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Review article

Unlocking the future of osteoarthritis: Material engineering and drug delivery confluence for advanced therapeutic approaches

Bhupendra Kumar [a,1], Laxmi Akhileshwar Jha [b,1], Prashant Pandey [c], Sayeda Fauzia Iqbal [a], Saahiba Thaleshwari [a], Kaushani Banerjee [d], Mohammad Imran [e], Shoaib Anwaar [e], Laxman Subedi [f], Vishal Dubey [b], Yousuf Mohammed [e], Nisha Panth [g], Philip M. Hansbro [g], Keshav Raj Paudel [g,*], Saurav Kumar Jha [a,**], Amitabha Bandyopadhyay [a,***]

[a] Department of Biological Sciences and Bioengineering (BSBE), Indian Institute of Technology, Kanpur, 208016, Uttar Pradesh, India
[b] Naraina Vidya Peeth Group of Institutions, Faculty of Pharmacy, Dr. A. P. J. Abdul Kalam Technical University, Kanpur, 0208020, Uttar Pradesh, India
[c] Department of Pharmaceutics and Drug Delivery, School of Pharmacy, The University of Mississippi, 38677-1848, United States
[d] Department of Genetic Engineering, SRM Institute of Science and Technology (SRMIST), Kattankulathur, 603203, Tamil Nadu, India
[e] Frazer Institute, Faculty of Medicine, The University of Queensland, Brisbane, Queensland, 4102, Australia
[f] Department of Biomedicine, Health & Life Convergence Sciences, BK21 Four, Mokpo National University, Muan-gun, 58554, Republic of Korea
[g] Centre for Inflammation, Centenary Institute and University of Technology Sydney, Faculty of Science, School of Life Sciences, Sydney, NSW, 2007, Australia

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ABSTRACT

The limited regeneration capacity of articular cartilage (AC) is attributed to the hypocellular nature of the cartilage tissue and the absence of vascularization. On the other hand, degenerative joint disease, such as osteoarthritis (OA), is characterized by irreversible AC degeneration and synovial inflammation, leading to pain, discomfort, and restricted joint mobility. The existing treatment options for OA mostly provide symptomatic relief. Therefore, it is vital to explore several approaches, such as cartilage regeneration and maintenance of cartilage homeostasis. During OA pathogenesis, significant changes are observed in the gene expression and phenotype of articular chondrocytes. Some of these changes include chondrocyte hypertrophy, expansion of the endoplasmic reticulum-Golgi apparatus, secretion of stiffer collagen matrix like collagen type X, increased matrix metalloproteinases (MMPs)-3, −9, and −13 and alkaline phosphatase levels; and decrease of SOX9, proteoglycans, and collagen type II. The changes seen in chondrocytes are similar to those observed during endochondral ossification. Therefore, modulating key molecular players like bone morphogenetic protein (BMP) and wingless-related integration site (Wnt) Wnt/β-catenin signaling pathways using their antagonists and agonists, respectively, has been shown to effectively inhibit OA progression. These advancements have been further explored in the context of cartilage tissue engineering to design artificial AC-like scaffolds that mimic former physicochemical properties and can be applied as a substitute for damaged cartilage. However, modern science still has unaccomplished objectives that can completely translate our understanding of AC maintenance into the complete restoration of healthy joints. Therefore, in this review, we looked at how understanding the cellular and molecular behavior of articular chondrocytes may be used in confluence with other existing non-surgical therapeutic approaches, such as nanomedicines, regenerative biology, and tissue engineering combined, to find a cure for OA.

1. Introduction

Unaddressed cartilage abnormalities may result in osteoarthritis (OA), characterized by persistent discomfort, rigidity, and diminished mobility of the joints [1]. This pathophysiological condition gradually destroys synovial joints, which are an anatomical feature unique to

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: keshavraj.paudel@uts.edu.au (K.R. Paudel), sauravj@iitk.ac.in (S.K. Jha), abandopa@iitk.ac.in (A. Bandyopadhyay).
[1] First author with equal contribution.

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vertebrates that connects two separate bones [2]. The articular cartilage (AC) transmits load and offers a sleek, lubricated surface for articulation inside the joint. In essence, this cartilage plays a crucial role in facilitating smooth and effortless movement. Consequently, maintaining ultralow friction and improving lubrication are crucial characteristics for maintaining the health of the AC. No drug has been licensed for human use that offers a complete cure for OA, despite decades of research and development [3]. Although, by slowing down the deterioration of cartilage or promoting the growth of new tissue, the course of the illness could be improved. Moreover, pain alleviation is an afterthought in the current therapeutic paradigm and confers only symptomatic relief in patients. Some of these drugs are already in the market, such as corticosteroids and hyaluronic acid (HA) suspensions, however their safety and/or effectiveness are still debated. With OA being a multifactorial disease, the therapeutic shortcomings and failure of clinical trials of various investigational drugs aimed at improving the condition must be traced back to the lack of combinatorial approach and inadequate amount of drug reaching to the required depths of AC [4,5]. Free drugs cannot remain in the joint region long enough to fulfil their biological aims, even when intra-articular (IA) injection (IA-injection) is used as a local delivery technique [6]. Small molecules administered into the synovial joint are swiftly eliminated (with a half-life of 1–4 h) because of the rapid movement of synovial fluid. This quick clearance often requires frequent injections of high drug concentrations into the joint, eventually leading to the development of toxicity [7]. In addition, drugs are usually wasted because the venules and lymphatic capillaries of the synovial membrane quickly drain the fluid with active pharmaceutical ingredients dissolved in it [7]. Furthermore, the drug must rely only on diffusion to reach the deeper zones of cartilage. Thus, investigators are looking into how to treat pain and inflammation with drugs that stay in the synovial fluids for longer durations and permeate efficiently up to the required zones of AC. Adding to the complexity, cartilage's highly anionic extracellular matrix (ECM) is very thick, and its pores are less than 15 nm in diameter, both of which greatly limit diffusion [8–14]. In this area, hydrogels, micelles, and polymeric particles have recently emerged as better ways to treat OA (Fig. 1). Moreover, it is highly desired to reduce the frequency of IA injections, considering patient compliance as one of the main priorities. Fortunately, promising results have been shown with innovative IA injectable formulation techniques based on synthetic biomaterials in recent years. There is potential for a sizable effect on the intervals between injections if IA penetration and half-life could be significantly enhanced through an efficient formulation design.

Currently, there are various potential medicines, such as the fibroblast growth factor (FGF) protein (FGF-18), that are being investigated in preclinical or clinical studies [15]. On the other hand, the clinical research community focused on OA is in a favorable position to conduct trials on emerging therapies. The current state of preparedness may be attributed, in part, to the many studies conducted in the past that regrettably failed to showcase the effectiveness of interventions. One potential explanation for the unsuccessful studies may be because of our limited comprehension of the underlying biological mechanisms driving the expansion of OA [16]. A possible approach to addressing this issue is to augment our understanding of its genetic underpinnings. Researchers looking into how OA affects the hand, hip, knee, and spine have found that the disease is strongly linked to genes, as it is passed down in a way called polygenic inheritance [15]. The timing of the occurrence of various events during the onset of OA is a subject of ongoing debate among scientists and clinical practitioners, with no definitive conclusion reached so far. Irrespective of the main pathological factor or the combined influence of multiple factors on OA advancement, there's a consensus that intervening during the initial stages of OA to delay the

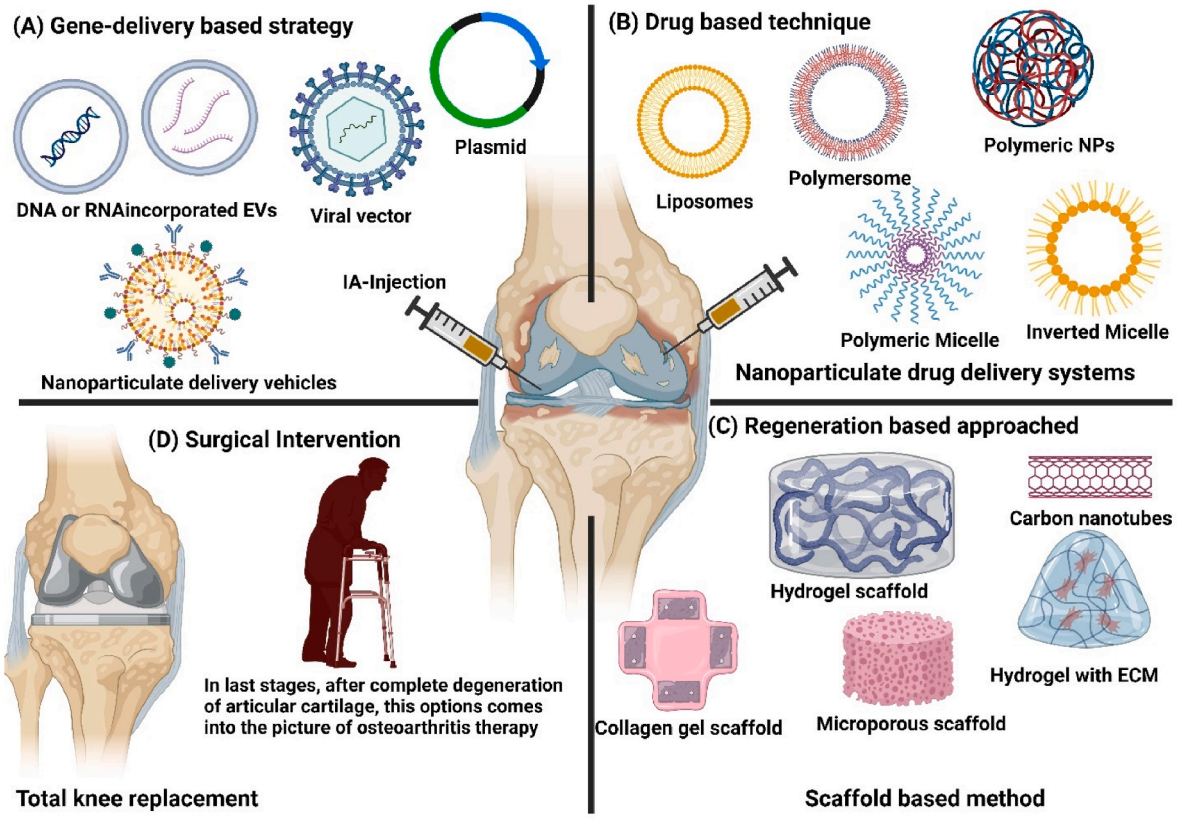

Fig. 1. Figure demonstrates the currently available various strategies to treat osteoarthritis. **(A),** regeneration of articular cartilage through the gene-based therapeutic approaches; **(B)**, treating osteoarthritis *via* drug incorporated nanoparticles; **(C)**, regeneration-based strategies through scaffold; **(D)**, joint replacement as a surgical option during the later stages of osteoarthritis. Figure created with BioRender.com.

progression is a more efficient and effective approach. This is preferred over other treatment options and resorting to joint replacement surgery during the later and more advanced stages of the disease [15–18]. Thus, it is essential for future research endeavors to focus on the precise modulation of crucial signaling pathways and important molecules that undergo substantial alterations during the first stages of the illness. This approach aims to effectively regulate the crosstalk between molecular pathways and among distinct compartments in the synovial joint. Moreover, it is imperative to evaluate the functions and regulations of signaling pathways, including wingless-related integration site (Wnt) Wnt/β-catenin, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), focal adhesion, hypoxia-inducible factors, transforming growth factor-β (TGFβ)/bone morphogenetic protein (BMP) (TGFβ/BMP), and FGF, as well as key regulators such as adenosine monophosphate-activated protein kinase (AMPK), mammalian target of rapamycin, and runt-related transcription factor 2, in the initiation and progression of OA. Consequently, therapeutic interventions should be designed to target these pathways to enhance the effectiveness of drugs used in the treatment of OA. This review emphasizes the recent progress in the field of OA regarding the pathogenesis of disease, as well as outlining the novel ideas employed in joint targeted drug delivery systems (DDSs). From this review, the readers can gain an overall insight on OA, treatment methods, and obstacles being faced for the practical translation of recently emerged technologies. Nevertheless, some recent progress made in the field of molecular and developmental biology in combination with nanomedicine and tissue engineering has been incorporated as well.

2. Systemic survey of literature

To conduct a comprehensive and methodical evaluation that effectively addresses the advancements in comprehending the pathophysiology and therapeutic approaches for OA, two prominent search engines, namely PubMed and Scopus, were used. Upon entering the designated keyword "OA" into the search engine, a total of 114,567 articles were retrieved, with a timeframe ranging from 1885 to 2023. Subsequently, our investigation commenced into the etiology of OA, yielding a total of 36,042 publications spanning the period from 1946 to 2023. This observation indicates that although humans had prior knowledge of this illness, comprehensive study of its pathophysiology did not begin until 1946. Subsequently, an effort was made to compile the existing literature pertaining to the field of nanomedicine and its application in OA. A total of 170 publications were obtained from the PubMed database, spanning the years 2009–2023. Additionally, our investigation was focused specifically on the application of nanomedicine in the context of AC targeting. As a result, we obtained a total of 27 scholarly papers published between the years 2014 and 2023. Further, we explored multimodal therapeutic interventions for the treatment of OA, yielding a total of 73 papers published between 2003 and this date. To get insight into the advancements achieved in the treatment of OA, we conducted a search for randomized clinical trial data on PubMed. A total of 6429 results were obtained during the period spanning from 1970 to the present. However, a limited number of search results were obtained while doing a search on randomized clinical trials related to the use of nanomedicine for the treatment of OA. This review has been compiled by using a range of scholarly sources, including papers (research and reviews), books, and clinical trial reports.

3. Articular cartilage

AC is a specific kind of connective tissue found in diarthrodial joints (Figs. 2 and 3). The primary purpose of this entity is to provide a seamless and lubricated surface for articulation, as well as to augment the transfer of loads with little friction. AC is a robust biomechanical milieu characterized by the absence of blood vessels, lymphatics, and nerves. Primarily, it should be noted that AC has a restricted ability to undergo repair and regeneration. But maintenance and preservation of AC plays an important role in ensuring the overall health of joints. The process of therapy and repairing or restoring defects presents significant challenges for patients, surgeons, and physical therapists, mostly owing to the distinctive and complex nature of AC. Further, the maintenance of AC is contingent upon its ordered construction. It is composed of hyaline cartilage and typically has a thickness that varies between 2 and 4 mm. The structure consists of a compact ECM and a limited distribution of highly specialized cells referred to as chondrocytes. The ECM is mostly made up of water, collagen, and proteoglycans. Noncollagenous proteins

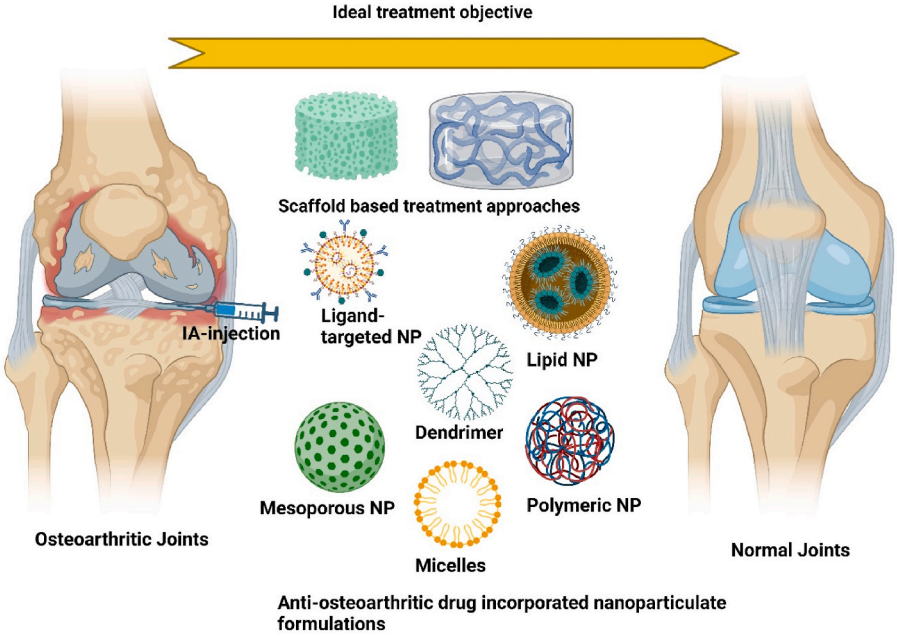

Fig. 2. The figure demonstrates the differences between normal and osteoarthritic joints, and various current treatment strategies based on scaffold-based treatment approaches and nanoparticulate drug delivery systems, such as ligand-targeted nanoparticles, lipid nanoparticles, dendrimer, polymeric nanoparticles, micelles, and mesoporous nanoparticles to treat osteoarthritis. **Abbreviation**: NP, nanoparticle; IA-injection, intra-articular injection. Figure created with BioRender.com.

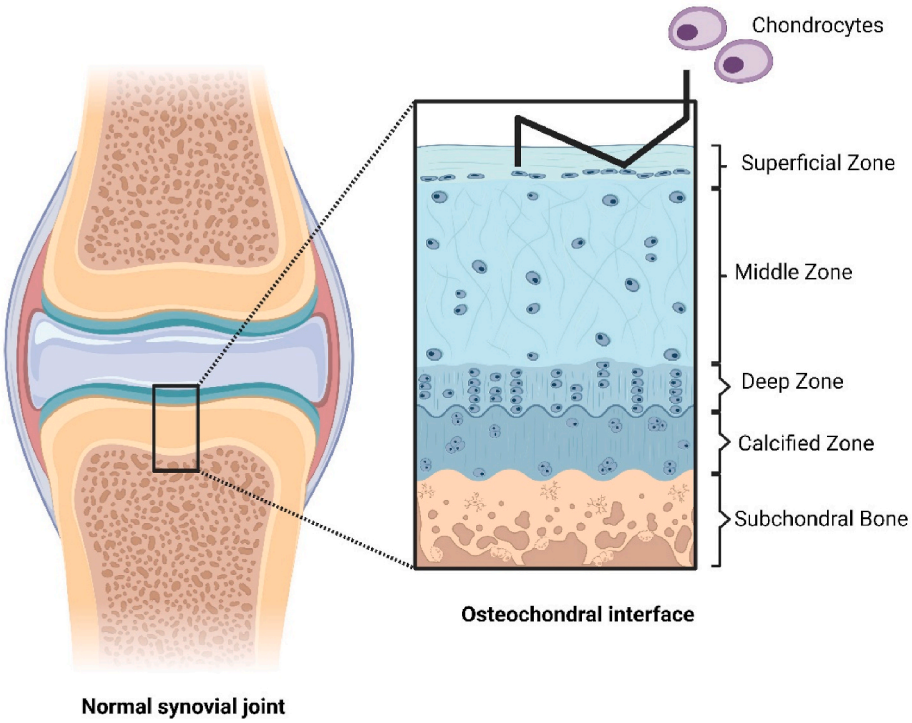

Fig. 3. Illustration of the anatomical composition of articular cartilage and the underlying subchondral bone. The articular cartilage surface is composed of four distinct zones, namely the superficial, intermediate, deep, and calcified zones, extending towards the underlying bone. Figure created with BioRender.com.

and glycoproteins are also part of the ECM [14,19]. These constituents collaborate to maintain water inside the ECM, a prerequisite for the preservation of its mechanical characteristics. The superficial zone, the intermediate zone, the deep zone, and the calcified zone of AC are all made up of chondrocytes, collagen fiber ultrastructure, and ECM. Within each of these zones, there is a subdivision into three specific regions: the pericellular area, the territorial region, and the interterritorial region.

3.1. Composition of articular cartilage

I. ***Water***: This substance makes up 65–80 % of cartilage's net weight, with 80 % of it being present in the superficial zone and 65 % in the deep zones. It enables the deformation of cartilage in reaction to the applied force. The former offers essential nutrients and functions as a lubricant, therefore creating a smooth surface characterized by low friction. The water content in OA exceeds 90 % due to heightened permeability and breakdown of the matrix. Consequently, the AC has a diminished modulus of elasticity, leading to a concomitant reduction in its ability to sustain loads [20].

II. ***Collagen***: AC comprises around 10–20 % of its wet weight with this material. The microfibrillar structure of AC is mostly composed of Type II collagen, which accounts for about 90–95 % of its composition. This collagen type plays a crucial role in imparting tensile strength to the cartilage. Table 1 provides a comprehensive overview of the many types of collagens that are found in AC, along with their respective biological activities [20].

III. ***Proteoglycans***: The protein polysaccharide molecules constitute around 10–20 % of the total weight of AC and contribute to its compressive strength. AC is made up of two different kinds of proteoglycans: aggrecans, which are big proteoglycan monomers that stick together, and smaller proteoglycans like decorin, biglycan, and fibromodulin [19]. Chondrocytes, produce these and then release them into the ECM. Glycosaminoglycans (GAGs) are subunits of proteoglycans, characterized by their GAGs structure. There are two types of disaccharide molecules: chondroitin sulfate and keratin sulfate. The aggrecan molecule is synthesized by the process of GAG attachment to the protein core. The GAG molecule's complex structure is formed by connecting this chain to a core HA chain. There are two variants (types 4 and 6) of chondroitin sulfate that are currently accessible. Type 6 has a lasting nature, while type 4 experiences a decline with time. The decrease of aggrecans has been identified as an early characteristic of experimental arthritis. Further, proteoglycans play a crucial role in the maintenance of the fluid and electrolyte equilibrium inside AC [19]. The macromolecules possess negatively charged sulfate and carboxylate groups, which selectively bind positively charged molecules while repelling negatively charged ones. This phenomenon leads to an elevation in the overall concentration of inorganic ions, such as sodium, inside the matrix. As a result, the osmolarity of AC rises, giving rise to the Donnan effect [19,20].

IV. ***Chondrocytes***: These highly specialized cells are sparsely distributed within the matrix, accounting for just 1–5% of the total volume. Chondrocytes are responsible for the synthesis of all matrix components as well as the regulation of matrix metabolism [20–23].

V. Characteristics of Chondrocytes

1. no cell-to-cell contacts, like osteocytes,
2. spheroidal in shape,
3. Type II collagen, huge proteoglycan aggregates, and non-collagenous proteins are synthesized by chondrocytes,
4. creation and maintenance of the specialized matrix,
5. Individual metabolic activity is high, but total activity is minimal owing of the relatively low overall volume,
6. receives nourishment *via* a dual diffusion barrier,
7. cells can survive with minimal oxygen levels and thus rely on anaerobic metabolism for their energy needs,
8. synthesize the enzymes accountable for breaking down the matrix,
9. the mechanical loading of joints affects how chondrocytes function.

3.2. Various zones of articular cartilage

I. Superficial zone

The outermost layer is defined by the presence of flattened ellipsoid cells, which exhibit a high degree of delicacy. The ligaments align in line with the surface joint and are protected by a layer of synovial fluid referred to as the 'lamina splendens'. This protein plays a role in facilitating the optimal gliding surface of the AC. The reason for the abundance of water in this zone is attributed to the chondrocytes inside it, which exhibit a notable synthesis of collagen at a comparatively low level of proteoglycan production. The parallel alignment of the fibrils contributes to the attainment of maximal tensile and shear strength. The perturbation of this region disrupts the mechanical characteristics of the AC, resulting in the progression of OA. The layer also serves as a barrier for sizable macromolecules, safeguarding the cartilage from potential immunological aggression originating from the synovial tissue [20].

II. Middle (radial) zone

The cells are spheroidal in shape and parallel to the surface. This zone has the most collagen fibrils and the most proteoglycans. This zone, on the other hand, has the lowest cell density [20].

III. Calcified cartilage zone

The presence of calcified cartilage characterizes this zone, which is closer to the bone. It acts as a transitional area between the subchondral bone below and the AC. The mechanical characteristics of the flexible cartilage gradually change to those of the hard bone due to the calcified cartilage. Because it contributes to the stability and integrity of the cartilage-bone contact, the calcified cartilage zone is vital to the joint's overall function. It also contributes to load bearing and force transfer between the underlying bone and the cartilage. Conditions relating to the joints, such as OA, can be exacerbated by alterations or injury to the calcified cartilage zone. OA can cause degenerative changes in the calcified cartilage and other joint components, which can cause pain, stiffness, and decreased joint function. To create therapies for illnesses connected to the joints, researchers and medical practitioners must have a thorough understanding of the anatomy and function of the various cartilage zones [20–23].

3.3. Articular cartilage differentiation and its relationship with OA

The process of appendicular skeleton development takes place in all vertebrates by the mechanism of endochondral ossification. This process involves the proliferation, branching, and segmentation of a pre-existing cartilaginous structure, resulting in the construction of a limb skeleton with clearly defined sections [24]. The formation of distinct sections occurs because of segmentation at predefined locations inside formerly continuous cartilage anlagen, ultimately leading to the development of joints [25]. Most of the cartilage present in the anlagen undergoes a transformation into bone *via* sequence of differentiation processes. This kind of cartilage is often known as transient cartilage. However, the cartilage located at the extremities of each individual segment maintains its cartilaginous structure permanently. This cartilage is referred to as permanent or AC. The differentiation of cells into AC on either side of the segmentation plane, as well as the differentiation of cells further away from the segmentation site into transient cartilage, establishes a close connection between joint cartilage formation and the process of segmentation [26,27]. The interzone is the location where potential joint development takes place, and previous research has shown that the removal of the joint interzone in a developing chicken limb bud impedes the creation of joints [28]. The establishment of the interzone is associated with the secretion of Wnt ligands [29–31], which in turn influences the development of cells in the sub-articular zone into AC [27]. Conversely, cells located farther away from the interzone are exposed to BMP signaling, leading to their differentiation into transient cartilage [27]. Jaswal and colleagues hypothesized a molecular process to explain the genesis of articular and transient cartilage [2]. Based on this concept, it is proposed that cartilage anlagen cells possess bipotential characteristics, whereby their development may lead to the formation of either AC or transient cartilage, contingent upon the specific signaling cues present in their surrounding environment. The exposure of interzone and/or subarticular cells to BMP signaling has been shown to result in the generation of ectopic temporary cartilage, while simultaneously causing a reduction in AC [32–35]. Even conditional BMP signaling activation at the joint site *via* IA-injection of BMP2 protein in adult mice induced chondrocyte hypertrophy, a necessary step in the transient cartilage differentiation that leads to an OA-like phenotype. Notably, elevated BMP signaling was found at the AC in post-traumatic OA etiology [36,37] (Fig. 4). However, local suppression with BMP signaling inhibitor *i.e.,* 4-[6-[4-(1-Piperazinyl)phenyl]pyrazolo[1,5-a]pyrimidin-3-yl]-quinoline hydrochloride (LDN-193189), blocked chondrocyte hypertrophy and mitigated the OA. Thus, inhibiting chondrocyte hypertrophy appears to be one of the promising treatment options for inhibiting OA progression when detected at early stage [36,37] (Fig. 4). Notably, this approach should be used in conjunction with current regeneration and/or nanomedicine-based technologies to provide significant improvements in the health of the AC at the late stage (Grade IV). The subsequent section will present a detailed analysis of the existing knowledge on the structure of synovial joints and its potential influence on the way drugs and pharmaceuticals interact with synovial fluids, as well as their impact on the pharmacokinetics and pharmacodynamics of drugs or therapeutic agents. It will also explore the potential of nanomedicine to improve drug delivery to specific tissues, thereby enhancing therapeutic effects for patients with OA.

4. Anatomy of synovial joints

Understanding the architecture of synovial joints is necessary for comprehending their function as well as the variables that influence joint health and mobility. The structural properties of different types of synovial joints, such as hinge joints, ball-and-socket joints, and pivot joints, vary depending on their unique roles and range of motion. A common synovial joint comprises four components: AC covering the bone ends, a synovial cavity containing synovial fluid, a capsule enveloping the joint space, and a ligament linking the two bones that articulate within the joint [37] (Figs. 2 and 3). Next, synovial fluid is a thick, non-Newtonian fluid made up of water and essential components such as HA, which influences the former viscoelastic characteristics. It also contains lubricin, proteoglycan 4, and phospholipids, all playing roles in facilitating boundary lubrication for contact within AC [38]. Lubricants (proteoglycan and phospholipids), nutritional factors, and other chemicals are reported to be released by fibroblast-like synoviocytes (FLS) lining the synovium, the inner side of the synovial capsule [39]. At significantly high pressures of 5 MPa or greater [40–42], a normal synovial joint exhibits remarkably low friction coefficient. The prevailing belief is that this exceptional lubrication arises from a combination of both fluid-film and boundary lubrication mechanisms [43]. Regarding fluid-film lubrication, a viscous thin film separates the articulating surfaces; hence, the specific viscoelastic properties of synovial fluid must be retained. When two surfaces make contact and move relative to each other, the molecules within the area referred to as the boundary layer significantly influence the lubrication characteristics. Specifically, phospholipids that form a lining on the surface of the cartilage, in conjunction with underlying molecules such as HA and lubricin, contribute to the reduction of friction coefficients through a mechanism known as hydration lubrication. This mechanism involves the exposure of the highly hydrated headgroup layer of the phospholipids to the interface, resulting in the reduction of friction [44–50].

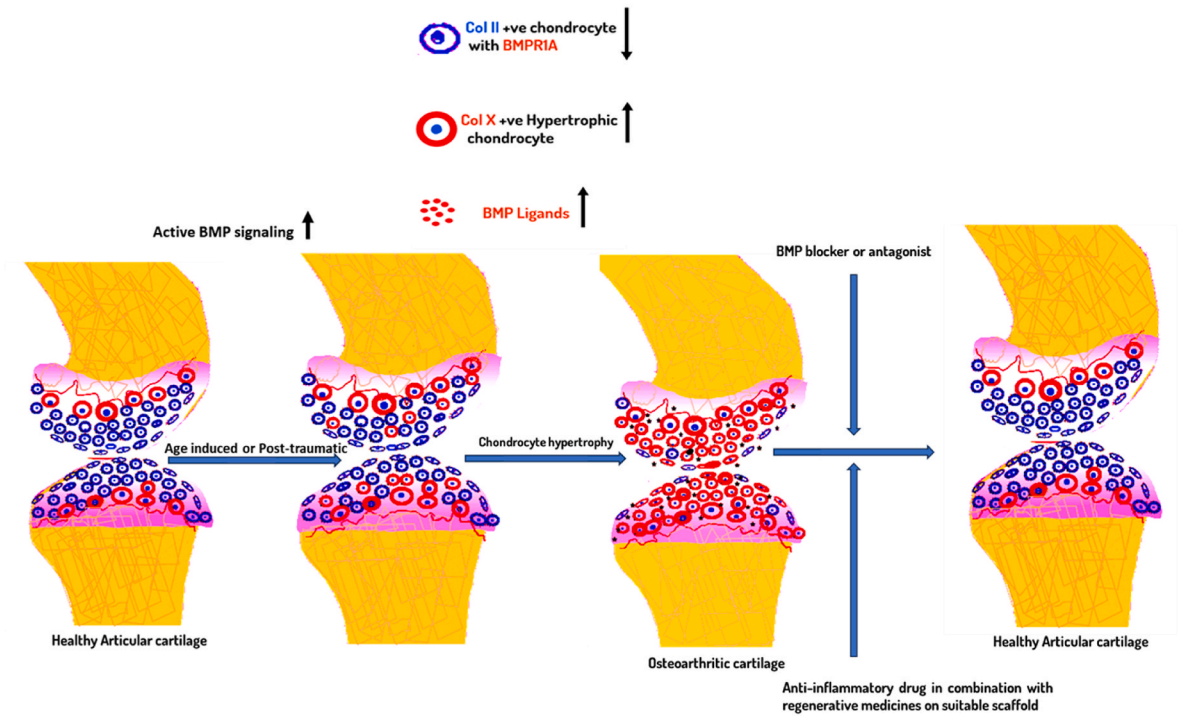

Fig. 4. Among various alterations occurring during OA (post-traumatic or age-induced), there is a trend toward a hypertrophy-like state (chondrocytes hypertrophy), distinguished by decreased levels of SOX9 and collagen type II (Col II) and increased expression of genes such as collagen type X (Col X), matrix metalloproteinases-13 and alkaline phosphatase. The phenotypic change that has been seen is like the changes that occur during endochondral ossification. Jaswal et al. by administering BMP antagonist (LDN-193189), were able to reverse back the OA phenotype changes at articular cartilage more alike normal joints in post-traumatic osteoarthritis [37]. For age-induced osteoarthritis our data is unpublished, however, the conclusion is illustrated in the form of diagram here.

5. Synovial fluids and its impact on the drug delivery

The transparent, viscous fluid inside the cavities of synovial joints—such as the knee, hip, and shoulder joints—is called synovial fluid. Its main job is to feed and lubricate the joints, giving the articulation of bones a smooth surface. The peculiar characteristics of synovial fluid may have an impact on drug delivery, particularly when treating joint ailments. Synovial cells primarily secrete cytokines, complements, polysaccharides, and water, which are all present in synovial fluid. A number of customized anti-OA drugs-incorporated nanoparticles (NPs) that are very selective for synovial fluid and can easily move through the layers of synovium have been successfully created. HA, a mucopolysaccharide with acidic properties, is present in significant quantities within synovial fluid. Its primary function is to provide lubrication to joints and reduce friction between AC surfaces. Altman et al. previously established that HA could accurately link with its surface receptors, such as toll-like receptors (TLR), LAYN, intercellular adhesion,molecule-1, and CD44, respectively [51]. Previously, Murakami, T et al. revealed that HA may reduce chondrocyte mortality through CD44 signaling and suggested that CD44 may be an acceptable targeting molecule for HA [52]. E. Ragni et al. revealed that CD44, a HA receptor, may bind CD44-containing extracellular vesicles (EVs). The results showed that when 2 mg/L of HA is added, the absorption of EVs by synoviocytes could be greatly improved. With OA, the composition of synovial fluid changes, as does the composition of cartilage ECM, resulting in a lower pH and a larger number of inflammatory agents like interleukin (IL) and tumor necrosis factor (TNF) (IL-1, IL-6, and TNF) [53]. Polylactic co-glycolic acid (PLGA) NPs loaded with rhein (Rh) and NHHCO (NH) were produced by Hu et al. These NPs released more therapeutic chemicals in a low-pH synovial fluid milieu, which is typical in OA [54]. In another instance, He, M., and colleagues also developed novel nanoparticulate vehicles composed of pH-sensitive polyacrylic acid and mesoporous silica NPs [55]. Their vehicles have also worked better in the acidic environment of OA, releasing more therapeutic molecules at the target site, and making them stay there longer. Overall, treatments for diseases of the joints, such as arthritis, may be more successfully administered if specific DDSs are created and synovial fluid's distinctive properties are recognized.

6. Treatment focusing on articular cartilage

A healthy articular chondrocyte matrix is rich in type II collagen. As the fate of chondrocytes changes during OA, the matrix enriches with collagen type X and loss of proteoglycan content is observed in a degrading cartilage matrix [56–58]. The development of therapeutic products aimed at resolving the degeneration of cartilage matrix has been of significant interest in the area [58,59]. To accomplish this objective, it is possible to identify novel combinations that specifically target previously unidentified targets. This encompasses the use of pharmacological combinations to target signaling pathways that are both anti-catabolic and anabolic, respectively. If subjected to additional investigation, this line of inquiry has the potential to facilitate the production of novel and efficacious supplementary components *via* the amalgamation of established pharmaceuticals and targets. For better classification, it's essential to distinguish between disease-modifying OA drugs (DMOADs) targeting the specific regulation of cartilage breakdown and building pathways, and reparative methods utilizing stem cells and their components. The subsequent section will discuss on detail on available drugs and/or treatment modalities focused to repair and regenerate AC.

6.1. Anabolic drug: sprifermin

Contrarily, anabolic medicines are often defined as compounds that

support the growth and development of tissues, including bones and muscles. A well-known example is the usage of anabolic steroids, which are frequently administered to improve muscular growth and sports performance. However, using anabolic steroids for non-medical purposes is typically not advised due to the numerous health dangers involved. One potential DMOAD is sprifermin, which is a recombinant form of human FGF-18. Sprifermin has been shown to enhance the proliferation of chondrocytes and promote the synthesis of cartilage matrix. Results from a phase Ib clinical study investigating the impact of injecting sprifermin directly into the joint in people with symptomatic knee OA revealed a notable reduction in the decline of overall femorotibial cartilage thickness and was dose dependent. These results were seen after a 12-month follow-up period [60]. Currently, there is an ongoing phase II multicentre randomized dose clinical research (NCT01919164) investigating the efficacy and safety of Sprifermin [61]. The administration of 100 g of sprifermin at regular intervals of 6 or 12 months to individuals with symptomatic radiographic knee OA, as compared to a placebo, led to a notable enhancement in the overall thickness of the cartilage in the femorotibial joint. This favorable result was observed throughout a monitoring duration spanning 24 months. Although the improvement was shown to be statistically significant, its therapeutic implications remained uncertain. The administration of a reduced dose of 30 g of sprifermin at intervals of either 6 or 12 months, with respect to a placebo, did not provide any statistically significant alterations. Furthermore, the duration of the observed effects remained uncertain [60].

6.2. Anabolic drug: BMP-7

BMP-7 is not a drug in the traditional sense; rather, it is a naturally occurring protein that plays a crucial role in bone and cartilage development. BMP-7 is a member of the TGF-β superfamily and is involved in various biological processes, including bone formation, kidney development, and joint maintenance. In the context of anabolic effects, BMP-7 has been studied for its potential role in promoting bone and cartilage growth (Table 2). Some researchers have explored its use in regenerative medicine, particularly in the treatment of bone and joint disorders.

Table 1
Type of collagen found in AC region [20].

Collagen type	Morphological location	Function
II	Main constituent of microfibril	Collagen type II gives cartilage stability and tensile strength, which helps it resist mechanical stresses and preserves the structural integrity of joints.
VI	Pericellular matrix	To keep tissues structurally intact and to keep cells anchored in the ECM, collagen type VI is essential. It contributes to the mechanical characteristics of tissues and gives cellular support.
IX	Cross-linked to surface of macrofibril	Collagen type IX is involved in maintaining the structural integrity of the cartilage matrix. It contributes to the mechanical properties of cartilage, helping to withstand compressive forces in joints.
X	Related to the hypertrophied cells in calcified cartilage layer	Normal bone mineralization and development depend on collagen X. It is particularly linked to the process of endochondral ossification, in which bone replaces cartilage throughout the formation of the skeleton.
XI	Within or on macrofibrils	Collagen types II and XI play critical roles in skeletal growth and joint formation. They help to establish and maintain the structural architecture of the cartilage in joints.

Table 2
Techniques implemented for regenerating cartilage using BMPs alone and in combination with other strategies [68].

BMPs alone or in combination with other therapeutics	Experimental conditions	Outcome
BMP-2	Human chondrocytes	Permits chondrogenic phenotypic expansion in human articular chondrocytes [69].
BMP-2 + matrilin-3	Chondrocytes	Suppresses the production of enzymes that degrade the matrix, while enhancing the development of collagen II and aggrecan; this helps maintain the tensile strength and flexibility of cartilage [70].
rhBMP-2/rhBMP-4 + alginate gels	osteochondral defect model	Alginate gels provide a completely biocompatible vehicle for BMPs, which demonstrated hyaline cartilage healing [71].
BMP-2 + SOX-9	Human chondrocytes	Promotes the development of cartilage by elevating the expression of aggrecan and type II collagen [72].
BMP-4 transfected rabbit ADSCs + PLGA scaffold	Rabbit osteochondral defect model	Facilitate the repair of AC [73].
BMP-4	Rat fascia-derived cells	The process triggers the development of cartilage [74].
BMP-6 + HA-TA	Human MSCs	Increases the expression of osteopontin and collagen type X while promoting the expression of chondrogenic marker [75].
Rabbit chondrocytes transfected with Ad.hBMP7-GFP	Rabbit chondrocyte	Enhances collagen II and HA levels, which aid in cartilage healing [76].
BMP-7 (knee injection)	Model for OA in rats caused by intense jogging	It slows down the course of OA, boosts BMP-7 levels in cartilage, and decreases IL-1β in the synovium, and it increases the creation of cartilage matrix [77].
rhBMP-7 + collagen I	Mini pig osteochondral defect model	Improves mechanical characteristics, cellular organization, ECM synthesis, and homogenous cellular distribution [78].
rhBMP-9	Human MSCs	Upholds the expression of ECM molecules unique to chondrocytes even when normal amounts of IL-1β associated with OA are present [79].
BMP-9 + MC-GAG scaffold	Human MSCs	Signaling *via* the non-canonical BMP receptor and an increase in Sox-9 [80].
BMP-7 modified exosomes	LPS-treated macrophages RAW264.7 and *in vivo* OA model	The polarization of synovial macrophages M2 reduced knee OA inflammation and cartilage damage *via* BMP-7-exosomes [81].

Abbreviations: BMP, bone morphogenetic protein; rhBMP, recombinant bone morphogenetic protein; ADSCs, Adipose-derived stem cells; PLGA, Polylactic co-glycolic acid; AC, Articular cartilage; HA-TA, tyramine derivative of hyaluronan; MSCs, Mesenchymal stem cells; Ad.hBMP7-GFP, adenovirus containing hBMP7 and green fluorescent protein; HA, Hyaluronic acid; OA, Osteoarthritis; IL, Interleukin; ECM, Extracellular matrix; MC-GAG, osteogenic nanoparticulate mineralized glycosaminoglycan scaffold; LPS, Lipopolysaccharides.

However, it's important to note that BMP-7 is not a pharmacological drug that is commonly administered for performance enhancement or muscle growth. Clinical applications of BMP-7 include its use in certain medical procedures, such as spinal fusion surgeries, where it can be applied to stimulate bone growth and aid in the fusion of vertebral segments. Three clinical trials in humans with knee OA looked at BMP-7. Two studies (NCT01133613 and NCT01111045) did not yield any positive outcomes, while one (NCT00456157) ended with results. Subsequent examinations revealed no evidence of dose-limiting harm. Many of the adverse effects were minor or moderate in nature, and they were comparable across the placebo and BMP-7 groups. Despite this, the BMP-7 group's response was equal to that of the placebo groups, as both groups saw a 20 % reduction in pain [7,56].

6.3. Anti-catabolic drugs: MMP inhibitors

One way to slow down the breakdown of cartilage might be to stop matrix metalloproteinases (MMPs) like MMP-13 and aggrecanases like ADAMTS-4 and -5 from doing their jobs. These are important enzymes that break down the cartilage matrix in OA [56,62,63]. Human therapeutic research (NCT00041756) that used the MMP inhibitor PG-116800 (PG-530742), which has limited affinity for both MMP-1 and MMP-7, was stopped because it was found harmful to the musculoskeletal system [59]. The most prevalent adverse event was arthralgia (35 % of patients), whereas 13 % of patients suffered hand adverse effects (edema, palmar fibrosis, Dupuytren's contracture, or persistent tendon thickness or nodules). Consequently, the MMP inhibitor PG-116800 was never studied further as a treatment for knee OA [64]. Other MMP-13 inhibitors are being investigated, including CP-544439, AZD-8955, and WAY-170523; however, no clinical data has been published [60]. Further, MMPs and aggrecanases are involved in cartilage matrix disintegration, and their activity must be managed for matrix homeostasis to be achieved. In the early stages of OA, an unbalanced protease activity that promotes rapid cartilage matrix breakdown may be identified as a new type of OA, making it a unique target for treatment. The results suggest that substances such as FGF18 and BMP-7 have promising pro-anabolic effects that can improve cartilage tissue. However, attempts to inhibit catabolic enzymes like proteases have not demonstrated satisfactorily advantageous effects on cartilage health due to the associated adverse outcomes.

6.4. Stem cell-based approaches for regenerative therapies

So far, approximately 144 clinical papers exploring the therapeutic potential of stem cells in OA and cartilage injuries have been published on www.clinicaltrials.gov, showing that regenerative medicine holds potential to be a promising treatment option for the management of OA [56] (Figs. 5 and 6). Initially, case studies recorded the invasive (surgical) implantation of mesenchymal stem cells (MSCs) (Table 2). Subsequently, a safe and feasible method was established *i.e.,* IA-injection of autologous mesenchymal MSCs. In fact, SCID mice were injected with MSCs intravenously (IV) and then engrafted directly into the injured area. This prevented the cells from spreading throughout the body and increased their chances of survival by maintaining AC [65–67]. Autologous MSCs and adipose-derived stem cells (ASCs) are being employed to treat knee OA, and there has been a significant surge in the application of stem cell therapy for traumatic cartilage injury and advanced-stage OA, in recent time [56].

6.5. Extracellular vesicles derived from stem cells

As per the literature, autologous stem cells derived from bone marrow stromal cells (BMSCs) and adipose tissue are preferred over other cell types for regeneration approaches. However, surgeons and researchers disagree on whether stem cells are the superior regenerative medicine technique. Even though stem cells exit the targeted tissue shortly after treatment, their enduring chondroprotective and immunomodulatory effects persist over an extended period. Because the therapeutic advantages seem to be independent of the engrafted cells, they are most likely paracrine in origin [56,82]. MSCs proliferate and exhibit a varied secretory profile when exposed to inflammatory cues. Proteomic analysis revealed 118 proteins that were differently expressed by human ASCs upon tumor necrosis factor-alpha (TNF-α) activation [83]. Paracrine effects, on the other hand, are not limited to soluble chemicals because stem cells and other cell types release EVs, which are tiny phospholipid-bilayer-enclosed particles carrying a variety of cytoplasmic components [84]. EVs are distinctive for their size and take part in a variety of cellular processes, such as horizontal mRNA and protein transfer for cell communication. Because of their specific physical and biological features, including good biocompatibility and innate targeting activity, EVs are considered as interesting therapeutic options [85].

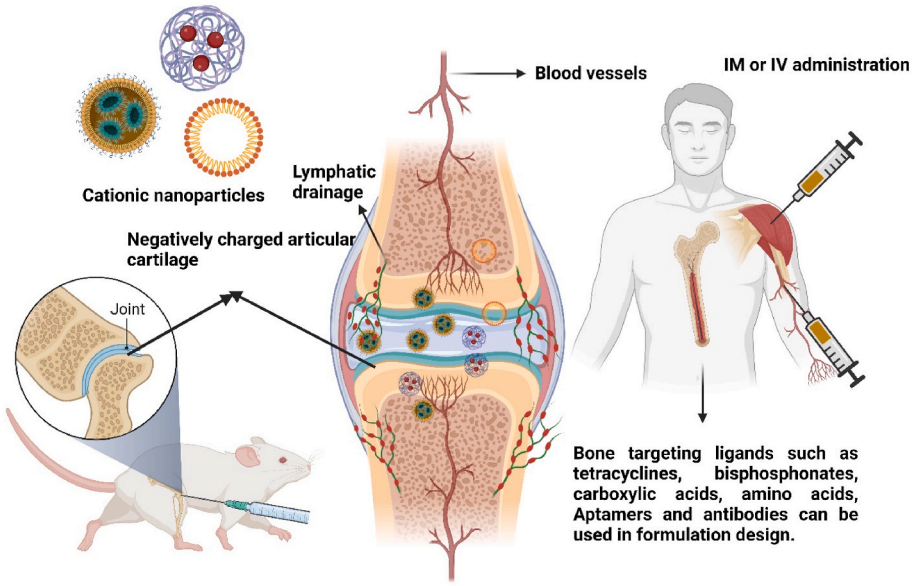

Fig. 5. The illustrations of technique employed to improve the delivery of drugs administered into the synovial joints and various bone targeting strategies for administering drug formulation *via* intramuscular (IM) or intravenous (IV) routes and its significance. Figure created with BioRender.com.

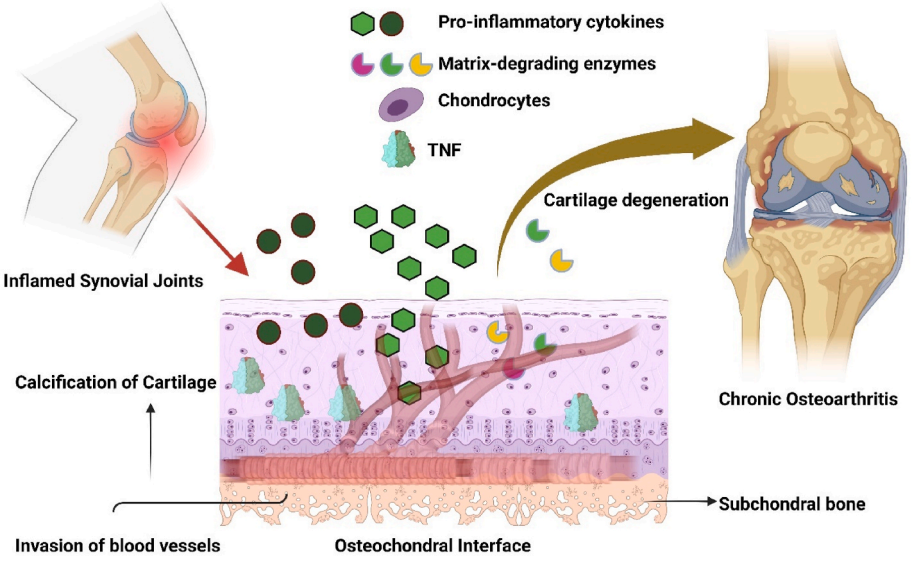

Fig. 6. A schematic representation of inflammation and consecutive degradation of articular cartilage by various pro-inflammatory cytokines. Abbreviation: TNF, Tumor necrosis factor. Figure created with BioRender.com.

Exosomes are one of the most widely explored EVs, and their size range of 10–150 nm implies that they could permeate passively across tissues [86]. A lot of researchers think that using stem cell secretomes and EVs to treat cartilage diseases and knee OA leads to a wide range of positive effects [87]. Also, the secretome and EVs had shown various properties, such as anti-catabolic, immunomodulatory, and regenerative during *in vitro* investigations. In addition, the data from *in vivo* studies revealed that EVs injections had a positive effect on the joint [88]. The administration of EVs improved gait abnormalities in an OA mouse model [89], while MSCs secretome infusions alleviated pain in treated mice as early as day 7 [90]. These data show that this regenerative technique has translational potential. *In vitro and in vivo* findings advocate the feasibility of such a novel therapeutic method, potentially opening new possibilities for natural cell component involvement in advanced therapeutic approaches. EVs are also widely considered as advanced biomarkers [87], hinting that EVs will play a significant role in future therapies for joint issues (Table 2). Surprisingly, since they are formed from cells but are not the cells, hence, they cannot proliferate or create tumors, making them a safe alternative to actual cell-based therapeutic procedures. EVs can be attached to scaffolds by being implanted inside the biomaterial matrix or bonded to their surface. Although stem cell therapy holds great potential for treating OA, it must overcome various obstacles to become a widely accepted therapeutic option [91]. Autologous stem cells, derived from the patient's own body, decrease the danger of immunological rejection [92]. However, factors such as the patient's age and overall health condition limit their use. Allogeneic stem cells obtained from donors require meticulous matching and carry the risk of immunological rejection. On the other hand, the use of embryonic stem cells presents ethical concerns and regulatory obstacles [93]. Adult stem cells and induced pluripotent stem cells (iPSCs) are less subject to debate, although they possess their own set of restrictions [94]. It is difficult to ensure that stem cells undergo differentiation into the specific cell type (chondrocytes) and not any other cell types [92]. In order to be functional, stem cells need to integrate with the pre-existing cartilage and ECM, which is an intricate process. Researchers are currently investigating the optimal method for administering stem cells to the damaged region, whether by direct injection, scaffolds, or hydrogels [95]. It is challenging to guarantee the retention, viability, and optimal performance of transplanted stem cells inside the joint environment. On the other hand, outcomes may significantly differ across individuals owing to variables such as age, severity of the illness, and general health condition. In addition, stem cell treatments may incur high costs, hence restricting the availability of treatment for several individuals. Several insurance companies exclude coverage for experimental therapies, posing a significant obstacle for individuals who are interested in pursuing stem cell therapy [93]. Nevertheless, uncontrolled stem cell proliferation poses a risk of tumor formation. To tackle these obstacles, it is necessary for scientists, doctors, and regulatory agencies to engage in continuous research and cooperation. The goal is to create stem cell treatments for OA that are both safe and effective while also being easily accessible [96].

7. Therapy addressing subchondral bone

The subchondral bone is important because it handles physiological and non-physiological stress, and supports the cartilage above it [56,97,98]. Consequently, any changes that affect bone cell metabolism and morphological integrity may render the bone more sensitive to excessive loading or even result in atypical responses to normal physiological stress. It was commonly believed for a considerable time that alterations in the structure of subchondral bone related to OA were a reaction of the bone to biomechanical shifts in the AC. New studies on animals and humans showed that changes in bone morphology can happen before and affect the development of conditions related to cartilage [99,100], and that changes in bone structure over time are linked to the development of chronic OA [99]. During the initial stages of OA, there is an expedited turnover of bone, leading to thinning of the bone plate and heightened porosity. Simultaneously, the trabecular compartment experiences augmented trabecular spacing and a decreased percentage of bone volume. As OA progresses, the subchondral bone plate thickens, trabecular thickness, and bone volume fraction increases, resulting in subchondral bone marrow lesions (BMLs) [99]. These BMLs, an OA feature, show up early on MRI and are linked with higher discomfort and cartilage deterioration [101].

7.1. Therapy with bisphosphonates

Bisphosphonates (BPs) significantly reduce bone turnover in osteoporosis by downregulating osteoclast activity, but their use in OA is uncertain [56,102]. There is evidence that BPs use may benefit a specific patient subgroup: in a randomized controlled trial, the administration of zoledronic acid *via* intravenous (IV) route decreased the BMLs size and the visual analogue scale (VAS) pain score after a six-month period, though the results were not confirmed in a second multicenter trial [103,

104]. Furthermore, Vaysbrot et al. showed similar outcomes when administering risedronate orally to BML patients [102]. A phase III trial of AXS-02 (disodium zoledronate tetrahydrate) against OA with BMLs reduced the pain in the knee significantly *via* modulating pro-inflammatory cytokines [56,105]. Undoubtedly, BPs could be beneficial for those with BMLs, or rapid bone turnover, in the early stages of OA. Surprisingly, pharmacologic medications like BPs that directly affect osteoclast activity effectively reduced pain [89,106]. However, additional investigation is needed to confirm the therapeutic roles of BPs alone or in combination with existing OA-based drugs for clear comprehension of their former advantageous effects in OA.

7.2. Bones-targeted drug therapy

One of the novel therapy methods to target bone is the nullification of cathepsin K, the principal osteolytic protease produced by osteoclasts. This small-molecule cathepsin K inhibitor, MIV-711, greatly improved joint pathology in a rabbit OA model [107] and slowed down the breakdown of bone and cartilage in phase IIa multicenter study of primary knee OA [56,108]. The study was only 26 weeks long, and MIV-711 did not alleviate pain throughout that time. Denosumab is a monoclonal antibody that targets receptor activator of NF-κB ligand and stops osteoclastogenesis. It is currently being tested on people with interphalangeal finger joint erosive OA (NCT02771860) and knee OA (DISKO, ISRCTN96920058), but no results have been released. TGF, which is elevated in OA synovial fluid [109], might be a therapeutic target for subchondral bone. In a mouse model of OA, blocking TGF slowed down the breakdown of bone and cartilage [110]. However, when targeting this molecule, it is important to remember that TGF is physiologically important as a differentiation stimulant for chondrocyte precursor cells [109]. Furthermore, anabolic therapies are also utilized to treat OA. Teriparatide is a synthetic parathyroid hormone that effectively slowed down the development of OA and decreased the death of chondrocytes in a surgical rat OA model. Its effectiveness is now being tested in a phase II knee OA study (NCT03072147) [111,112]. However, for better therapeutic performance of this anabolic therapy, bone-targeting approaches must be employed. Tables 3 and 4 and Fig. 5 summarize strategies to target bones and novel therapeutic agents in clinical trials to treat OA, respectively [113].

7.3. Vitamin D3 as dietary supplements

Dietary supplements such as vitamin D3 (cholecalciferol) could be considered as a strategy to specifically enhance and fortify bones in OA, as they have the potential to enhance the absorption of calcium and phosphate in the intestines and have a direct influence on the metabolism of bone cells [56]. On clinicaltrials.gov, several studies have explored the impact of vitamin D3 supplementation in patients with OA. However, the evidence regarding the connection between vitamin D levels and a heightened risk of OA onset and progression has been inconsistent and variable [120]. A thorough review of randomized controlled trials revealed that OA patients who took 2000 IU of vitamin D3 had less pain on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and better joint function [121]. However, the degradation of cartilage remained unaffected. In general, vitamin D3 intake could help the population since its deficiency is a global issue. Furthermore, the older population, and particularly women, who are at a greater risk of OA, could be supported *via* vitamin D3 intake together with other OA treatment options [122].

8. Treatment targeting inflammatory mediators and pathways

The consensus now acknowledges that OA involves an inflammatory aspect, potentially more prominent in certain subsets of patients, and specific tissues within the joints like synovium (Fig. 6). Synovitis is a common feature of inflammatory OA, and advancements in imaging

Table 3
Various frequently reported ligands utilized as bone targeting strategies [113].

Ligands for bone targeting	**Tetracyclines**	Tetracycline and its derivatives are absorbed by the newly formed bone, creating a luminescent region when exposed to UV light. This response, occurring in bone deposition areas, can be used to identify calcification. Tetracycline absorption occurs on all surfaces, including non-growing ones, and is not influenced by live bone cell activity or intercellular components' physical characteristics. This process occurs in all viable organisms [114].
	BPs	BPs, a chemical class with a direct affinity for hydroxyapatite, effectively inhibits osteoclast-mediated bone resorption, providing targeted treatment for degenerative bone diseases. Its potential use in cancer therapy is also evident. BPs medications have shown efficacy against osteoporosis, primary and metastatic bone tumors, and enhance bone imaging. The use of bone-binding chemicals facilitates the transportation of pharmaceutical substances to bone tissue [115].
	Aspartic acid (Liner)	Rotman et al. developed a biodegradable microsphere carrier that contains antibiotics and has a targeted affinity for bone mineral. The carrier, made of poly (-caprolactone) (PCL) and cPVA, was prepared using oil-in-water emulsion procedures and modified with aspartic acid oligomers, enhancing its targeting ability towards bone [116].
	Aspartic acid (Dendrimer)	Yamashita et al. developed self-assembled NPs consisting of polyethylene glycol-conjugated, and other polymers for the higher targeting to active bone turnover zones linked with the etiology of bone metastases [117].
	Ser-Asp-Ser-Ser-Asp (SDSSD)	Sun et al. characterized the osteoblast-targeting peptide (SDSSD) and synthesized SDSSD-modified polyurethane nanomicelles for targeted drug delivery to osteoblasts. The study found that SDSSD-PU can target bone-formation surfaces and osteoblasts *in vivo*, maintaining biocompatibility and avoiding toxicity or immune response. Researchers used the SDSSD-PU delivery system to administer anti-miR-214 to osteoblasts in an ovariectomized osteoporosis mouse model, resulting in enhanced bone production, microarchitecture, and improved bone mass. This suggests SDSSD-PU as a potential strategy for delivering small nucleic acids to treat bone disorders caused by excessive osteoblast activity [118].
	Aptamer (CH6)	Liang et al. conducted a screening of the aptamer CH6 using the cell-SELEX method. They then constructed lipid NPs (LNPs) functionalized with the CH6 aptamer to encapsulate siRNA targeting osteogenic pleckstrin homology domain-containing family O member 1 (Plekho1). The LNPs showed enhancements in bone production, microarchitecture, bone mass, and mechanical characteristics in both osteopenic and healthy rats, primarily through macropinocytosis. The study suggests that using osteoblast-specific aptamer-functionalized LNPs could be a novel bone anabolic approach based on RNA interference, enhancing

(*continued on next page*)

Table 3 (*continued*)

	targeted delivery of osteogenic small interfering RNAs to the cellular level [119].

Abbreviations: BPs, Bisphosphonates.

modalities like ultrasonography and magnetic resonance imaging (MRI) have found synovitis in a considerable proportion of patients at different phases of disease. Various pre-clinical animal models and clinical studies have shown the production of several pro-inflammatory mediators, including prostaglandins, cytokines, and chemokines [56,140]. As per the recent studies, cells and components of the innate immune system are identified as the key drivers of OA inflammatory processes [141, 142]. A number of stressors, such as abnormal mechanical pressures, metabolic syndrome, aging, and cartilage ECM or crystal fragments, may also cause these mediators to be released from various types of responsive joint tissue cells [143]. Treatment of inflammation-driven OA involves the use of NSAIDS and glucocorticoids; however, they are inefficient and have significant side effects when taken long-term [127, 144,145]. This section of the review will focus on the role of inflammation and various anti-inflammatory inhibitors to treat or manage OA (Table 5) [146].

8.1. Anti-cytokine therapy

Anti-cytokine treatment attempts to reduce inflammation and can slow down the disease's course by modulating or inhibiting certain cytokines that are involved in the inflammatory process. TNF-α, IL-1, and IL-6 are a few cytokines linked to OA. Most biologics used for managing inflammation associated with OA were originally created for treating rheumatoid arthritis (RA), which is a more common inflammatory disease. Biological treatments that focus on inflammatory cytokines like IL-1 and -6, as well as TNF-α, have not shown a significant reduction in OA-related pain or the progression of structural changes. Granulocyte/macrophage colony-stimulating factor (GM-CSF) was associated with inflammatory pain in a rat OA model and appeared more significant with hip over knee OA, in studies investigating the function of mononuclear cells in synovial inflammation [56,160]. Otilimab, an anti-GM-CSF antibody (GSK3196165), was used in a study to treat erosive hand OA and showed good results (NCT02683785) [56,161]. Mavrilimumab, a GM-CSF receptor inhibitory antibody that proved effective in RA, may hence have OA therapy potential. Single cytokine blocking may not have had much of an impact because low-grade, non-systemic inflammation is a hallmark of OA [161]. Focusing on certain types of OA, like erosive hand OA with more obvious inflammation, may help find a group of patients who can benefit from anti-cytokine biologics. Identifying the sole major cause of inflammation in OA appears challenging, suggesting that broader strategies aimed at general components of pro-inflammatory signaling pathways might offer greater benefits. Moreover, OA is a complex condition, and its pathophysiology involves multiple factors. Further, targeting specific cytokines may be effective for some patients but not others. Additionally, long-term safety and potential side effects need to be thoroughly assessed [56].

8.2. Interference with pro-inflammatory signaling pathways

Interfering with pro-inflammatory signaling pathways is a key strategy in the treatment of various inflammatory conditions and diseases. Inflammatory signaling pathways are complex networks involving various molecules, receptors, and intracellular signaling cascades. Modulating these pathways can help regulate the immune response and reduce inflammation [145]. Monoclonal antibodies or soluble receptors can be used to neutralize or block the activity of specific pro-inflammatory cytokines. Examples include drugs like adalimumab (anti-TNF-α) and tocilizumab (anti-IL-6). Similarly, inhibitors that target various components of the NF-κB signaling pathway can help reduce the transcription of inflammatory genes. This includes drugs like corticosteroids and small molecules that inhibit NF-κB activation. Janus Kinase (JAK) inhibitors block the activity of JAKs, which are crucial for signal transduction from various cytokine receptors. Drugs like tofacitinib and baricitinib are examples of JAK inhibitors that could be beneficial to treat OA. Furthermore, drugs that inhibit complement activation, such as eculizumab, can be used in conditions where dysregulated complement activation is a contributing factor [56,160]. So far, single-cytokine targeting has had minimal impact on treating OA. Recent efforts are being made to disrupt other upstream initiators of the pro-inflammatory signaling cascade. TLR 7/9 is suspected to be involved in the action of hydroxychloroquine, a chloroquine derivative used to treat malaria and inflammatory autoimmune diseases such as RA [56, 162]. Several studies using hydroxychloroquine in hand OA have so far failed to show benefits, while the results of a study in knee OA are not yet available (NCT01645176) [163,164]. TLR molecules include MyD88, TRAF3/6, p38 MAPK, JAKs, and transcription factors including NF-κB [165]. Multiple attempts have been made to control OA inflammation by interfering with signaling molecules. In four knee OA trials (NCT01113333, NCT01598415, NCT01511549, and NCT01463488), an IκB kinase inhibitor known as SAR113945 was looked at. However, a larger proof-of-concept study did not show improved effectiveness [166], even though it had a good safety and tolerability profile. A small fraction of people with effusion at baseline had a lower WOMAC pain score after 56 days. In a study using mice with destabilizing OA, a strong p38 MAPK inhibitor (PH-797804) injected into the joint reduced joint damage and inflammation [167]. The efficacy of PH-797804 was compared to naproxen in a clinical study including knee OA patients; however, the results have not yet been published (NCT01102660). In a phase I/II knee OA trial (NCT01291914), FX-005, which is another therapeutic p38 MAPK inhibitor with sustained-release kinetics, helped with pain more than a placebo after 4 weeks. Directly targeting TLRs might have an even bigger effect on stopping the immune system from activating in OA. For example, a miR-21 inhibitor that targets TLR7 was able to relieve pain in a rat model of OA for a long time [168]. In summary, a careful evaluation of individual patient inflammatory states will most likely benefit finding more responsive patient subgroups or joints when it comes to anti-cytokine medication.

8.3. Senolytic drugs

Cellular senescence is a biological process associated with aging and age-related diseases. It is characterized by a decline in the ability of cells to divide and functional changes. Cellular senescence has been recognized as a contributing factor to the development and progression of OA. The term senescence-associated secretory phenotype (SASP) refers to an accumulation of biologically active substances that cells frequently release during senescence [169]. Pro-inflammatory cytokines, chemokines, and MMPs are components of the senescence-associated secretory phenotype (SASP) [56,170,171]. The ongoing low-grade inflammation that the SASP generates could act as a prime contributor of chronic low-level inflammation in the joints of people with OA [172,173]. Further it has been reported that chondrocyte senescence is induced by oxidative stress, as demonstrated by Martin et al. [173,174], and is anticipated to have a role in the development of the aberrant inflammatory conditions seen in OA. Chondrocytes have a minimal level of metabolic activity and are well-suited to the low-oxygen conditions in the joint. However, excessive lack of oxygen, known as hypoxia, can lead to inflammation in the synovial tissue, which is associated with OA. This inflammation contributes to the progression of the disease [174,175]. In addition, research has shown that osteoarthritic joint tissues have a greater number of senescent cells compared to healthy joint tissues. It is believed that the buildup of these senescent cells exacerbates the degenerative processes linked to OA. DNA damage and oxidative stress

Table 4
Recent novel therapeutic agents in clinical trials to treat OA.

	Drug	Mode of action/Identifier	Route of delivery	Specifications and references
Drugs in clinical trial to treat OA	**Otilimab**	Block the interaction of GM-CSF with its cell surface receptor. (NCT04333147, phase III; NCT02799472, phase II)	Subcutaneous injection	Otilimab is a monoclonal antibody that inhibits GM-CSF, a cytokine involved in inflammation, aiming to reduce inflammation and potentially alleviate symptoms of conditions like RA [123].
	Lorecivivint (LOR; SM04690)	Wnt pathway inhibitor, (NCT02536833, phase IIa completed; NCT03122860, phase IIb completed; NCT03706521, Phase II completed; NCT03727022, NCT03928184,phase II completed; NCT04385303, phase III completed; NCT04520607, phase III completed)	IA-injection,	LOR, also known as SM04690, is a small-molecule inhibitor of the Wnt pathway. The Wnt pathway plays a role in cell development, and its dysregulation has been implicated in various diseases, including OA. The purpose of LOR is to alter the Wnt pathway to potentially impede the advancement of OA. The 24-week Phase 2b research demonstrated that LOR had a high tolerance and safety profile in addition to being able to achieve substantial therapeutic goals [124,125].
	JTA-004	Anti-inflammatory and analgesic (NCT02740231, phase II and III completed)	IA-injection	JTA-004 is a non-animal-derived HA formulation combined with triamcinolone hexacetonide, aimed at providing short-term pain relief and long-term improvement of knee OA symptoms. It is injected directly into the joint cavity to relieve discomfort associated with injection and chronic pain in knee OA patients [126].
	Botox®, Botulinum toxin A	Influences the regulation of central sensitization-induced chronic pain, peripheral nociceptive transduction, and neurotransmitter release modulation. (NCT02230956, phase II completed)	IA-injection	Botulinum toxin A, when administered intra-articularly, has shown promising results in improving functional outcomes and reducing pain in individuals with knee OA diagnoses. However, further investigation is needed for validation, as larger randomized trials are essential for confirmation [127].
	ZYN002, CBD gel	synthetic transdermal cannabidiol (NCT03802799, phase II and III)	Transdermal	Zynerba has developed the first patent-protected permeation-enhanced synthetic CBD gel, ZYN002, for treating OA, Fragile X Syndrome (FXS) syndrome, and refractory epilepsy. This transparent gel is designed for consistent, regulated CBD transdermal administration with twice-daily dosages [128].
	MIV-711	cathepsin K inhibitor (NCT02705625, phase II completed)	Oral	MIV-711, an inhibitor of cathepsin K, has been shown to reduce cartilage disease and subchondral bone loss in two OA animal models. It also reduces bone and cartilage biomarkers usually involved in cartilage degeneration, and that are clinically achievable in humans too; indicating potential for further research as an OA therapy [107]. A phase 2a research study found that while cathepsin K inhibitor MIV-711 may reduce cartilage volume loss and bone remodeling, it does not improve pain outcomes in people with OA [129].
	Tanezumab	an antibody directed against nerve growth factor (NGF) (NCT02709486, phase III completed)	IV	Yang and colleagues. found that anti-NGF antibodies may decrease pain and improve function in those with OA and chronic low-back pain [130].
	AXS-02	Disodium Zoledronate Tetrahydrate (NCT02504008, phase III)	Oral	AXS-02 is a non-opioid, targeted treatment for chronic pain. It decreases osteoclast activity by attaching to bone minerals and inhibiting the farnesyl pyrophosphate synthase enzyme. Developed for chronic low back pain, knee OA pain related to bone marrow lesions, and CRPS, Phase 3 studies are underway. AXS-02 is an experimental medication that the FDA has not yet authorized [56].
	Invossa™	A cell and gene-based therapy, phase III completed	IA-injection	Invossa™ is a cell and gene therapy for knee OA, combining gene therapy and cell therapy to provide a long-term solution. It involves inserting a DNA plasmid into joint cells, expressing therapeutic proteins TGF-β and IGF-1, which are believed to aid in cartilage repair and regeneration. A Phase III trial showed that Invossa™ significantly decreased pain, sports activities, and quality of life in individuals with knee OA compared to a placebo control [17,131].
	Sprifermin	FGF-18 (NCT01919164, phase II completed)	IA-injection	Sprifermin, a recombinant human FGF-18, is being studied as a potential treatment for OA. FGFs are proteins involved in cell growth, development, and tissue repair. Sprifermin's potential is to stimulate the repair and regeneration of AC in joints [132].
	Ampion™	a low molecular weight fraction of human serum albumin (HSA) (NCT03182686, phase III completed)	IA-injection	Ampion™ is a NSAID derived from human serum albumin, used to treat inflammatory conditions like OA. It modulates the immune response and reduces inflammation. It is designed for injection into affected joints to alleviate pain and improve joint function. Recent research shows that Ampion™ reduces

(*continued on next page*)

Table 4 (*continued*)

Drug	Mode of action/Identifier	Route of delivery	Specifications and references
			inflammation by altering pathways linked to overproduction of specific inflammatory proteins and encouraging the expression of anti-inflammatory proteins involved in tissue healing and regeneration [133].
Human platelet-rich plasma	Cartilage regeneration and repair (NCT03491761, phase II ongoing)	IA-injection	Soliciting the migration, proliferation, and enhancement of collagen and matrix formation by the local mesenchymal cells [134].
Transforming growth factor-β	Allogeneic human chondrocytes modified to express TGF-β1 (NCT03291470, phase III ongoing; NCT03203330, phase III ongoing; NCT01221441, phase II completed)	IA-injection	Facilitating the repair of damaged cartilage or the growth of new cartilage [135].
Metformin	AMPK modulator, (NCT04767841, phase I and II undergoing)	Oral	Activates AMPK and facilitates the cartilage regeneration [136].
Teriparatide	Showed anti-inflammatory, analgesic, and cartilage-and subchondral bone-repairing properties. (NCT03072147, phase II completed)	Subcutaneous injection	Subchondral bone remodeling [137].
Strontium ranelate	Impacts on bone turnover and inflammation linked to this condition (ISRCTN41323372, phase III completed)	Oral	Subchondral bone remodeling [138].
Vitamin D	Cartilage regeneration (NCT04739592, phase IV ongoing)	Oral	Promoting the production of proteoglycans and the mineralization of bone [139].

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; RA, rheumatoid arthritis; OA, osteoarthritis; AC; articular cartilage; CRPS, complex regional pain syndrome; FDA, Food and Drug Administration; TGF-β, Transforming growth factor-β (TGF-β); IGF-1, Insulin-like growth factor 1; FGF-18, Fibroblast growth factor 18 (FGF-18); NSAID, non-steroidal anti-inflammatory drug; IA-injection, intra-articular-Injection; IV, intravenous.

are two examples of factors that may cause cellular senescence [56,171]. Within the context of OA, the DNA of chondrocytes experiences damage because of age-related alterations, mechanical strain, and the conditions present in the joint, could result in cellular senescence. Therefore, a potential therapeutic approach for OA is to use anti-OA drugs. Eliminating senescent cells may reduce the secretion of pro-inflammatory cytokines and other substances, resulting in a joint environment with lower levels of inflammation. Although preclinical research in animal models has shown encouraging outcomes, the progression of senolytic treatments to human clinical trials for OA is still in an early phase [170]. Researchers are studying the safety and effectiveness of senolytic medicines in human subjects to assess their potential as a therapy for OA. It is crucial to acknowledge that while senolytic medications have potential, further study is necessary to get a deeper understanding of their prolonged impacts, possible adverse effects, and the most effective treatment plans for OA. The area of senolytics is characterized by its dynamism, and continuous research endeavors will enhance our comprehension of their significance in the treatment of age-related ailments, like OA [170,171].

9. Gene therapies

Anti-inflammatory genes are being explored into patients as part of gene treatments, which aim to control inflammation and lessen joint damage. Gene treatments may entail the insertion of genes that either stimulate the synthesis of healthy cartilage or block the enzymes that tear it down. Directly altering certain genes linked to OA is possible with the use of CRISPR-Cas9 and other gene editing techniques. This may entail fixing or swapping out faulty genes to treat the disease's underlying causes [176]. Clinical phase I research is now underway to evaluate the safety of novel genetic methods to treat OA (Fig. 7). Included in the list of interventions are the administration of recombinant adeno-associated virus type 2/5 (rAAV2.5) vector encoding IL-1 receptor antagonist (IL-1Ra) *via* injection into a single knee joint of individuals with moderate OA of the knee (NCT02790723), as well as the utilization of FX201, a helper-dependent non-integrating adenovirus carrying the human IL-1Ra gene regulated by an inflammation-responsive promoter (NCT04119687). Interferon (INF) and XT-150, specifically the rAAV2.5 vector producing human IFN- under the control of an NF-κB promoter (ART-I02) and a plasmid DNA containing a variation of the human IL-10 transgene respectively, have emerged as novel gene therapy targets for individuals with RA and who have active hand arthritis [176]. These targets are being investigated in clinical trials registered under the identifiers NCT02727764 and NCT03477487, respectively. Despite the present lack of knowledge on the outcomes of these research, gene therapy has significant potential as a therapeutic approach due to its ability to provide medications directly to joints in a regulated and sustained manner. The effectiveness of virus-related delivery systems compared to traditional delivery systems is a topic of interest [176]. However, it is crucial to give due attention to safety concerns such as vector immunogenicity, off-target, and long-term effects. These safety considerations should be thoroughly examined and analysed in relation to the effectiveness of genetic therapy before any decisions are made [177]. The study conducted in the field of equestrian research using AAV2.5-mediated delivery of IL-1Ra has yielded encouraging findings with regards to pharmacodynamics and safety [178].

10. Methods and available drug delivery vehicles for delivering therapeutics to the joint

For OA treatment, IA injection procedures include directly injecting therapeutic substances into the synovial fluid of the affected joint. These approaches have the potential to reduce systemic side effects by delivering targeted and customized treatment. In addition, this section will focus on the existing information on drug delivery inside joints and cartilage, as well as the use of cartilaginous organoids, nano-decoys, and nanoparticulate DDSs in combination. Furthermore, in this part, we have classified the phases or grade of OA as per the diseases severity, and examined the most effective treatment choices for each stage. We have also provided a concise overview of the benefits and limitations of these treatments (Tables 6 and 7).

10.1. Intra-joint delivery

The primary contributors to knee joint soreness is the synovium, the outer-third of the meniscus, and the osteochondral junction [14,179]. The occurrence of this phenomenon in OA can be attributed to the expansion of the capillary network, known as angiogenesis. This expansion leads to synovitis, which is characterized by the hypertrophy of synovial macrophages and FLS. Additionally, it contributes to osteochondral degradation and the formation of osteophytes [3,179]. Thus,

Table 5
Summary of recently emerged anti-inflammatory mediators to treat osteoarthritis.

	Drug	Mode of action/Identifier	Route of delivery	Specifications and references
Recently emerged anti-inflammatory pathway mediators to treat OA	**ABT-981 (Antibody)**	Anti-IL-1α and -1β (NCT05139602, phase II completed; NCT02087904, phase 2; NCT02384538, phase II completed.)	IP/Subcutaneous injection	ABT-981 has favorable pharmacological characteristics, such as high affinity, potency, specificity, extended half-life, and stability, making it acceptable for assessment in human clinical trials [147].
	Adalimumab (Antibody)	Anti-TNF (NCT00195702, phase III completed).	Subcutaneous injection	Adalimumab is a pharmaceutical compound categorized as a TNF-α inhibitor. It is used for the treatment of autoimmune disorders and inflammatory illnesses [148].
	Etanercept	Decoy receptor to TNF (NTR1192; phase III, double-blind, randomised, multicentre trial completed)	Subcutaneous injection	Its mechanism of action involves the binding of TNF-α and inhibition of its interaction with receptors on the cell surface. Etanercept reduces inflammation and relieves symptoms of autoimmune diseases by decreasing TNF-α [149].
	PG-116800	MMP family inhibitor (NCT00041756, phase III completed)	Oral	The MMP inhibitor PG-116800 has an inadequate risk-benefit balance in knee OA patients, making it unsuitable for further development. This study supports the idea that MMP inhibitors are unsuitable for treating OA due to their side effects [64].
	ALS1-0635	MMP-13 inhibitor	Oral	It inhibited bovine AC degradation in dose dependent manner. However, additional clinical trial is needed to access the safety [150].
	CL82198	MMP-13 inhibitor	IP	As shown by OA grading, histology, histomorphometry, IHC, and TUNEL staining, respectively, intraperitoneal injection of CL82198 slowed meniscal-ligamentous injury-induced OA development, raised proteoglycan and type II collagen levels, and prevented chondrocyte death as compared to saline therapy [151].
	GLPG1972	ADAMTS-5 inhibitor (NCT03595618, phase II).	Oral	The mouse cartilage explants demonstrated verified anticatabolic efficacy, with an IC_{50} value of less than 1.5 μM [152].
	M6495	Nanobody against ADAMTS-5 (NCT03583346, phase Ib completed)	Subcutaneous Injection	By suppressing ADAMTS-5 mediated cartilage degradation and total tissue degeneration in *ex vivo* cartilage cells, M6495 demonstrated cartilage protective properties in a dose-dependent manner [153].
	Anakinra	IL-1 receptor antagonist (NCT00110916, phase II completed)	IA-Injection	Well regarded for its safety record and shorter duration of action [5,154]
	AMG108	A monoclonal antibody against IL-1 receptor type (NCT00110942, phase II completed)	Subcutaneous or IV	Patients suffering from knee OA reported no more side effects when administering AMG108 subcutaneous or IV compared to a placebo. Although there was no statistically significant difference between the groups, patients given AMG 108 reported numerically greater pain reductions. There was little to no therapeutic benefit with AMG108 [155].
	Gevokizumab (XOMA-052)	IL-1 inhibitors (NCT01683396, phase II completed; NCT01882491, phase II completed)	Subcutaneous Injection	For OA, gevokizumab shows promise as a medication that is both effective and safe [156].
	Canakinumab	IL-1 inhibitors (NCT01160822, phase II completed)	Subcutaneous, IM, IA-Injection	Canakinumab 150 mg was far more effective than triamcinolone acetonide 40 mg in reducing inflammatory symptoms and discomfort, and it worked much more quickly to treat gouty arthritis [157].
	Curcuma longa extract	Potential senolytic and anti-inflammatory action (NCT02409381, phase IV completed)	Oral	When comparing Curcuma longa extract to placebo for knee OA, the Curcuma longa extracts demonstrated superior functional improvement and pain reduction. Additionally, the WOMAC total score and VAS for pain both had effect sizes larger than the minimal clinically significant differences [158].
	Turmeric extract	Potential senolytic and anti-inflammatory action (NCT04500210, phase III completed)	Oral	According to the study's findings, bioavailable turmeric extract is just as efficient as paracetamol in alleviating pain and other symptoms associated with knee OA. It was shown to be safer and more effective in lowering CRP and TNF-α [159].

Abbreviations: TNF-α, tumor necrosis factor-alpha; MMP, matrix metalloproteinases; OA, osteoarthritis; IHC, immunohistochemistry; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; IC_{50}, half-maximal inhibitory concentration; ADAMTS-5, A disintegrin and metalloproteinase with thrombospondin motifs 5; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; VAS, Visual Analogue Scale; CRP, C-reactive protein; IP, intraperitoneal; IA-Injection, intra-articular-Injection; IV, intravenous; IM, intramuscular.

current efforts in the advancement of DDSs are primarily concentrated on prolonging the IA retention of pain and inflammation relievers. The objective is to attain sustained efficacy over an extended period by administering a single dose of a low concentration. Moreover, the recent advancements of DDSs to administer drug into the joints have mostly focused on three main areas: hybrid systems, smart environment-responsive systems, and systems that demonstrate selectivity towards intra-joint components, such as synoviocytes and vasculature. Hybrid systems uses drug delivery techniques that combine particles and hydrogels to optimize their effectiveness. As an example, a study conducted over a span of four weeks observed the therapeutic potential of micelles containing the antioxidant eicosapentaenoic acid (EPA), after encapsulating former inside a gelatin hydrogel matrix. The results indicated that these micelles exhibited controlled release of medicine within the joints of mice [180]. The IA administration of EPA hydrogels in mice with destabilized median meniscus at 8 weeks led to a

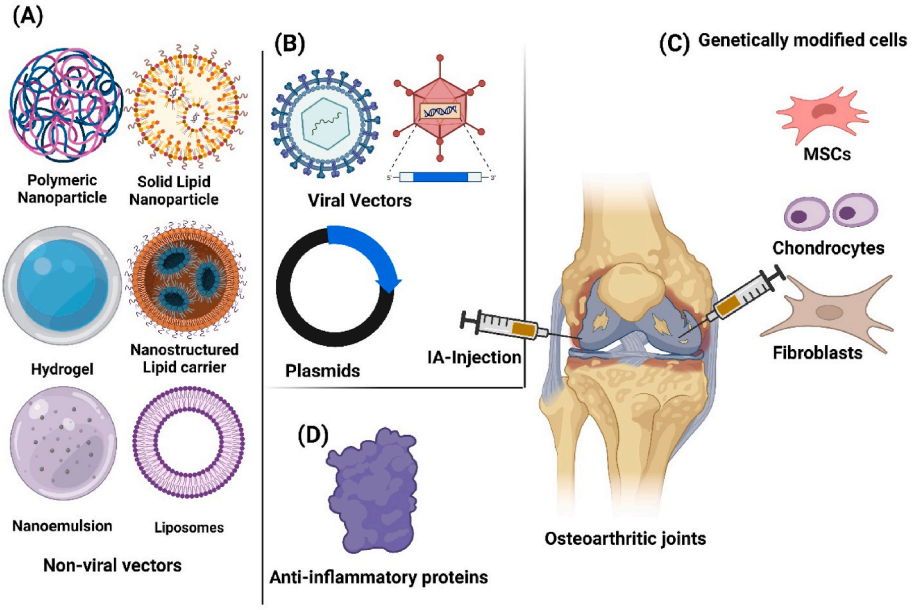

Fig. 7. The illustrations of various methods generally employed for effectively delivering gene-based therapeutics to treat osteoarthritis. (**A**), delivering the gene by incorporating into the nanoparticles; (**B**), administering the genes through plasmids and viral vectors; (**C**), intra-articular (IA) injection, IA-injection of genetically modified cells for cartilage regeneration; (**D**), using anti-inflammatory proteins to inhibit cartilage degeneration. Abbreviation: MSCs, mesenchymal stem cells; IA-injection, intra-articular injection. Figure created with BioRender.com.

significant reduction in GAG loss, as well as a decrease in the expression of IL-1 and MMP-13, as compared to the administration of EPA alone [180]. In a second investigation, gold NPs were utilized in conjunction with fish oil protein to generate a hydrophilic architecture, which was afterwards enclosed inside a hydrophobic liposome composed of dipalmitoyl phosphatidyl-choline with a diameter of 295 nm. The purpose of this approach was to enhance the duration of joint retention and provide lubrication [181]. The application of liposomal encapsulation to NPs led to a more pronounced suppression of NF-κB and iNOS, as well as other catabolic markers present in synovial fluid, in arthritic mice knees. This effect was seen after a 15-day treatment period, in comparison to the use of gold NPs alone tagged with fish oil [181]. In a recent study, a hybrid approach was used to enhance the stability and release of a chondrogenic agent, Kartogenin (KGN), by incorporating it inside the liposomes. These liposomes were then embedded within a photo-crosslinkable Gelatin methacryloyl (GelMA) matrix [182]. The GelMa@Lipo@KGN composite device, with a diameter of 100 nm, was introduced into the rat joints [with surgical destabilization of the medial meniscus (DDM)]; and notably, former was maintained for a duration exceeding 5 weeks, in contrast to liposomes which were retained for just 2 weeks. This extended period of retention led to the release of 75 % of KGN over a span of 25 days and a subsequent decrease in the production of osteophytes [183]. Similarly, the hydrophobic medication, Celastrol (CSL), was encapsulated inside mesoporous silica NPs (CSL@HMSNs-Cs) that were coated with chitosan and had a hollow structure with a size of 275 nm. This encapsulation strategy was used to take advantage of the pH-responsive nature of the NPs and the acidic environment present in the synovial fluid of OA patients [184]. In an *in vitro* environment, it was shown that under acidic conditions with a pH of 6, the drug release was three times higher compared to neutral conditions, after a duration of 24 h. In *in vivo* condition, it was observed that the administration of CSL@HMSNs-Cs, resulted in a greater improvement in paw withdrawal threshold and a reduction in cartilage degradation compared to the administration of free Celastrol and drug-free NPs [184]. In a similar manner, the researchers used PLGA NPs that were loaded with ammonium bicarbonate and HA to achieve pH sensitivity. This approach led to the sustained release of HA for a duration of 10 days in acidic conditions with a pH of 5. The DMM mice were then subjected to a 35-day experiment whereby pH-responsive NPs were introduced into their knee joints. The results demonstrated a substantial reduction in osteophyte production when compared to the non-pH-responsive NPs [185]. Moreover, in another study, researcher modified metal-organic frameworks (MOFs) to exhibit pH sensitivity. The MOFs demonstrated a drug release rate of 23 % at pH 5.6, compared to 13 % at pH 7.4. These pH-sensitive MOFs were further modified by incorporating HA and loading them with an anti-inflammatory drug. The results of the study showed that the modified MOFs led to more significant reductions in synovial inflammation and expression of inflammatory markers in rats with anterior cruciate ligament transection after 8 weeks, when compared to the administration of the free drug alone [186]. Furthermore, the study conducted by a research team [187], shown that poly-beta-amino-ester-curcumin NPs that can be activated by acid, exhibited an extended drug release period of 7 days in acidic environment. These modified curcumin NPs were found to be more effective in reducing the production of inflammatory cytokines in the joints of mice with OA over a period of 28 days compared to unmodified curcumin. In a recent study [188], it was shown that chitosan-modified molybdenum disulfide (MoS2), a thermoresponsive DDS, had the ability to release dexamethasone (Dex), a small molecule, into the knee joint cavity of mice upon exposure to near-infrared light originating from an external source. Interestingly, the research conducted by Deloney et al. utilized the thermosensitive characteristic of N-isopropyl acrylamide to produce NPs with a 'hollow' core. The researchers prepared these particles at a temperature of 4 °C, which is below the lower critical solution temperature. This condition caused the structure to expand, enabling the removal of non-crosslinked cores and consequently enhancing the capacity for drug loading. The core NPs with a hollow structure had a higher capacity for loading and releasing MAPKAP kinase inhibitory peptides compared to solid NPs. Consequently, this led to an enhanced suppression of IL-1 and stimulated IL-6 production in chondrocytes [189]. Moreover, the process of deswelling facilitated a reduction in the size of these particles to 200 nm at a temperature of 37 °C, therefore mitigating any inflammatory reaction often seen with particles of higher dimensions [189]. The NPs were seen to exhibit retention inside the knee joints of rats for a duration of 7 days after IA administration [189]. Nevertheless, the design of DDSs has also prioritized the targeting of

Table 6
Various drug loaded nanoparticles to treat osteoarthritis.

Types of Formulation	Active pharmaceutical ingredients	Results	References
Liposomes	Hyaluronan-Loaded Liposomal Dexamethasone–Diclofenac NPs	The findings demonstrated that the novel liposomal drug-releasing formulation is both safe and effective, making it a potential option for managing OA pain.	[240–242]
	Resolvin D1 liposomes	Results clearly showed the potential of lipo-RvD1 as an anti-OA agent.	
	Liposome-anchored teriparatide	The author demonstrated that administering hydrogels by IA-injection in a mouse model with OA stimulates the production of GAGs and safeguards the cartilage from deterioration. These findings provide evidence for the prospective use of this biomaterial in the treatment of OA.	
Polymeric NPs	The therapeutic composition consists of a polymeric nanoparticle, a ligand specifically chosen to activate an EGFR receptor (such as TGFα), and a linker that connects the nanoparticle and the ligand	The administration of medication directly into the joint significantly reduced the deterioration of cartilage, the hardening of the bone plate underneath the cartilage, and the discomfort in the joint caused by surgery.	[217, 243–245]
	The adenosine molecule is attached to a PLA nanoparticle using a PEG linker.	Administering the treatment directly into the joint cavity reduced the onset of OA in a rat model of post-traumatic OA.	
	Poly(amidoamine) NPs including disulfide bonds and a physiologically active component such as siRNA, miRNA, DNA, (oligo)peptide, or proteins.	Primary chondrocyte transfection and 3D ECM-rich constructions (bCH pellets and tendon-like structures).	
Inorganic NPs	Gold NPs (AUNPs) and Diacerein® (DIA)	Serum inflammatory cytokines, metabolic parameters, estrogen level, hepatic and renal oxidative indicators, hepatic DNA fragmentation, genomic template stability, and cartilage joint histology of OA-rats were all significantly improved by AuNPs and DIA. Both the combination therapy and the individual treatment proved to be more successful than DIA and AuNPs, respectively.	[223,246, 247]
	Silver NPs	According to the experimental findings, silver NPs greatly decreased neutrophil infiltration into the synovial tissue as well as synovial hyperplasia. As a result, their study shows how to identify a unique OA approach and offers a theoretical foundation for stopping knee-OA from developing.	
	Cationic mesoporous silica NPs	Polyethylenimine (PEI)-functionalized diselenide-bridged mesoporous silica NPs (MSN-PEI) with cell-free DNA (cfDNA)-binding with anti-oxidative properties. Investigator demonstrated that these cationic NPs reduced cartilage degradation and offered substantial chondroprotection against joint injury in models of collagenase- and surgery-induced arthritis.	
Dendrimers	Fluorinated polyamidoamine dendrimer-mediated	Here, miR-23b is delivered *via* a fluorinated polyamidoamine dendrimer (FP) to suppress inflammation by inducing apoptosis in macrophages and preventing their inflammatory response. In experimental RA models, FP/miR-23b NPs are injected IV. The NPs exhibit therapeutic effectiveness with decreased bone and cartilage attrition, decreased inflammatory response, suppressed synoviocyte infiltration, and restored mobility.	[248,249]
	PAMAM dendrimers functionalized with an anti-TNF α antibody	The objective of this study was to create poly(amidoamine) dendrimers (PAMAM) that have anti-inflammatory effects by being coated with anti-TNF-α antibodies (Abs) and functionalized with chondroitin sulfate (CS). The effective production of anti-TNFα Abs-CS/PAMAM dendrimer NPs was confirmed by physicochemical characterization. According to the *in vitro* research, CS/PAMAM dendrimer NPs showed excellent cytocompatibility and hemocompatibility and had no effect on the metabolic activity and proliferation of the ATDC5 and THP-1 cell lines. In addition, anti-TNF-α Abs-CS/PAMAM dendrimer NPs demonstrated appropriate TNF α capture capability, which makes them attractive for novel immunotherapies in patients with RA.	
Hydrogel	Injectable nanocomposite hydrogels composed of polygallate-Mn (PGA-Mn) NPs, oxidized sodium alginate, and gelatin.	The therapeutic potential of injecting nanocomposite hydrogels into rat knee joints using an OA model has been established *via in vivo* research. These experiments have successfully reduced the production of osteophytes and protected the cartilage from wear and tear.	[250–252]
	Piezoelectric hydrogel	Introducing an injectable, biodegradable piezoelectric hydrogel that promotes cartilage repair by the self-production of localized electrical cues upon ultrasonic activation. The hydrogel is composed of short electrospun poly-L-lactic acid nanofibers contained inside a collagen matrix.	
	Hymovis™ versus placebo in knee OA (Hymovis); Non-crosslinked HA Alkylamide (Hymovis)	WOMAC pain sub-score (NCT01372475, phase III completed)	
	IA polyacrylamide hydrogel in knee OA (Polyacrylamide hydrogel with silver ions "Argiform")	Change of the total WOMAC score (WOMAC-T) in grade II-III OA patients (NCT03897686)	
	PAAG-OA treatment for knee OA (IDA) (Polyacrylamide hydrogel)	WOMAC pain sub-score (NCT04179552)	
	Aquamid reconstruction for OA of the knee (Polyacrylamide hydrogel (Aquamid))	Change from baseline in the pain sub-score of the WOMAC (NCT03067090)	

(*continued on next page*)

Table 6 (*continued*)

Types of Formulation	Active pharmaceutical ingredients	Results	References
	EUFLEXXA® is a hyaluronate hydrogel produced from bacteria	To identify imaging markers for characterizing the biochemical profiles in synovial fluid and cartilage in knee OA 3 months after HA injection (NCT01895959, phase IV completed).	
pH-responsive nanoparticles	Cartilage-targeting and dual MMP-13/pH responsive theranostic nanoprobes	Investigators developed a new kind of cartilage-targeting and MMP-13/pH-responsive ferritin nanocages called CMFn, which are biocompatible and sensitive to changes in pH and MMP-13. These nanocages are loaded with an anti-inflammatory Hydroxychloroquine (HCQ), resulting in a formulation called CMFn@HCQ. This formulation is intended for both imaging and treatment of OA. Authors discovered that CMFn may be selectively activated to produce light for optical imaging in response to the overexpression of MMP-13 in the microenvironment of osteoarthritis (OA), which correlates with the severity of OA.	[237]

Abbreviations: OA, osteoarthritis; IA-injection, intra-articular-injection; GAGs, Glycosaminoglycans; ECM, extracellular matrix; NPs, nanoparticles; TNF α, tumor necrosis factor-α; RA, rheumatoid arthritis; IV, intravenous; WOMAC, Western Ontario and McMaster Universities Arthritis Index; HA, hyaluronic acid.

macrophages, FLS, microvasculature endothelium (MVE), and angiogenesis, all of which are overly expressed inside an inflamed joint. In another instance, a peptide dendrimer nanogel (PDN) with a positive charge was synthesized. The PDN was composed of cross-linked polyhedral oligomeric silsesquioxane core-based generation 3 poly (l-lysine) dendrimers. The purpose of the PDN was to specifically target macrophages. This was achieved by physically encapsulating carbon monoxide releasing molecules within the nanogel and modifying its surface with folic acid-modified HA [190]. In addition, the researchers made modifications to a zeolitic imidazolate framework (ZIF)-8, which is geared towards macrophages and sensitive to changes in pH. These modifications included the addition of an anti-CD16/32 antibody. Because of these modifications, the ZIF-8 exhibited longer retention inside synovial macrophages and intra-joint spaces [191]. Recent investigation elucidated the methodology and production of dextran sulfate-triamcinolone acetonide conjugate NPs, which exhibit potential for treating OA *via* targeted interaction with scavenger receptor class A on activated macrophages [192]. The successful implementation of this approach led to a notable reduction in cartilage degradation over a period of 3 weeks. Notably, a study conducted by investigators, aimed to enhance the production of cyclic adenosine monophosphate to prevent or treat OA. This was achieved by the surface modification of polylactic

Table 7
Treatment strategies as per the stage of osteoarthritis.

S. No	Stages of OA	Characteristics	Current treatment strategies	Proposed treatment strategies	Advantages and drawbacks	References
1.	Stage 1: Minor (Grade 1, doubtful)	Minor wear-and-tear in the joints, with little to no pain. Often identified through X-rays	Symptoms are generally manageable with over-the-counter medications like NSAIDs. Medicine usually prescribed at this stage are acetaminophen, capsaicin, IA glucocorticoid shots, and tramadol.	If the case is diagnosed at this stage in clinic, from here on itself, techniques to safeguard the cartilage deterioration, such as application of chondrogenic agents, and BMP2 blocker should be employed. At this stages, nanoparticulate drug delivery formulation could be employed for addressing drug delivery related issues in joints	NSAIDs relives patients from pain, and discomfort. Still use of NSAIDs has propensity for gastrointestinal, cardiovascular, and nephrotoxic adverse effects. It is recommended that regenerative approaches should be initiated from stage 1, so that circumstances leading to joint replacement surgery could be postponed as much as possible	[298]
2.	Stage 2: Mild (grade 2, minimal)	More noticeable bone spurs, possible joint pain after a long day of walking or running, and greater stiffness after periods of inactivity.				
3.	Stage 3: Moderate (Grade 3)	More frequent pain and discomfort during daily activities, such as walking, running, bending, or kneeling. Stiffness, swelling, and noticeable joint damage may also occur. X-rays at this stage reveal significant cartilage loss, and the space between the bones will narrow. The patient might experience increased pain and swelling in the affected joints.	Management may include physical therapy, medications (such as NSAIDs), and lifestyle changes like weight management and low-impact exercise. Recently evolved techniques also suggests bone marrow stimulation and IA injection of triamcinolone and HA could improve the treatment outcomes at this stage.	At this stage multiple strategies like safeguarding the additional cartilage deterioration, and techniques such as micro fracture, stem cells therapy, BMSCs laden-scaffold and/or BMSCs incorporated cartilaginous organoids could be employed		[299]
4.	Stage 4: Severe (Grade 4)	Severe pain, significant discomfort during daily activities, and possible disability. There is often a substantial decrease in the quality of life. X-rays at this stage demonstrates significant cartilage loss, large bone spurs, and very narrow or non-existent joint space. The bones may be in direct contact, causing significant pain.	In addition to the treatments for moderate OA, surgical options such as joint replacement and/or knee resurfacing may be considered.	Metallic materials and composites, and bioceramics could be employed for increasing success rate and long-term solution. In addition, application of technologies such as treating with the stromal vascular fraction with and without platelet-rich plasma (PRP) could be a regenerative treatment.		[300]

Abbreviations: OA, osteoarthritis; NSAIDs, nonsteroidal anti-inflammatory drugs; IA, intra-articular; BMP2, bone morphogenetic protein 2; BMSCs, bone marrow stromal cells; HA, hyaluronic acid.

acid (PLA)–polyethylene glycol (PEG) NPs with adenosine. The modified NPs were designed to target both macrophages and chondrocytes, and their anti-inflammatory effects were evaluated *in vitro* and *in vivo* [193]. The peptide SFHQFARATLAS, also known as HAP-1, has been previously used to specifically target FLS cells [194]. According to recent research, it was discovered that HAP-1-modified microgels, which include PLGA NPs, exhibited *in vitro* binding capabilities to both rat and human synoviocytes. Moreover, these microgels were shown to remain localized within the synovial membrane and joint space of rats for a duration of 3 weeks, without inducing any degenerative activity [195]. In another instance, the delivery of methotrexate using peptide-NP encapsulation resulted in the preferential homing of the peptide sequence CKSTHDRLC to the synovial MVE [196]. This homing effect was present over a period of 7 days after IV treatment and was observed to effectively diminish arthritic activity in rats. Further, researchers used CKPFDRALC, a peptide that targets MVE, to coat liposomes encapsulating Dex [197]. The application of this peptide successfully inhibited the progression of arthritis in rats over a period of 3 weeks. Hence, the use of hybrid systems, characterized by their intelligence, environmental sensitivity, and synovium-targeting capabilities, has promise in extending the duration of drug residence inside joints. This, in turn, enables regulated release of drugs and enhances their long-term therapeutic effectiveness. However, it is important to note that these delivery technologies need thorough formulation procedures, which may impose limitations on their practical applicability. Moreover, due to their inability to penetrate the deep regions of cartilage where most target sites are located, the efficacy of these carriers is restricted to pain management and inflammation treatment [198].

10.2. Intra-cartilage drug delivery and challenges to be overcomed

Several approaches are being explored to improve drug delivery to cartilage, particularly in the context of treating conditions such as OA [199]. AC has a complex structure and thick ECM, making drug administration challenging since even nm-scale medications cannot penetrate its deep depths [4,200]. Further, aggrecans consist of numerous GAG side chains that are highly sulfated, giving the tissue a high anionic fixed charge density. This characteristic allows for hydration, swelling pressures, and the stiffness required for compression [20, 200]. When joints bear weight, the increased electrostatic repulsion between anionic charged groups within the cartilage helps resist deformation, allowing the tissue to rebound by re-swelling and re-forming [20]. While these anionic aggrecans are crucial for tissue function, they pose a challenge for medication to penetrate and distribute within the cartilage [20,200–202]. Although these negatively charged aggrecans are necessary for tissue function, they make drug penetration and distribution into cartilage extremely difficult; although, pharmaceuticals and drug carriers must reach the tissue deep zones because they contain most cells and matrix target locations [201,202]. Targeted and sustained release of therapeutic medicines with minimal systemic adverse effects is the aim of intra-cartilage drug delivery. This area of study is still being investigated, and developments in materials science, nanotechnology, and biotechnology are helping to provide more accurate and efficient medication delivery methods for diseases affecting the cartilage.

10.3. Recently developed nanoparticles to treat osteoarthritis

Advancements in nanotechnology have led to the development of NPs specifically designed for OA treatment. The NPs serve the functions of augmenting medicine delivery, reducing inflammation, and promoting cartilage regeneration. This section will provide a comprehensive analysis of the progress made in improving the therapeutic efficacy of currently available powerful OA medicines [203–205].

I. Liposomes

Liposomes are lipid bilayer structures with the capacity to encapsulate drugs and deliver them to specific sites inside the body [206,207]. They have the capability to encapsulate anti-inflammatory medicines, DMOADs, or other therapeutic agents and deliver them directly to the affected joint [208]. This very precise delivery system allows the medication to specifically target the area of inflammation or cartilage degradation, resulting in a decrease in overall negative side effects and an improvement in therapy efficacy [209] (Tables 6 and 7). Developing liposomes with controlled release properties can lead to a sustained therapeutic effect. This is particularly advantageous in the context of OA, since it typically necessitates continuous management of symptoms for an extended duration. In addition, liposomes possess biocompatibility, enabling them to bypass the immune system and thus decreasing the probability of adverse responses [210]. Furthermore, their surface can be altered and/or modified using ligands or antibodies to improve their targeting abilities [211]. Notably, novel drugs that change the way on how OA progress, like glucosamine, chondroitin sulfate, or newer compounds that stop cartilage from breaking down, can be carried by liposomes [212]. Nevertheless, targeted and extended release of drugs may improve their effectiveness in preserving joint function and reducing pain. Liposomes have the potential to convey genetic material, such as siRNA or plasmid DNA, to certain cells in the joint [213]. This strategy has the ability to control the activity of genes that are responsible for causing inflammation and breaking down cartilage. This offers a novel approach to altering the trajectory of illnesses at the molecular level.

II. Polymeric nanoparticles

Polymeric NPs (PNPs) are becoming more popular as a good way to treat OA because they can deliver healing substances directly to the affected joints in a precise and long-lasting way [209]. These polymers have the ability to enclose many types of pharmaceuticals, including anti-inflammatory drugs, growth factors, and gene therapy vectors [214, 215] (Tables 6 and 7) PNPs have the capability to transport anti-inflammatory medications, such as NSAIDs or corticosteroids, directly to the specific location of inflammation in the joint [216]. This targeted delivery helps alleviate pain and reduce swelling. Notably, PNPs have been reported to regulate the immune response, decreasing the autoimmune aspects of OA and safeguarding cartilage from further harm [217–219]. PLGA is a frequently used polymer for drug administration because of its exceptional biocompatibility and ability to break down naturally [220]. Research has shown that PLGA NPs can efficiently transport anti-inflammatory drugs and growth factors to the joint, resulting in a reduction of inflammation and stimulation of cartilage restoration [217]. In addition, investigators have widely used chitosan, a naturally occurring polymer from chitin, to produce NPs for drug and gene delivery [221]. These NPs possess both medicinal and diagnostic capabilities, making them multifunctional. Overall PNPs have the potential to greatly enhance the management of OA and improve the quality of life for patients by overcoming the constraints of existing therapies and delivering therapeutic substances in a sustained and targeted manner.

III. Inorganic nanoparticles

Due to their unique properties, such as a large surface area, changeable surface chemistry, and the ability to interact only with biological molecules, inorganic NPs have shown promise for treating OA [222]. NPs composed of materials such as gold, silver, silica, and metal oxides have many benefits in terms of delivering therapeutic drugs directly to damaged joints and regulating disease processes [223–225] (Tables 6 and 7). This delivery system can facilitate the regeneration of injured cartilage by administering growth factors or genes that stimulate cartilage repair. Certain NPs have inherent properties that protect against cartilage deterioration. Oxidative stress plays a crucial role in

the development of OA. Cerium oxide NPs have the ability to remove reactive oxygen species, thereby decreasing oxidative harm to joint tissues [226]. Silver NPs have antibacterial properties that may effectively prevent or cure joint infections, thereby improving OA symptoms [227]. In summary, the ability of inorganic NPs to deliver therapeutic agents in a targeted, controlled, and multifunctional way makes them a very promising way to treat OA.

IV. Dendrimers

Dendrimers are highly branching, arborescent polymers that have gotten a lot of attention in the field of drug delivery because of the unique ways they are structured and how they work [228]. Dendrimers consist of a central core, numerous branching layers, and a multitude of functional groups on their surface (Tables 6 and 7). This architecture offers a high level of surface functionality and interior voids for drug encapsulation [228]. Dendrimers have constant and predictable pharmacokinetics due to their homogenous size and shape, enabling reliable drug administration [229]. In addition, dendrimers surface groups can be altered to enhance their solubility, biocompatibility, and target selectivity [230]. Moreover, they have the capability to be modified with ligands or antibodies that selectively bind to certain cells or receptors in the joint [231]. This modification leads to an increased concentration of the medicine at the site of inflammation or cartilage destruction. Furthermore, dendrimers can carry growth factors or gene therapy vectors that aid cartilage repair and rejuvenation, potentially stopping the degenerative processes that occur in OA [152,232]. Investigators can design dendrimers to modulate the immune response, thereby reducing autoimmune processes that cause cartilage degradation in OA [233]. Previous reports has shown that dendrimers may efficiently transport anti-inflammatory drugs directly to the inflamed joints, resulting in a reduction in pain and swelling in models of OA [234]. Overall, research in this domain of nanoparticulate drug delivery holds promise for potentially curing OA.

V. Hydrogel-based nanoparticles

Researchers are investigating hydrogel NPs as a potential therapy for OA due to their unique properties, which include a high-water content, the capacity to directly encase and transport therapeutic chemicals to injured joints, and the ability to interact with living things [12] (Tables 6 and 7). These compounds are excellent delivery vehicles for osteoarthritic joints because of their high-water content, which makes their appearance similar to that of cartilage. They often use materials that are highly compatible with the human body to reduce the risk of toxicities. Engineers can also design the former to deliver therapeutic medications in a controlled manner, a crucial feature for treating long-term diseases such as OA [235].

Notably, by genetically modifying them to specifically target specific tissues or cells, we can enhance the effectiveness of the therapy and minimize the occurrence of adverse effects throughout the body. Scientists are investigating several substances for hydrogel NPs, such as natural polymers like chitosan and synthetic polymers like PEG. On the other hand, advances in encapsulating methods are improving the stability and release characteristics of drugs incorporated into hydrogel NPs [236]. Furthermore, efforts are underway to improve the targeting abilities of hydrogel-based NPs by anchoring ligands that can attach to particular cell receptors in the joint. Several hydrogel nanoparticle formulations are now moving forward through preclinical studies and early-phase clinical trials, showing promise for improving joint health and easing the pain of OA.

VI. pH-responsive nanoparticles to treat osteoarthritis

NPs that respond to pH changes have significant promise for OA treatment because they can selectively target specific regions inside joints that exhibit varying pH levels [237]. Engineers and formulation scientists can fabricate NPs sensitive to pH changes to detect the acidic conditions commonly observed in OA-affected inflammatory joints [238] (Table 6). They can adjust their activities or discharge drugs in response to the pH changes, ensuring precise administration to the affected region. Notably, the acidic pH of OA joints can make them release the drugs right where the inflammation is happening [239]. This targeted-drug distribution reduces the occurrence of general adverse effects and improves the treatment's efficacy. Ongoing research is now prioritizing the enhancement of the design of pH-responsive NPs for OA treatment. This includes efforts to improve the efficiency of drug loading, stability, and to ensure a controlled and prolonged release of the medication, resulting in extended therapeutic benefits. Although there is potential, there are still ongoing research efforts to address problems in creating pH-responsive NPs for OA therapy. These issues include maintaining stability under physiological circumstances, optimizing the release of drugs over time, and scaling up production. Overall, pH-responsive NPs shows enormous promise for delivering drugs specifically to the affected areas of OA. This technique has the advantage of improving the therapy's effectiveness while minimizing any negative effects that are often associated with traditional therapies.

10.4. Ideal characteristics of nanoformulation for effective joint and cartilage delivery

Nanotechnology is being considered for application in OA therapy with the hopes of resolving issues with focused medication administration, extended therapeutic results, and decreased side effects. NPs, micelles, or liposomes are tiny carriers that may encapsulate the poorly soluble and permeable drugs and enhances its absorption to the site of action [253–255]. This method improves the stability of the drug, allows for regulated release, and shields it against degradation. Moreover, the targeted delivery of medications to the injured joint, with less systemic exposure and fewer adverse effects, is possible with the use of NPs engineered for IA-injection. In addition, to alleviate inflammation in the joint, NPs laden with anti-inflammatory drugs like corticosteroids or NSAIDs can be used. Although nanomedicine has immense promise as a therapy for OA, it is important to remember that studies in this area are still in their early stages and that clinical translation need thorough testing to ensure safety and effectiveness. The potential for creating more precise and efficient treatments for OA is always growing because of advancements in nanotechnology [10]. This section will elaborate on the prerequisites of NPs for effective joint delivery.

I. Particle Size

The regulation of DDSs permeability is significantly influenced by particle size, making it a vital component in this context. To improve the permeability of delivery system, it is necessary to modify the particle size of the drug within an acceptable range. The cartilage hierarchical pore system was investigated by DiDomenico et al. focusing on the range of gaps between GAG chains (4–6 nm) and collagen fibers (50–100 nm). The study examined the relationship between diffusion rate and particle radius across the range of 0.1–16 nm, revealing an inverse association [14,256]. Moreover, it should be noted that the diffusivity of solutes in cartilage is significantly affected by their size, particularly in terms of volume diffusivity and partition coefficient. However, it is important to acknowledge that not all solutes, especially those of larger size, exhibit consistent diffusivity throughout the cartilage [13,257,258]. Based on the findings of Bajpayee et al. it was shown that solutes with hydrodynamic diameters below 10 nm were able to permeate the whole layer of bovine cartilage explant. Conversely, particles with diameters of 15 nm were unable to penetrate beyond the surface due to the presence of a spatial barrier. In another study, it has been shown that a peptide with a 7 nm demonstrates effective penetration into the ECM, suggesting its potential use as a carrier for drug delivery purposes [259]. Another

investigation demonstrated that within 24 h, dextran measuring 4.3 nm managed to permeate the entire layer of healthy bovine cartilage. However, dextran measuring 10 nm could only penetrate halfway through the tissue's thickness over a period of four days [259]. The effective pore size of the ECM may undergo an increase during OA due to the deterioration of cartilage. This increase in pore size allows for the penetration of larger particle sizes into the cartilage tissue. Hence, the effective pore size exhibits variation in accordance with the severity of OA. Further, the literature provides evidence that NPs within the size range of 100–300 nm exhibit a preference for infiltration into osteoarthritic cartilage, while showing limited entry into healthy cartilage [260]. Bajpayee et al. conducted a study comparing the penetration depth of positively charged quantum dots (QD) with amino-modified neutral QD in both normal and OA cartilage. According to *in vitro* investigations, it was shown that after a duration of 24 h, 15 nm QDs exhibited surface entrapment on healthy cartilage, whereas they were able to penetrate deeper into OA cartilage. This research used trypsin-treated cow cartilage as an *in vitro* model for OA cartilage. The tissue retained around 40 % GAG content. Notably, it was shown that under pathological circumstances, the absence of GAGs allowed the entry of sizable particles that would otherwise be unable to permeate the cartilage [259]. In conclusion, a reduction in particle size leads to an enhancement in the penetration of drugs into the AC. The depth of particle penetration into the ECM is influenced by many factors, including particle size, direction of penetration, and cartilage composition. Since OA may result in different levels of cartilage deterioration, it is more probable for drug delivery vehicles to infiltrate the ECM. Hence, particles of diverse sizes may be used to more efficiently penetrate OA cartilage compared to healthy cartilage. In the future, it will be necessary to design DDSs with particle sizes that align with the various stages of OA progression. This is crucial to achieve extended release of medicine and enhance the drug permeability.

II. Surface Charge

The ECM is a complex network of proteins and carbohydrates that provides structural and biochemical support to cells within tissues. The surface charge of the ECM can play a role in various cellular processes, including cell adhesion, migration, and signaling. Additionally, the surface charge of the ECM can influence the targeted delivery of drugs and therapeutic agents. The ECM components, such as proteoglycans and glycoproteins, often carry charges due to the presence of negatively charged sulfate or carboxyl groups. These charges contribute to the overall electrostatic properties of the ECM. The electrostatic interactions between the charged components of the ECM and cell surface receptors can influence cell behaviour and function. The aggregation of proteoglycan GAGs and the polymerization of collagen are primarily responsible for the negative charge of ECM. This high negative charge of ECM has implications for the penetration of drug carriers since surface charges play a role in this process. Hence, drug vehicles with a cationic surface charge have the potential to effectively penetrate AC cells. In their investigation, Bajpayee et al. conducted a study on the permeability of 7 nm avidin and neutral avidin inside isolated bovine cartilage. The researchers noticed that, during a 24-h period, avidin was able to permeate the whole thickness of the cartilage, whereas neutral avidin was only able to reach the surface [14,259]. Furthermore, it is important to acknowledge that the magnitude of the surface charge has the potential to impact the permeability of drug carriers. While an increase in cationic surface charge might enhance the uptake of drug carriers; although, it is important to note that a higher surface charge does not always correlate with increased permeability. Overcharging the drug carrier may cause the drug carrier and the ECM to interact for a longer period, which would prevent further penetration of drug. The study conducted by Vedadghavami et al. used positively charged polypeptide modified NPs to investigate the influence of surface charge on macromolecule uptake in alternating current systems [200]. The researchers concluded that a surface charge of +14 exhibited the highest level of permeability. An irreversible connection between the cationic polypeptide and the ECM was seen when the surface charge exceeded +14, leading to a restricted permeability of the polypeptide [14]. The electrostatic binding between the cationic peptide and cartilage components may be further stabilized by short-range hydrogen bonds and hydrophobic interactions. The study demonstrated that arginine-rich cationic peptides exhibit stronger binding affinity towards anionic aggrecan and GAGs in cartilage compared to lysine-rich cationic peptides. The influence of synovial fluid on articular cavity charge should not be underestimated. Multiple studies have shown that cationic dimethylaminoethyl methacrylate-co-butyl methacrylate NPs experience charge reversal when exposed to synovial fluid, resulting in a decrease in their ability to penetrate tissues [261].

III. Biocompatibility

DDSs that possess favorable biocompatibility can endure the effects of degrading enzymes inside the joint cavity for a prolonged duration. This characteristic allows the DDSs to effectively permeate the cartilage. In their study, Q et al. conducted surface modifications on HA by introducing sulfate groups. This modification was aimed at mitigating the rapid degradation of HA. The results of the following tests indicated that the introduction of sulfate groups did not have any discernible impact on the activity of stem cells [14,262,263]. Further, Das et al. developed a hydrogel formulation that exhibits sustained release properties for white protein and dexamethasone. This hydrogel was designed to facilitate tissue penetration through the incorporation of HA modifiers and gelatin [263]. In addition, like plasma, a phenomenon known as 'protein corona' occurs when proteins are adsorbed onto the surface of DDSs. The size, charge, and surface properties of the delivery vehicles all play a role in regulating the encapsulating "protein corona" of the DDSs. The adsorption of proteins onto drug carriers has the potential to alter their basic characteristics, leading to a modification in the properties of the former. This change in attributes might pose challenges in the clinical translation of DDSs. Simultaneously, the protein crown that is affixed to the structure exhibits biological functionality, and the potential immune reaction poses a concern for the clinical use of this technology [264,265]. In their study, Wang et al. used small interfering RNA (siRNA) in combination with LNP delivery systems to address OA, yielding remarkable results [266]. A recent study done in a preclinical setting showed that LNP formulations may cause inflammation and other undesired effects in mice. This might be because they contain ionizable lipid components [267]. Consequently, to enhance the efficacy of clinical translation, further investigation into the biocompatibility of LNPs is warranted. In conclusion, the use of inert materials or the implementation of surface modification techniques to enhance biocompatibility represents a promising approach for the advancement of DDSs in cartilage. This strategy has potential for mitigating adverse responses and ensuring the overall safety of the DDSs in this context.

10.5. Nano-decoys as futuristic therapy to treat OA

An innovative treatment strategy that shows promise for treating OA is the use of nano-decoys. By using tiny structures to imitate characteristics of cells or biomolecules, the notion of nano-decoys aims to deflect pathogens from target areas and slow down the progression of illness. Targeting inflammatory chemicals, proteases, or other factors that contribute to cartilage degradation and joint inflammation might be the goal of designing nano-decoys in the context of OA. Nano-decoys can be customized for precision or personalized medicinal methods. Moreover, former can be created to specifically target the unique features of an individual patient's OA, such as the main inflammatory pathways implicated, so offering a more individualized therapy approach. In recent years, there has been a lot of buzz about a new therapeutic approach that makes use of micro and NPs to treat various diseases

[268–272]. Notably, particles that are based on cellular membranes have received a lot of attention in this area of research recently [273, 274]. MSCs have been demonstrated to have a substantial impact on the control of inflammatory processes, and so have been examined as a potential approach for the treatment of OA. Nano-ghosts or nano-decoys are a novel kind of NPs made from MSC cytoplasmic membrane (Fig. 8). The capacity of nano-ghost to maintain the surface characteristics of MSCs while lacking the underlying machinery of cells is what gives them their immunomodulatory capabilities and immune-evasive nature. This remarkable combination protects nano-ghosts against host-induced changes. D'Atri et al. employed the *in vitro* and *in vivo* capability of nano-ghosts to target cartilage tissues while also controlling inflammation. The immunomodulatory effects of nano-ghosts were shown *in vivo*, suggesting their potential use in treating cartilage degradation. The nano-ghost system is clearly shown as a viable nano-carrier platform and as a possible immunomodulatory medication for numerous inflammation-related disorders by their findings and previously published data [275]. It's essential to understand that although the idea of nano-decoys is intriguing, there are several obstacles that must be overcome before these concepts can be turned into practical treatments. These include of addressing potential off-target effects, maximizing the pharmacokinetics of nano-decoys, and guaranteeing biocompatibility. Furthermore, before broad clinical use of nano-decoys for OA is explored, extensive preclinical and clinical research is required to confirm their safety and effectiveness.

10.6. Cartilaginous organoids to manage OA

The use of cartilaginous organoids (CORGs) as a possible treatment for OA appears promising. Organoids are three-dimensional objects that resemble organs in both shape and function; and they are created from stem cells or tissue samples. With the explicit goal of mimicking the properties of cartilage tissue, CORGs offer a platform for research into the genesis of cartilage, the causes of diseases, and possible treatments [23,276]. More precisely, CORGs are three-dimensional cellular aggregates that are generated by the differentiation of embryonic stem cells, iPSCs, or adult stem cells. These organoids have the capacity to undergo self-renewal and self-organization, which is facilitated using bioactive materials. CORGs could mimic the shape and some functions of cartilage tissue, and they may be significantly proliferated in huge quantities by *in vitro* cultivation. Various biocompatible materials, including as matrigel and synthetic alternative hydrogels, are often used to facilitate the construction of tissue-engineered constructs known as CORGs. Former, being a novel model, exhibit considerable promise as proficient biological models for tissue formation, disease investigation, and pharmaceutical testing platforms aimed at evaluating the efficacy of OA drugs [23,276]. In addition to callus organoids, CORGs are also used for the recruitment of osteogenic precursors to facilitate bone healing and the development of AC grafts. Although organoid technology has shown amazing advancements in liver and kidney research [23,277,278], there is a notable absence of study and use of organoid culture in the skeletal system, particularly in relation to cartilage tissues. The process of creating cartilage organoids involves two primary phases, as seen in Fig. 9. The first step is the identification of appropriate sources of chondrocytes, which may be obtained from the body's own cartilage tissue or derived from autologous or allogeneic stem cells. During the second stage, it is important to verify the appropriate conditions for the development of organoids. Biomaterials have the potential to serve as a suitable matrix for facilitating the development and differentiation of cellularized organoid structure. The typical cultural environment used for cartilage organoids typically comprises of matrigel and cartilage organoid medium. The formulation of the culture medium plays a crucial role in influencing the growth and differentiation of CORGs. Conversely, the presence of matrigel is not an obligatory element for the development of cartilaginous organs. In recent literature, there is an increasing focus on the development of alternative organoid culture techniques that do not rely on matrigel, instead emphasizing the use of ECM derived from decellularized tissues. Presently documented chondrocyte-derived organoids have demonstrated the capacity to substitute natural cartilage in certain capacities, including the expression of cartilage-specific molecular biology, emulation of cartilage formation processes, and remediation of cartilage or bone defects.

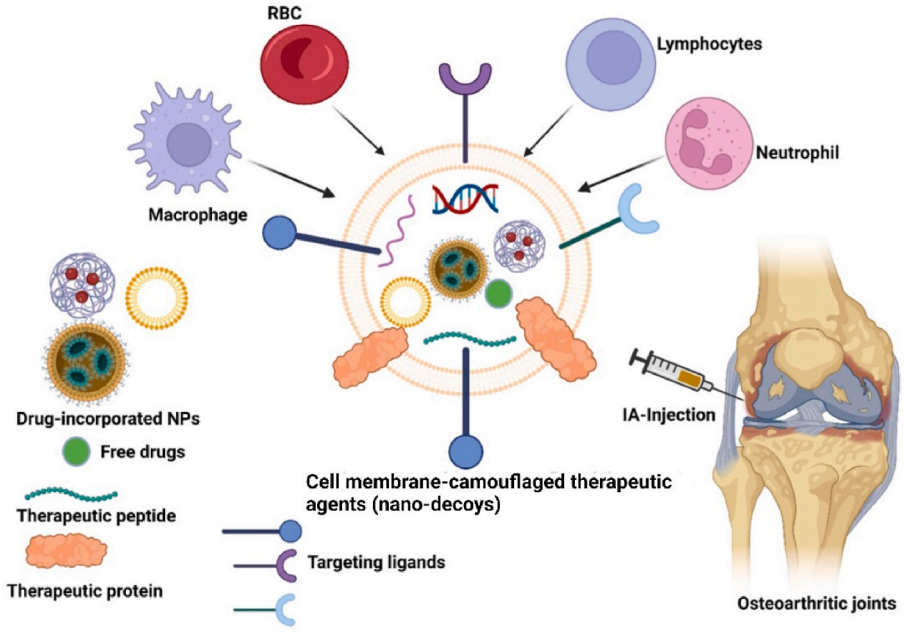

Fig. 8. Red blood cell (RBC) or white blood cell (WBC)-derived membrane (Nano-decoys)-based strategy to delivery therapeutic agents like anti-osteoarthritic drug, drug-incorporated nanoparticles (NPs), DNA or RNA, therapeutic protein, and peptides to the joints. The therapeutics agents are camouflaged with RBCs or WBCs membranes and various targeting ligands are anchored in the outer membrane of decoys for effective drug targeting. **Abbreviations**: NP, nanoparticle; IA-injection, intra-articular-injection. Figure created with BioRender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

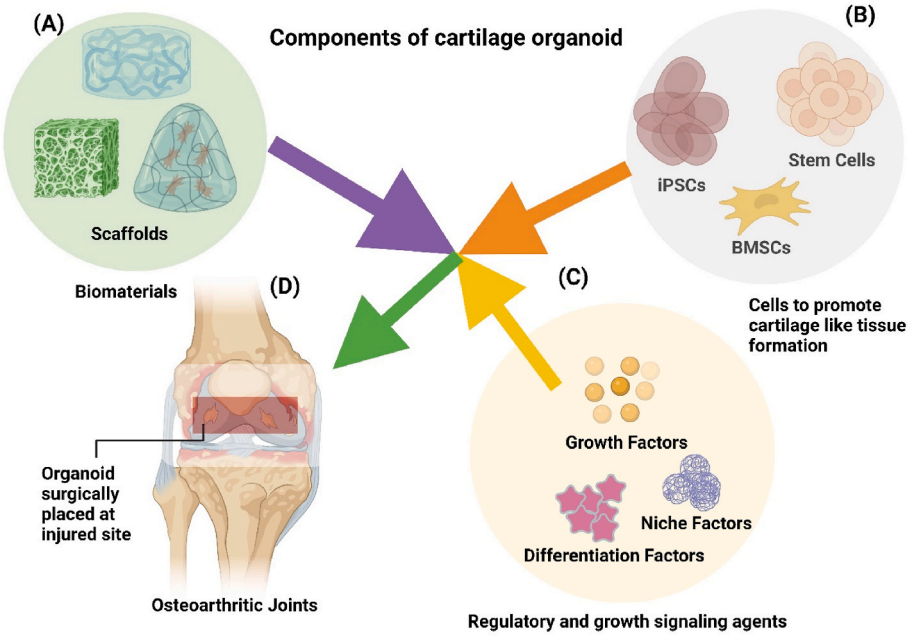

Fig. 9. Different components of cartilaginous organoid are illustrated in figure. (**A**), various biomaterial-based scaffolds as a platform to administer various therapeutic agents including (**B**) genetically modified cells for cartilage regeneration and (**C**) growth, niche, and differentiation factors to promote chondrocytes proliferations (**D**), surgically placing the fabricated or customized scaffold into the defect site**. Abbreviations**: BMSCs, bone marrow stem cells; iPSCs, Induced Pluripotent Stem Cells. Figure modified with permission from Yu et al. [23]. Figure created with BioRender.com.

However, achieving all the functionalities of natural cartilage within an integrated CORG remains unfeasible, and researchers encounter challenges in precisely regulating each stage of stem cell differentiation towards cartilage. In the foreseeable future, as biomaterials continue to advance and organoid technologies further improve, CORGs are poised to undergo a transformative era of dynamic growth [23,276]. Even though cartilaginous organoids are still in their infancy, current research indicates that they may one day be used to treat OA. But before they can be widely used in therapeutic settings, issues like attaining the structural complexity of natural cartilage and maximizing the scalability of organoid manufacture must be resolved. Therefore, to fully utilize cartilaginous organoids in the setting of OA, it is imperative to include developments in stem cell technologies, biomaterials, and tissue engineering combined [23,276].

10.7. Bioceramics to manage OA

Researchers are extensively improvising and using bioceramics for OA management because of their compatibility with living tissues, ability to stimulate biological responses, and capacity to facilitate bone growth and healing [279] (Table 7). Hydroxyapatite is a naturally occurring mineral that exists in the form of calcium apatite, and is widely used as a components to fabricate bioceramics [280]. Similarly, bone transplants and implants often use calcium hydroxyapatite, the primary mineral constituent of bone and teeth [281]. Tricalcium phosphate, for example, is a material that the body may absorb and gradually replace with natural bone, making up calcium phosphate ceramics [282]. Notably, bioactive glasses are recognized for their capacity to adhere to bones and promote osteogenesis [199]. Zirconia and alumina are used in joint replacements because of their exceptional strength and resistance to wear [283]. Certain bioceramics possess the ability to induce the specialization of precursor cells into osteoblasts, thereby facilitating the generation of new bone tissue. Bioactive bioceramics have the ability to establish a connection with bone and the tissues surrounding it, thereby improving implant integration [284]. Furthermore, biomedical engineers are conducting ongoing research to explore the potential of bioceramics in facilitating cartilage regeneration, a critical aspect of treating OA. Complete hip and knee replacements frequently uses bioceramics due to their robustness and ability to integrate well with bone tissue. Moreover, they rectify bone deficiencies and facilitate bone regeneration in compromised joints [285]. To additionally improve its efficacy, engineers and formulation scientists might use bioceramic scaffolds in conjunction with cells and growth factors and/or drug-incorporated NPs to regenerate new cartilage and bone tissue, effectively. Ongoing research aims to improve the composition, structure, and application techniques of bioceramics in order to boost their effectiveness in treating OA.

10.8. Metallic materials, and composites

Metallic materials and composites are essential in the management of OA, especially in joint replacement therapies and regenerative treatments. Titanium and titanium alloys are often used in the fabrication of joint replacements, including hip and knee implants [286] (Table 7). Biocompatibility, resistance to corrosion, and exceptional mechanical qualities of these materials makes them a better choice for application in joint replacement. On the other hand, polymer-metal composites are used in load-bearing implants and prostheses [287]. This technology integrates the robustness and rigidity of metals with the adaptability and reduced mass of plastics. In addition, they can be engineered to replicate the inherent characteristics of bone. Notably, polyethylene that has been strengthened with carbon fibers are often used in the manufacturing of joint replacement bearings [288]. Moreover, polymer-ceramic composites are used in the medical field for bone grafts and as coatings for metal implants [289] due to their improved ability to support bone growth, compatibility with living tissue, and superior physical characteristics. Similarly, hydroxyapatite coatings on titanium implants facilitate bone development and integration [290]. Next, carbon fiber composites are being increasingly utilized in a variety of orthopedic applications. This material has a high ratio of strength to weight, it is resistant to fatigue, and it is transparent to X-rays [291,292]. Notably, carbon fiber reinforced polymer are materials that consist of polymers reinforced with carbon fibers and can be used for joint replacement and/or total hip arthroplasty [293]. Total hip arthroplasty

is a surgical procedure that involves the substitution of a dysfunctional hip joint with a prosthetic implant composed of metallic materials such as titanium or cobalt-chromium alloys, as well as polymers like polyethylene [294]. On the other hand, knee resurfacing is a procedure that involves replacing just the damaged parts of the knee joint with metal and polyethylene components, rather than replacing the complete joint [295]. Apart from the application in total hip arthroplasty and joint replacement, polymer-ceramic composites are also used to fabricate scaffolds to facilitate bone regeneration. These components can be manipulated to enhance the process of cell attachment, proliferation, and differentiation, hence assisting in the restoration of osteoarthritic bone [296]. Overall, biodegradable composites are now under investigation for their possible use in cartilage repair. These composites include the combination of polymers, such as PLA, with bioceramics to form scaffolds that facilitate the regeneration of cartilage [297].

11. Conclusion

According to recent research, it is projected that over 1 billion individuals will be afflicted with OA by the year 2050. At present, it is observed that a proportion of 15 % of those who are 30 years of age or older suffer from OA. The study, which was recently published in The Lancet Rheumatology, examines a three-decade span of OA data (1990–2020), including over 200 nations [301]. The present investigation reveals a notable escalation in the incidence of cases during the preceding three decades, primarily attributed to three key determinants: the process of aging, population expansion, and the prevalence of obesity. According to available data, the prevalence of OA was estimated at 256 million individuals in 1990. By the year 2020, the figure had seen a considerable surge, reaching a total of 595 million individuals. This marked a substantial growth of 132 % in comparison to the figures recorded in 1990. According to projections, it is anticipated that by the year 2050, this figure will approach the threshold of 1 billion. At present, there is a lack of therapeutic interventions capable of mitigating the process of cartilage stiffening and its subsequent detrimental effects. Various therapeutic approaches, including exercise, weight reduction, physical therapy, pharmacological agents, and joint arthroplasty, are implemented with the objective of mitigating discomfort and enhancing functional mobility. The variables are particularly relevant in the context of knee OA since the degeneration of cartilage is not attributed to a single event, and the most significant factor for predicting susceptibility is the process of aging. However, the pipeline for drugs to treat OA has not been deficient. Recent studies have investigated the potential of lorecivivint (SM04690, Biosplice) and TPX-100 (OrthoTrophix), a 23-amino acid peptide that can be delivered through IA injections, along with other interventions, in modulating the Wnt pathway. Nevertheless, several studies have lately shown favorable or encouraging outcomes; an equal, if not greater, number of such trials have traditionally resulted in disappointing impasses. However, strong rules say that new and experimental methods like transcutaneous electric nerve stimulation, chondroitin, platelet-rich plasma injections, and stem cell injections should not be used. According to the experts in the field, it is recommended that rheumatologists and researchers direct their efforts toward using a multimodal strategy for the management of OA. This entails providing medical care to individuals in accordance with their specific symptoms, requirements, and objectives. It is important to consider this approach, whereby treatment strategies are tailored to the patient's symptoms, impairments, and objectives of care, acceptability, safety, and practicality. Furthermore, it is important to consider that therapeutic interventions may be reassessed and reconsidered at various stages along an individual's OA trajectory. Altogether, highly sophisticated nanoparticulate drug delivery strategies modulated as per the insights of the molecular alterations occurring during OA could yield more favorable results soon.

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Bhupendra Kumar: Writing – original draft, Conceptualization. **Laxmi Akhileshwar Jha:** Writing – review & editing, Writing – original draft, Software, Conceptualization. **Prashant Pandey:** Writing – review & editing, Writing – original draft. **Sayeda Fauzia Iqbal:** Writing – review & editing. **Saahiba Thaleshwari:** Writing – original draft. **Kaushani Banerjee:** Writing – review & editing. **Mohammad Imran:** Writing – review & editing, Software. **Shoaib Anwaar:** Software. **Laxman Subedi:** Writing – review & editing. **Vishal Dubey:** Writing – review & editing. **Yousuf Mohammed:** Writing – review & editing. **Nisha Panth:** Writing – review & editing. **Philip M. Hansbro:** Writing – review & editing. **Keshav Raj Paudel:** Writing – review & editing, Supervision, Conceptualization. **Saurav Kumar Jha:** Writing – review & editing, Supervision, Software, Conceptualization. **Amitabha Bandyopadhyay:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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