as a tricyclic antidepressant for 3 months was shown on reduction of pain in knee OA	128
	Tanezumab	Clinical trial	In this study, 450 patients diagnosed with knee OA were randomly assigned to receive tanezumab at varying doses (10, 25, 50, 100, or 200 *μg/kg* of body weight) or a placebo on days 1 and 56. The findings revealed that tanezumab treatment was associated with reduced joint pain and improved function in patients with moderate to severe knee osteoarthritis. Additionally, patients experienced mild to moderate adverse events	129
	Tanezumab	Meta-analysis	The evidence (n=1839) suggests that tanezumab may offer relief from pain and enhance functionality for individuals with knee OA. Nonetheless, given the relatively small number of studies, it is prudent to interpret this conclusion with care. Additional clinical randomized controlled trials are necessary to confirm the effectiveness and safety of tanezumab for knee osteoarthritis	130
	CR4056	Phase 2 trial	In an exploratory phase 2 trial, 213 patients were assigned to receive either placebo (69 participants) or CR4056 (women: 100 *mg* twice daily; men: 200 *mg* twice daily) for 14 days. Following this period, median WOMAC pain improvements were observed to be 10 points in the placebo group and 14, 20, and 16 in women, men, and the combined CR4056 groups, respectively, indicating that CR4056 could be an effective analgesic for knee OA pain	131

Contd. table 1.

for osteoarthritis therapy	Statin	prospective population-based cohort study	This study, involving 2921 patients, revealed that statin usage led to a reduction of more than 50% in the overall progression of knee OA, although no significant effect was observed on hip OA progression	132
	Statin	Meta-analysis study	This study encompassed 23 investigations with over 6,000,000 participants. The findings indicated that statin use was linked to an elevated risk of OA	49
	Curcuminoid capsules	Randomized controlled trial	In a study involving patients with mild-to-moderate primary knee osteoarthritis, participants were divided into two groups: one receiving curcuminoid capsules (1500 *mg*/day in 3 divided doses; n=19) and the other receiving placebo capsules over a six-week period. Results indicated that short-term intake of curcuminoids decreased systemic oxidative stress in patients with OA, suggesting that this antioxidant action may contribute to the therapeutic advantages of curcuminoids in relieving osteoarthritis symptoms	51
	Curcuminoid	A systematic review and meta-analysis	In a study encompassing 1258 individuals diagnosed with primary knee OA from eleven trials, it was discovered that curcuminoids exhibited significant efficacy compared to comparators in reducing VAS and WOMAC pain scoresNevertheless, no significant disparity in pain relief or adverse events was observed between high-dose and low-dose curcuminoid treatments	133
	Metformin	Systematic review of pre-clinical and human studies	Fifteen studies (ten pre-clinical and five human) were reviewed. The majority focused on knee osteoarthritis, with 10 pre-clinical and three human studies. Pre-clinical studies assessed metformin's impact on structural outcomes, immunomodulation, pain, and molecular pathways, while human studies examined structural progression, pain, and immunomodulation. Overall, pre-clinical findings consistently support metformin's chondroprotective, immunomodulatory, and analgesic effects in osteoarthritis, primarily mediated by adenosine monophosphate-activated protein kinase activation	54
Aging therapy	CoQ10-micelles	Animal model	Male Wistar rats were induced with OA using monosodium iodoacetate (MIA) and treated orally with CoQ10-micelles, comparing their effects with celecoxib. The CoQ10-micelles significantly alleviated OA symptoms, including pain, tissue degradation, and inflammation. Additionally, they reduced the expression of inflammatory cytokines and markers of inflammatory cell death in synovial tissues, indicating a potential for mitigating OA synovitis	118
	Methylene blue	Animal model	Using 120 male New Zealand white rabbits, this study explored Methylene Blue's (MB) impact on OA pathogenesis. Findings revealed MB as an effective treatment for OA-related pain	57
Anti-inflammatory therapy	MTX	Open-label pilot study	In this study involving 30 patients with knee OA, administering a weekly dose of 15–20 *mg* of MTX over 6 months indicated an analgesic benefit	134
	Anakinra	Clinical trial	Anakinra, administered as a single 50-*mg* or 150-*mg* intra-articular injection, was well tolerated by patients with knee OA. However, it did not lead to improvements in OA symptoms compared to placebo	135
	Hydroxy-chloroquine	Systematic review and meta-analysis	Hydroxychloroquine does not offer any advantages in alleviating pain or enhancing physical function among individuals with osteoarthritis affecting the hands or knees	136
	Adalimumab	Clinical trial	Adalimumab, administered at a dosage of 40 *mg* via two subcutaneous injections spaced 15 days apart, did not demonstrate superiority over placebo in reducing pain for patients with hand OA who were unresponsive to analgesics and NSAIDs, as observed over a 6-month monitoring period	137
	Infliximab	Observational longitudinal study	Patients in the study had the option to receive infliximab infliximab was administered at a dose of 3 *mg/kg* every 8 weeks. Dosage adjustments occurred if patients showed inadequate response, with increases up to 6, 7.5, and 10 *mg/kg* based on disease activity scores. Infliximab treatment decreased incident secondary osteoarthritis (OA) in proximal interphalangeal joints (PIPJs)	138

Contd. table 1.

	Etanercept	Clinical trial	Patients received etanercept (50 *mg*/week for 24 weeks, followed by 25 *mg* per week) or placebo. The results revealed that anti-TNF treatment did not effectively alleviate pain after 24 weeks in erosive osteoarthritis	139
	lLutikizumab, (an anti-interleukin-1α and anti-interleukin-1β)	Phase IIa	Patients with at least one erosive joint and a minimum of three tender and/or swollen hand joints were randomly assigned to receive either placebo or lutikizumab at a dose of 200 *mg* subcutaneously every 2 weeks for 24 weeks. The results revealed that lutikizumab did not demonstrate improvements in pain or imaging outcomes in erosive Hand Osteoarthritis (HOA) when compared to placebo	140
	SAR113945	*In vitro* experiments	An IκB kinase inhibitor (SAR113945) inhibits the NFκB signaling pathway which is an attractive procedure in treatment of patients with OA	141
Drug delivery	Gold microparticles	Clinical trial	Intra-articular injections of 20 *mg* gold microparticles (20–40 *μm* in diameter) were administered. After 8 weeks, a reduction in WOMAC scores for pain, stiffness, and activity was observed compared to baseline assessments. At the 2-year follow-up, WOMAC scores showed a decrease compared to baseline	142
	Flavopiridol-loaded microparticles (Intervantional study)	Animal model	An intraarticular injection of either blank (unloaded) or flavoperidol-loaded microparticles was used to treat a rat knee injury model of PTOA. In comparison to soluble flavopiridol, a significant joint retention of flavopiridol microparticles was observed, confirming the particles' prolonged release characteristic	143
	RAPA@Lipo@HMs	In vivo (animal study)	In vivo data indicate that RAPA@Lipo@HMs can mitigate joint wear and slow the advancement of OA. These microspheres offer effective lubrication and have the potential to alleviate friction-related conditions like osteoarthritis	144
	Nanocurcumin	Clinical trial	Patients underwent nanocurcumin capsule (40 *mg*) every 12 hours over a period of six weeks. Nanocurcumin significantly alleviates the symptoms of OA in patients	145
	Chitosan-based nanoparticles	Review article	Chitosan-based nanoparticles, evaluated for sustained release of berberine chloride, hold potential for treating osteoarthritis (OA). They decrease the drug's blood concentration but enhance its retention in synovial fluid compared to free solution. These nanoparticles demonstrate anti-apoptotic effects in OA and are swiftly absorbed by macrophages in rheumatoid arthritis (RA). Nevertheless, limitations include low water solubility, reduced charge at physiological pH, and hurdles in transfection efficiency and targeting	146
	Novel nano platinum	In-vitro study	At high concentrations of up to 100 *ppm*, OA chondrocytes showed over 50% cell viability in a new nano platinum coated with chondroitin sulfate. This implies that it could be used to treat OA	147
	TLC599	Clinical trial	Intra-articular injection of 12 *mg* Dex-sodium phosphate incorporated liposome (TLC599) led to greater suppression of pain from week 1 through week 24 than placebo	148
Bone remodeling therapy	Denosumab	Clinical trial	In a monocentric clinical trial spanning 48 weeks, 100 patients diagnosed with erosive hand OA were randomly assigned to either receive a placebo or subcutaneous denosumab (60 *mg* every 3 months). Denosumab exhibited clear structural modification effects in erosive hand osteoarthritis compared to the placebo group. Significant reduction in erosive progression was noted after 24 weeks of treatment, with the treatment effect further improving by the end of the 48-week period Additionally, sustained treatment led to noticeable improvement in symptoms	149
	Tetracycline	Systematic review	Tetracyclines have the potential to benefit osteoarthritis patients via multiple mechanisms	92
	Vitamin D	Systematic review	The meta-analysis results underscored the statistical significance of vitamin D supplementation on WOMAC scores among KOA patients, spanning pain, function, and stiffness domains. Subgroup analysis revealed that supplementation with less than 2000 IU of vitamin D notably reduced stiffness scores. Additionally, vitamin D supplements exhibited efficacy in curbing the progression of synovial fluid volume in KOA patients. Nevertheless, there were no statistically significant improvements observed in tibia cartilage volume, joint space width, or bone marrow lesions	150

Contd. table 1.

Bisphosphonates	Systematic review and meta-analysis	The analysis, covering 3832 participants with Osteoarthritis (OA) in various joints, found that risedronate 15 *mg* showed higher odds ratios favoring placebo for WOMAC pain (1.73), function (2.03), and stiffness (1.82) in knee OA. However, 61.5% of trials reported bisphosphonates improving pain by VAS scores, with 38.5% reporting significant WOMAC pain score improvement. Evidence on bisphosphonate efficacy for OA pain is limited due to variations in treatment duration, dosage, administration route, and lack of long-term joint structure data. More targeted studies are needed to better understand bisphosphonates' role in OA pain management	151
Strontium ranelate	Clinical trial	Patients with knee OA received either strontium ranelate at doses of 1 *g*/day (n=558), 2 *g*/day (n=566), or placebo (n=559). The results indicated that treatment with both 1 *g*/day and 2 *g*/day of strontium ranelate significantly impacted knee OA structure. Additionally, the higher dosage of 2 *g*/day showed a beneficial effect on symptoms	152
Cathepsin K Inhibitor (MIV-711)	Clinical trial	244 participants with primary knee OA were administered either MIV-711 at doses of 100 *mg* daily (n=82) or 200 *mg* daily (n=81), or received a matched placebo (n=77). The study findings indicated that MIV-711 did not outperform placebo in alleviating pain; however, it notably reduced bone and cartilage progression while maintaining a reassuring safety profile	153
Estrogen	Meta-analysis	The impact of estrogen on tissues like bone has been extensively researched. Based on a meta-analysis study in 2023, estrogen has the potential to exert diverse beneficial impacts on OA, effectively alleviating its pathological progression in patients. This suggests that ER could emerge as a viable alternative for treating OA in the future, thereby enhancing the health and quality of life for affected individuals	154
Zoledronic acid	Clinical trial	Administration of intravenous methylprednisolone with Zoledronic acid did not reduce acute phase responses bone marrow lesion size over 6 months, however, in contrast to placebo or Zoledronic acid, it may have a beneficial effect on symptoms	155

Visual Analogue Scale-VAS

management of degenerative joint diseases. These innovations may not only enhance the effectiveness of existing therapies but also provide entirely new avenues for cartilage regeneration, pain management, and joint preservation. Ultimately, the integration of nanotechnology in OA therapy could pave the way for more personalized, precise, and impactful treatments, offering patients a better quality of life and improved long-term outcomes.

Conflict of Interest

There was no conflict of interest in this manuscript.

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