Targeted treatment for osteoarthritis: drugs and delivery system

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**ABSTRACT**

The management of osteoarthritis (OA) is a clinical challenge due to the particular avascular, dense, and occluded tissue structure. Despite numerous clinical reports and animal studies, the pathogenesis and progression of OA are still not fully understood. On the basis of traditional drugs, a large number of new drugs have been continuously developed. Intra-articular (IA) administration for OA hastens the development of targeted drug delivery systems (DDS). OA drugs modification and the synthesis of bio-adaptive carriers contribute to a qualitative leap in the efficacy of IA treatment. Nanoparticles (NPs) are demonstrated credible improvement of drug penetration and retention in OA. Targeted nanomaterial delivery systems show the prominent biocompatibility and drug loading-release ability. This article reviews different drugs and nanomaterial delivery systems for IA treatment of OA, in an attempt to resolve the inconsonance between \textit{in vitro} and \textit{in vivo} release, and explore more interactions between drugs and nanocarriers, so as to open up new horizons for the treatment of OA.

1. **Introduction**

As life expectancy has increased over the past half-century, the prevalence of Osteoarthritis (OA) has been increasing prominently. In Europe, the United States and other developed countries, 10%–15% of adults over 60 years old suffer from OA due to the severity of the aging population, with a significantly higher prevalence rate in older women than older men (Bijlsma et al., 2011; Prieto-Alhambra et al., 2014; Wallace et al., 2017). Substantial evidence indicates that age, as the strongest risk factor for OA, interacts with multiple risk factors throughout the pathological process. Obesity is another non-negligible risk factor for OA, increasing the risk by more than three times (Blagojevic et al., 2010; Silverwood et al., 2015; Reyes et al., 2016). Obesity increases the load on the large joints of lower limbs (hip, knee and ankle) and further affects the biomechanics of the joints. Meanwhile, the increase of adipokines and inflammatory cytokines caused by obesity promotes the development of OA (Kulkarni et al., 2016; Wang & He, 2018; Liu et al., 2019; Misra et al., 2019). Different types of joint injury are an important basis for the pathogenesis of OA. Long-term high-intensity exercise training is one of the susceptibility factors of OA and post-traumatic osteoarthritis (PTOA) is a representative type (Bodkin et al., 2020; Rothrauff et al., 2020). Injuries of the anterior cruciate ligament (ACL) and meniscus are the most common causes of PTOA (Ajuied et al., 2014; Li et al., 2019; Wang et al., 2020). Knee ligament, meniscus, muscle, bone, and tendon injuries or surgery increase the risk of knee arthritis by at least four times (Muthuri et al., 2011; Poulsen et al., 2019). The joint biomechanical abnormalities caused by congenital or acquired joint anatomical dysfunction may lead to the occurrence of OA under the influence of self and environmental factors. Hip dysplasia, varus and valgus, femoracetabular impingement, quadriceps atrophy, lower limbs length inequality will affect the pathological process of OA in varying degrees (Nishida et al., 2017; Wyles et al., 2017; Kim et al., 2018; Lynch et al., 2019; Hernandez et al., 2020; Springer et al., 2020; Xu et al., 2020). Genomic studies of OA patients and their families have revealed new biogenetics insights of OA pathogenesis and multiple gene loci were found relevant to the pathogenesis of OA (Zeggini et al., 2012). Similar to aging, changes in modern lifestyle also affect the incidence of OA. Physical inactivity and changes in dietary structure contribute to obesity and metabolic syndrome which result in abnormal regulation of bone metabolic factors such as dyslipidemia, impaired glucose tolerance and hypertension (Berenbaum et al., 2018) (Figure 1).

2. **Pathogenesis of OA**

OA is the most common degenerative disease of the whole joint, progressively affecting the articular cartilage, synovium, subchondral bone, and periarticular tissues like ligaments, capsule, and periarticular muscles (Glyn-Jones et al., 2015; Martel-Pelletier et al., 2016; Sharma, 2021). The main pathological manifestations are degeneration of articular cartilage, thinning of subchondral bone, osteophyte formation around the joint, meniscal alterations, synovial fluid inflammation,
ligament injury, and joint capsule hypertrophy (Hügle & Geurts, 2017; Roseti et al., 2019). Cardinal symptoms include pain, swelling or even deformity of the joints, stiffness (especially severe and transient morning stiffness), popping or crepitus during joint motion, and mobility disorder (Fu et al., 2018; Bacon et al., 2020; He et al., 2020). Traditionally, OA is regarded as a passive degenerative disease or injury caused by long-term wear and tear. However, new insights suggest that OA is actually an active dynamic process arising from imbalance of joint damage and repair. Initially, erosion begins on the surface of the cartilage and gradually deepens into the calcified cartilage area. During this process, chondrocytes attempt to repair the damage by enhancing proliferation and differentiation, but the accompanying inflammatory response inhibits chondrocyte function. Then the subchondral bone proliferates pathologically and erodes the cartilage layer. The endochondral pathologic enhancement of osteogenesis results in the formation of osteophytes around the joint margins (Figure 2).

3. Management of OA

3.1. Non-pharmaceutical strategies

Almost all guidelines recommend regular and individualized exercise in the different pathological stages of OA. The most common exercise for OA treatment includes aquatic exercise, aerobics, resistant exercises, multimodal and combined exercise (Luan et al., 2019). However, the effect of exercise intensity on the outcome of OA rehabilitation has not been fully elucidated, especially in the acute stage of OA. Inappropriate exercise prescription may aggravate the development of the disease.

Physical therapy (PT) has a prominent therapeutic effect on OA including therapeutic ultrasound, electrical stimulation, phototherapy, hydrotherapy, magnet therapy, cryotherapy and thermotherapy. PT has a significant relief effect on the symptoms of osteoarthritis, including pain, edema, and joint motion disorders, which is suitable for emergency management in the acute phase (de Oliveira Melo et al., 2016; Aciksoz et al., 2017; Rothenberg et al., 2017; Langella et al., 2018). Physical factors are also effective triggers for stimulus-responsive NPs for controllably releasing agents in IA treatment and this will be introduced blew.

OA patients usually require assistive devices to compensate for decreased strength, impaired balance, pain during movement. Common devices include splints, braces, walking canes, functional footwear and other training equipment. Splint shows remarkable improvement of pain relief for base-of-thumb osteoarthritis with time dependence of efficacy (Rannou et al., 2009; Gomes Carreira et al., 2010; Becker et al., 2013). Daily cane use can diminish pain and maintain a normal gait which is crucial for OA patients to preserve joint function and muscle strength in the early stage of rehabilitation (Jones et al., 2012; Moe et al., 2012). Although clinical studies have yielded some positive results, questions remain about the necessity for assistive devices and their long-term safety.

Acupuncture is a non-pharmaceutical treatment of traditional Chinese medicine (TCM). Acupuncture plays a certain role in relieving pain and restoring function for OA treatment. The therapeutic effect of acupuncture may come from the regulation of inflammatory factors (Lin et al., 2020; Shi et al., 2020). However, evidence showed incertitude of acupuncture in treating OA, in particular the obvious difference between electroacupuncture and manual acupuncture (Wang et al., 2020; Tu et al., 2021), and in a small sample study, no difference was observed in the eight-week (three sessions per week) acupuncture intervention (Lin et al., 2018). In addition, non-pharmaceutical strategies include health education,
lifestyle changes such as diet, physical activity, and weight control, and Self-management is an important measure to prevent OA (Figure 3).

### 3.2. Pharmacological management

Considering that many patients with OA are unable to identify independent risk factors for intervention and there is still uncertainty about the efficacy and adaptability of non-pharmacological treatment. Pharmaceutical drugs remain the primary treatment for OA including topical, oral and injectable intervention. First-line drugs include non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, analgesics, capsaicin, and glucocorticoids and show remarkable efficacy in symptom control (Hochberg et al., 2012; Bannuru et al., 2019; Kolasinski et al., 2020). However, both topical and oral drug use have certain limitations in that topical drugs have lower systemic drug levels than oral, but they are limited by drug penetration, retention and high-frequency medication. In addition, long-term use of NSAIDs and cyclooxygenase 2 (COX2) is an inconvenient risk of gastrointestinal and cardiovascular systems (Nissen et al., 2016; Chan et al., 2017; Solomon et al., 2017). With the deepening of research, an increasing number of drugs are being developed for the treatment of OA.

Another class of commonly used drugs is referred to as cartilage protectors including glucosamine and chondroitin sulfate products. Although some studies have shown the anti-inflammatory and analgesic effects of glucosamine and glucosamine in OA treatment, thus alleviating clinical symptoms and delaying disease progression, the effect is only better than that of a placebo, lacking favorable evidence and relevancy (Bruyère et al., 2014; Sharma, 2021). Hyaluronic acid is a high-molecular-weight GAG in synovial fluid and cartilage which is widely used as a viscous supplement to lubricate joints and absorb impact. A large number of meta-analysis results showed that the clinical efficacy and outcome correlation of hyaluronic acid was not explicit, and the new treatment guidelines no longer recommend hyaluronic acid for OA treatment (Rutjes et al., 2012; McAlindon et al., 2014).

### 3.3. Surgical management

Surgical treatment is suitable for severe OA caused by some specific etiological factors like trauma, congenital joint deformity and dysplasia, osteonecrosis. Common techniques include arthroscopic debridement and lavage, cartilage transplantation, meniscus resection and arthroplasty. Arthroscopic debridement shows obvious clinical results in elbow OA, and joint foreign body and impingement are considered potential indications (MacLean et al., 2013; Carlier et al., 2019; French Arthroscopic Society, 2019). Some studies showed that arthroscopic debridement and lavage are also effective in the improvement of symptoms in shoulder, knee and thumb OA (Furia, 2010; Bexkens et al., 2018; Lo Presti et al., 2020). However, some clinical trials and the systematic review showed unsatisfactory results for debridement and lavage procedures that the outcomes after surgery are temporary or no different from placebo procedures (Moseley et al., 2002; Kirkley et al., 2008; Skelley et al., 2015). Although some minimally invasive procedures are well established, surgical treatment is also different degrees of trauma to the joint.

Osteochondral allograft transplantation (OCA) shows dependable improvement of pain, function and symptom scores in chondral lesions. In multiple follow-up studies over 10 to 20 years, OCA shows significant prognostic effects, greatly delayed the time of arthroplasty, and reduced reoperation rate (Frank et al., 2017; Pascual-Garrido et al., 2017; Stone et al., 2017; Ekman et al., 2018; Frank et al., 2018). Nonetheless, OCA shows definitely cost-effective which means the clinical outcomes are largely dependent on the overall cost of the operation, particularly the cost of the graft, which will increase the financial pressure on the patients (Mistry et al., 2019). OCA can help athletes return to
competition, but there is a high probability of reoperation, requiring debridement and removal of the free body (Crawford et al., 2019). In addition, the study found an intractable relationship between the thickness of the graft and the prognosis that thin grafts may result in high risk of subchondral cysts and thicker grafts may delay osseous graft integration after surgery (Ackermann et al., 2019).

4. Targeted nanomaterial drug delivery systems

4.1. DDS targeting the inflammation of synovium and cartilage

Lornoxicam (Lnx) is a thienooxazine derivative NSAIDs of oxicam class with properties of anti-inflammatory, analgesic and joint repair (Berry et al., 1992; Kidd & Frenzel, 1996; Hall et al., 2009). However, due to poor aqueous solubility and upper digestive tract absorption, oral administration and simple interarticular injection have many restrictions, such as gastrointestinal reactions, low absorption rate, and rapid clearance rate (Hamza & Aburahma, 2009). Zhang (Zhang et al., 2012) et al evaluated the biocompatibility, systemic toxicity, retention time and anti-inflammatory effect of Lnx-loaded PLGA microspheres (Lnx-MS) in papain-induced OA rats. Lnx-MS showed remarkable retention time in joint tissue and persistent low level in plasma during 96 hours after injection. Lnx suspensions distribution in plasma peaked in 24 hours and they were cleared within 24 hours in joint tissue. Lnx-MS was verified to be biodegradable and safe to proliferate and differentiate chondrocytes. Pharmacodynamics showed a reduction in joint swelling and proteoglycan loss. Researchers used chitosan/tripolyphosphate MS carrying Lnx to intervene monosodium iodoacetic acid (MIA) induced OA rats. Lnx-MS showed remarkable retention time in joint tissue and persistent low level in plasma during 96 hours after injection. However, due to poor aqueous solubility and upper digestive tract absorption, oral administration and simple interarticular injection have many restrictions, such as gastrointestinal reactions, low absorption rate, and rapid clearance rate (Hamza & Aburahma, 2009). These results suggest the potential of PCLA-PEG-PCLA copolymer loaded with Clx showed similar results with acetyl-capped polymer but longer release time (van Midwoud et al., 2018). These results suggest the potential of PCLA-PEG-PCLA for OA targeted treatment injection.

Polyesteramide (PEA) MS is another high-profile Clx-loaded NPs. Maarten Janssen (Janssen et al., 2016) et al reported that Clx was released sustainedly up to 80 days in vitro and inflammation responsive release was observed in the Hl-60 cell line. In OA-induced (ACLT + pMMx) rats, degradation of PEA MS was higher than health rats which verified inflammation responsive release again. Regrettably, no difference was observed in cartilage degeneration changes between 0.9% NaCl, single MS and Clx-loaded MS. A later similar study showed that Clx-loaded PEA MS reduced the osteophytes, subchondral ossifying, bone cysts, and synovial inflammation in surgery-induced OA rats (Tellegen et al., 2018). Ian J Villamagna (Villamagna et al., 2019) et al optimized the structure of PEA MS and demonstrated different toxicity in vitro and in vivo.

Recently, poly (D, L-lactic acid) (PDLLA) microparticles (MP) and hyaluronan nanocapsules were developed to load Clx for rats OA model research. Two different kinds of PDLLA MP (drug in solution MP and nano-drug embedded MP) showed good biocompatibility, drug loadings rate, entrapment efficiencies and long action sustained release of Clx. PGE2 decreased in IL-1β induced human articular synoviocytes after two MP interventions (Salgado et al., 2020). Clx-loaded hyaluronan nanocapsules showed remarkable entrapment efficiency and release time in vitro. In addition, nanocapsules improved knee joint swelling, morphology, histomorphology and inflammation in MIA-induced rats OA model (El-Gogary et al., 2020).

Diclofenac (Dcf) is also commonly used in the targeted treatment of OA by loading nanomaterials. Bryan B Hsu (Hsu et al., 2014) et al first reported a new polymer–Dcf conjugate system of biodegradable thin films using a layer-by-layer (LBL) self-assembly process and achieved sustaining small molecule release. Dcf is firstly activated with triethylene glycol (TriEG) to form a TriEG-Dcf produg conjugate and then conjugated to poly (I-glutamic acid) to complete integral PGA-TriEG-Dcf formulation assembly. After conjugating to poly(I-lysine) to form PLL/PGA-TriEG-Dcf, the release time...
increased significantly, exceeding several months. PLL/PGA-TriEG-Dcf showed a prominent anti-inflammatory effect by COX inhibition and no deleterious effects appeared in synthetic procedures. Adrian Sulistio et al. (Sulistio et al., 2017) developed a new polymer-Dcf conjugate (PDCs) and found that PDCs provide high drug loading and a sustained steady release of Dcf. Notably, by regulating the feed ratio of PEG co-monomers and the amount of PDCs, Dcf loading and release kinetics can be continuously optimized to achieve precise control. The hydrogel films of poly(n-vinylcaprolactam) NPs (vPVCL) were reported temperature-responsive on the basis of high drug loading by the LBL assembly technique (Zavgorodnya et al., 2017). After being loaded with Dcf, different layers of vPVCL show different performance of drug loading and release, and when (vPVCL)30 is in the artificial skin film at 30°C (average skin temperature), the cumulative drug release in 24 hours is 12 times that of 22°C. Kuan Zhang (Zhang et al., 2020) et al reported a dual-functional nanospheres PNIPAM-PMPC loaded with Dcf prepared by emulsion polymerization. PNIPAM-PMPC nanospheres show higher drug release at 37°C than 22°C. Meanwhile, it has prominent lubrication by forming a compact hydration layer outside. Dcf-loaded PNIPAM-PMPC nanospheres have good biocompatibility, which increase anabolic genes and inhibit catabolic genes of chondrocytes. Toshio Kawanami (Kawanami et al., 2020) et al developed a novel Dcf-hydrogel conjugate system produced by 2-pyridylamino-substituted 1-phenylethanol (PAPE) which reduced the production of the lactam in regular ester conjugates of Dcf. Besides, this hydrogel conjugate has an optimizable release rate regulated by physiological microenvironment. Recently, inartificial clay mineral attapulgite (ATP) was used to produce an enhanced supramolecular hydrogel by cyclodextrin pseudopolyrotaxane (PPR) system (Ha et al., 2021). This ATP hybrid hydrogel appears to sustained release of Dcf, good biocompatibility and remarkable anti-inflammatory in vivo test.

Etoricoxib (Ecx) is a highly hydrophobic selective inhibitor of COX-2 and is commonly used for acute pain caused by rheumatoid arthritis and OA. However, due to low solubility, severe pH dependence, and cardiovascular risk, oral or systemically administration of Exm remains many challenges (Okumura et al., 2009). Polycaprolactone (PCL) MP is early used for Exx-loaded targeted delivery. PCL MP showed satisfactory biocompatibility, hypotoxicity and long-term sustained release in vivo and in vitro tests (Arunkumar et al., 2016a). Loading PCL MP with chitosan gel to form novel injectable gel MP can enhance the duration of Ecx in synovial (Arunkumar et al., 2016b). Pingju Liu (Liu et al., 2019) et al developed novel PLGA-PEG-PLGA copolymer NPs loaded with Ecx. NPs showed sustained release in vitro and significant anti-inflammatory effects in subchondral bone, synovium, and cartilage in vivo. Aala H Salama (Salama et al., 2020) et al reported Ecx-loaded PLA-CS NPs synthesized from polyactic acid and chitosan hydrochloride. By adjusting the ratio of surfactant, the formula with the smallest particle size and the most obvious slow-release effect was optimized. PLA-CS NPs showed cytocompatibility and enhanced ALP activity in vitro test.

In addition to chemically synthesized nanomaterials, organometalic materials are also used for drug-loaded targeted therapy. A UiO-66 metal-organic framework (MOF) was used as DDS for ketoprofen by introducing functional groups (NH3, NO2) (Li et al., 2019). Ketoprofen-loaded UiO-66-NH3 showed good biosafety and sustained drug release. NSAIDs are relatively mature in delivery systems research (Table 1).

4.2. DDS targeting cartilage protection and regeneration

Dicerein (Dcn) is a chondroprotective agent metabolized by acetyl esterases and it exerts anti-inflammatory and cartilage protective effects by metabolizing rhein (Jain et al., 2015; Lohberger et al., 2019). Dcn does not affect the production of prostaglandins, and there are few reports of gastrointestinal disorders, so it is recommended as a first-line drug for OA, especially for patients contraindicated to NSAIDs (Bartels et al., 2010; Pavelka et al., 2016). However, low water-solubility limits the oral bioavailability of both diazepine and rhein.

Achint Jain (Jain et al., 2013) et al developed Dcn-loaded solid lipid NPs (Dcn-SLN) by ultrasonication technique and characterized its physicochemical properties. Dcn-SLN shows sustained drug release in vitro and high bioavailability of oral management in a rat model. Mubashar Rehman (Rehman et al., 2015) et al optimized Dcn-SLN by mixing proportionally of solid and liquid lipids to form binary SLNs. This novel formula demonstrates not only sustained Dcn release but, more importantly, rapid release at high temperatures. This thermoresponsive release property makes it possible to combine it with OA thermal therapy. In subsequent studies, Dcn-loaded niosomes and self-nano emulsifying gel based on GLC and TPGS were successively developed (El-Say et al., 2016; Eltobshi et al., 2018). Both DDS showed good drug release performance in vitro and anti-inflammatory effect in vivo after optimization. Dcn or rhein-loaded PLGA NPs showed excellent biocompatibility and inflammatory inhibition in vitro (Gómez-Gaete et al., 2017; Jung et al., 2020). Dcn-loaded PLGA NPs could effectively protect the cartilage injury and inhibit the progression of inflammation after interarticular injection in vivo. Diana E Aziz (Aziz et al., 2018) et al developed a novel Dcn delivery system using elastosomes for transdermal delivery thereby avoiding oral adverse effects (Table 2).

Chondroitin sulfate (CS) is a sulfated GAG and an important component of the cartilage extracellular matrix (Aleassi et al., 2021). It is widely used in the adjuvant therapy of OA due to its anti-inflammatory, anti-oxidative and anti-apoptotic effects (Henrotin et al., 2010). Studies showed that polymer-modified CS significantly increased the inter-tissue retention time. CS-encapsulated PLGA copolymers with different lactide and glycolide ratios showed different CS burst releases, and this may be potential for controlled drug release (Jiang et al., 2011). Priyanka Dwivedi (Dwivedi et al., 2015) et al combined gold NPs with CS to reinforce drug delivery. AuNps-CS was demonstrated to enhance chondrocyte proliferation and promote ECM production in vitro. Besides, a novel polymer agent formulated by CS-cysteine
| Drugs       | Delivery system          | Physical properties | In vitro findings                                                                 | Rat model                  | In vivo performance                                                                 | Refers                      |
|-------------|--------------------------|---------------------|------------------------------------------------------------------------------------|---------------------------|-------------------------------------------------------------------------------------|-----------------------------|
| Lnx         | PLGA MS                  | None                | None                                                                               | 4% papain induce          | Low circulating concentration; long drug retention; biocompatibility safe; reduce joint swelling; histological improvement | Zhang & Huang (2012)        |
| Chitosan/TPP MS | Particle size (L9): 5.4 μm; EE%: 59.5% | pH and particle size dependent; Sustained release over 8 days | 3mg/50μl MIA induce          | Prolongation of retention time; reduce joint swelling; inhibit IL6; histological improvement | Abd-Allah et al. (2016) |
| Mx          | CMC-MC-P hydrogels NPs  | EE% (N2): 87.5%; Low degradation and swelling behavior | Sustained release in 90 days                                                | None                      | None                                                                                 | Fattahpour et al. (2020)   |
| Acetyl-capped PCLA-PEG-PCL thermogels | Particle size: 10–100 μm | More degradation of PEA in inflammatory environment; Sustained release over 80 days | ACLT and pMMx surgery        | Biocompatibility safe; sustained release over 12 weeks; reduce degradation of PEA; no cartilage pathology difference | Janssen et al. (2016) |
| PEA MS      | Average molecular weight: 70 kDa | Sustained release over 28 days | ACLT and pMMx surgery             | Dose-dependently release over 120 hours; subchondral bone protection, osteophyte reduction, histological improvement | Tellegen et al. (2018) |
| PDAI          | PLGA-PEG-PLGA NPs | Average diameter: 339 nm; Zeta potential: 1.68 ± 0.85 mV | Sustained release over 30 days; Bio-safe                                       | ACLT surgery              | Maintain ECM; histological improvement; subchondral bone protection                | Liu et al. (2019)          |
| PEG-ELDI-PHB-MG | Average diameter: 237 ± 97.9; Zeta potential: −16.7 mV; EE%: 41.7%; LC%: 11.1% | Sustained release over 14 months; inhibition of COX-1 | None                                                                               | None                      | None                                                                                 | Zavgorodnya et al. (2017)  |
| PDLLA MP     | 20 to 40 μm mean size; 10% to 50% w/w drug loading; EE% > 80% | Sustained release over 90 days; inhibit PGE2 release | None                                                                               | None                      | None                                                                                 | Salgado et al. (2020)      |
| Dcf PLL/PGA-TiEG | Dfc loading densities: 295 μg/mm3 (30wt%) (40 bilayers); Thickness: 2.7 ± 0.5 μm | Sustained release over 14 months; inhibition of COX-1 | None                                                                               | None                      | None                                                                                 | Hsu et al. (2014)          |
| PEG-ELDI-PHB-MG co-monomer vPVCL nanogel | pH-dependent nanogel size; Temperature sensitive swelling | Temperature-responsive release; sustained release over 24 h at 32°C | None                                                                               | None                      | None                                                                                 | Sulistio et al. (2017)     |
| PNIPAM-PMPC nanospheres | Average diameter: 237 ± 97.9; Zeta potential: −16.7 mV; EE%: 41.7%; LC%: 11.1% | Temperature-responsive; 66.8% and 73.4% release with 24 h and 72 h, 81.2% and 87.5% at 37°C; lubrication; biocompatible, no cytotoxicity and chondroprotective | None                                                                               | None                      | None                                                                                 | Zhang et al. (2020)       |
| ATP Hybrid-PPR Hydrogel | EE%: 77.3% to 96.4% | Good biocompatibility; Sustained release 70%-90% over 4 days | 100 μL of carrageenan solution (1%) induced | Prolong retention time to 7 days; Histological improvement | Ha et al. (2021) |
| Ecx PCL MP; PCL-CICG MP | Average size: 16.26 ± 10.14 μm; EE%: 83.7 ± 3.27%; LC%: 2.67 ± 0.11% | Controlled release for 28 days; Bio-safe                                       | Healthy                  | Prolong the retention time to 4 weeks in the synovia                                | Arunkumar et al. (2016)    |
| PLA- chitosan NPs | Average diameter: 339 nm; Zeta potential: 1.68 ± 0.85 mV | Sustained release over 30 days; Bio-safe                                       | ACLT surgery              | Maintain ECM; histological improvement; subchondral bone protection                | Liu et al. (2019)          |
| PLA- chitosan NPs | Smallest size: 420.30 ± 40.16 nm; Zeta potential: 25.95 ± 1.34mV; EE%: 92.15 ± 0.78% | Quick release after first 2h, sustained release over 28 days | None                                                                               | None                      | None                                                                                 | Salama et al. (2020)      |

(continued)
conjugate showed remarkable bioadhesive properties and low biotoxicity in rat primary chondrocytes (Suchaoin et al., 2016).

4.3. DDS targeting GAG loss and ROS of chondrocyte

Glucocorticoids have obvious anti-inflammatory effects, but long-term repeated use of large doses can lead to a variety of local or systemic side effects. Dexamethasone (Dex) is the most commonly used glucocorticoid for OA treatment. In order to improve the efficiency of drug use and reduce side effects, a variety of DDS has been developed. Bajpayee (Bajpayee et al., 2016; 2017) et al conjugated avidin nanoparticle carriers with Dex by two linkers (ester and hydrazone). Ester linker had faster drug release than hydrazone linker and avidin-Dex rescued IL-1-induced GAG loss with does dependence. Subsequent animal experiments confirmed that the avidin-Dex could penetrate cartilage and retain for 3 weeks, improve morphology and inhibit the formation of osteophytes, but increased Dex load was needed to further reduce the loss of GAG. Dex-carbon nanotubes were developed to restrain TNF-α induced inflammation in synovial fibroblasts (Lee et al., 2017). Nanotubes showed higher Dex uptake by caveolin-dependent endocytosis and efficient intracellular release to inhibited ROS production by targeting mitochondria.

Stefano Perni (Perni & Prokopovich, 2020) et al greatly increased the drug uptake of Dex-poly-beta-amino-esters (PBAEs) by continuously optimizing the polymer structure. Dex-PBAEs inhibited GAG loss induced by IL-1α in cartilage explants cultured and improved the chondrocyte activity. Dex-loaded PLGA MP showed significant sustained release, pro-anabolic and anti-inflammatory factor effects in vitro and in vivo (Stefani et al., 2020). Tengfei He (He et al., 2020) et al developed a novel multi-arm avidin NPs, which greatly increased the drug load with crosslinkers. These multi-arm avidin NPs showed remarkable control of drug release and cartilaginous permeability. In vitro tests indicated that it inhibited the generation of ROS, protected the activity of chondrocytes, and reduced the loss of GAG and collagen.

The glucocorticoid-loaded DDS shows great potential for OA intraarticular targetted treatment. At the same time, some studies confirmed that the biological effects of the NPs DDS are affected by the dynamic changes of the joint environment, such as the changes of proteins, hyaluronic acid and phospholipids in the synovial fluid (Magri et al., 2019).

4.4. Novel drug molecules targeting osteagenesis

In recent years, some new drug molecules introduced to different DDS showed remarkable therapeutic effects of OA in experiments, which has laid a foundation for clinical application (Table 3). Human stromal cell-derived factor 1α (rhSDF-1α) is a significant chemokine facilitating stem cell migration and homing to injured tissue and promoting tissue repair (Hattori et al., 2001). rhSDF-1α-loaded fibrin/HA hydrogel was used to filled chondral defects and it recruited chondrogenic progenitor cells to chondral defects, which improved the
| Drugs | Delivery system | Physical properties | In vitro findings | Rat model | In vivo performance | Refers |
|-------|----------------|---------------------|------------------|-----------|-------------------|--------|
| Dcn   | SLN            | Particle size: 382 ± 16 nm; Zeta potential: −1966 ± 21 mV; TDC (%): 985 ± 02% | Sustained-release up to 12 h | Healthy | Anti-diarrhoeal; enhanced oral bioavailability; | Jain et al. (2013) |
|       | SLNs-GNPs      | Particle size: 6.9–9.7 nm; EE%: 79–97%; Zeta potential: −22.7–38.6 mV | Thermoresponsive release; Sustained-release up to 72 h | None | None | Rehman et al. (2015) |
| Glc   | TPGS self-nanoemulsifying DDS | Uniform and homogeneous surface; Crystalline anhydrous nature; Drug stability | Enhanced drug release | 0.1 mL of 1% w/v 1,3-carrageenan | Edema and inflammation inhibition; histopathological improvement; TNF-α and caspase-3 inhibition | Eltobshi et al. (2018) |
|       | Niosomal gel- 3% HPMC | Particle size: 7.33–23.72 μm; EE%: 9.52–58.43% | Sustained-release up to 8 h | 0.1 mL of 1% carrageenan | Edema and inflammation inhibition | El-Say et al. (2016) |
|       | PLGA NPs       | Particle sizes: 200–320 nm; Loading efficiency: 81.76 ± 3.26% DIA (1%) and 80.85 ± 7.51% DIA (5%) | Sustained release up to 63 days; non-toxic; Inhibit IL-1, IL-6, TNF-α, MMP-3, MMP-13, COX-2, and ADAMTS-5 | 50 μL of 10 mg/mL MIA | Histological improvement; cartilage protection; inhibit inflammation | Jung et al. (2020) |
|       | EA-based vesicular nanocarriers | EE%: 96.25 ± 2.19%; Particle sizes: 506.35 ± 44.61 nm; Zeta potential: −38.65 ± 0.91 mV | Sustained-release up to 8 h | Transdermal delivery | Biocompatibility safe; | Aziz et al. (2018) |
| Rhein | PLGA MP        | Mean diameter: 4.23 ± 0.87 μm; EE%: 63.8 ± 3.0%; Loading efficiency: 1.60 ± 0.07%; Zeta potential: −21.4 mV | Sustained-release up to 30 days; noncytotoxic; inhibit IL1β, TNF-α and ROS | None | None | Gómez-Gaete et al. (2017) |
| CS    | PLGA MS        | Particle sizes: 75–500 μm; EE%: 70–80% | Microsphere size-dependent release; multiple burst release noncytotoxic | None | None | Jiang et al. (2011) |
| Au-NPs|               | Average particle size: 13 nm | Promote cell proliferation; Increase GAG and collagen production | None | None | Dwivedi et al. (2015) |

**Abbreviations:** Dcn: Diacerein; SLN: solid lipid nanoparticles; GNPs: gold nanoparticles; Glc: gelucire; TPGS: d-α-tocopheryl polyethylene glycol 1000 succinate; HPMC: hydroxypropylmethyl cellulose; ROS: reactive oxygen species; EA: edge activator; CS: chondroitin sulfate; Au: gold.
| Drugs       | Delivery system                  | Physical properties | In vitro findings                                                                 | Rat model | In vivo performance               | Refers               |
|------------|----------------------------------|---------------------|-----------------------------------------------------------------------------------|-----------|-----------------------------------|----------------------|
| rhSDF-1α   | Fibrin/hyaluronic acid hydrogel  | None                | Sustained-release up to 14 days; bio-compatible; recruit chondrogenic progenitor    | None      | None                              | Yu et al. (2015)     |
|            |                                  |                     | cell; regeneration of cartilage tissue                                            |           |                                   |                      |
| IGF-1      | PAMAM dendrimers                 | Generation 6: 58 kDa| No histotoxicity                                                                   | ACLT + MMx surgery | Penetrate cartilage; Sustained-release 30.4 days; rescue cartilage degeneration; reduces osteophyte formation | Geiger et al. (2018) |
| BMP2       | GO flakes                        | Most abundant size: 1,598.5 nm | Sustained-release up to 40 days; inhibit inflammation; promote differentiation       | ACLT surgery | Histological improvement; inhibit inflammation | Zhong et al. (2017)  |
| TGF-β3     | GO 3D nano-scaffold              | Average size 10–40 μm; drug adsorb >99 % | Sustained-release up to 28 days; no cytotoxicity; promote chondrogenic differentiation | None      | None                              | Zhou et al. (2019)   |
| Glutathione| Chitosan-gelatin based hydrogel  | Pore size: 1.667 μm | No cytotoxicity; sustained-release up to 48 h; rescue oxidative damage; down-regulate inflammation | None      | None                              | Cheng et al. (2017)  |
| KGN        | PEG-PAMAM                        | Average size: 33.3–36.4 nm; drug loading: 5.50 ± 0.23 (wt. %); Zeta potentials: +5mV | Low cytotoxicity; promote chondrogenic differentiation and ECM production;          | Healthy and 4% papain injection | Sustained-release up to 21 days | Hu et al. (2017)     |
| NPPs       |                                  |                     | Up-regulate Acan, Sox9, and Col2a1; Low cytotoxicity; improve chondrogenesis         | None      | None                              | Maudens et al. (2018) |
| 3D Tri-Copolymer Scaffolds | Mean pore size: 20 to 30 μm |                   | Sustained release 62% drug in 3 months; bio-safe                                   | DMM surgery | Histological improvement; cartilage protection; inhibit inflammation | Chen et al. (2021)   |
| TPCA-1     | Nanosomes                        | Average size: 50–200 nm | Low cytotoxicity; inhibit NO, LDH, PGE2, EPAS-1, MMP-13, ACAN and COL2A1           | None      | None                              | Bhatti et al. (2019) |
| Adenosine  | PLA-b-PEG NPs                    | Diameter size: 129–144 nm | None                                                                               | ACLT surgery | Inhibit NF-κb activation; chondroprotective; histological improvement | Liu et al. (2019)    |
| HCQ        | CMFn nanocages                   | Diameter:22 nm; loading ratio: 48%; embedding ratio: 5% | MMP-13/pH-responsive release; low cytotoxicity; increase Col2a1 and decrease inflammatory factors | None      | None                              | Chen et al. (2019)   |

Abbreviations: rhSDF-1α: Human stromal cell-derived factor 1α; PAMAM: Amine terminal polyamidoamine; GO: Graphene oxide; KGN: Kartogenin; NPPs: nanocrystal–polymer particles; TPCA-1: [5-(p-Fluorophenyl)-2-ureido] thiophene-3-carboxamide; LDH: lactic dehydrogenase; PGE2: Prostaglandin E2; HCQ: hydroxychloroquine; CMFn: ferritin nanocages; DMM: Destabilization medial meniscus.
morphology, proteoglycan density and cartilage ultrastructure (Yu et al., 2015).

Anabolic growth factors are efficient for OA treatment by enhancing chondrocyte activity and promoting matrix production. An earlier study found that insulin-like growth factor 1 (IGF-1) fused to heparin-binding domain had a distinct prolongation of intraarticular retention and rescued cartilage degeneration in the rat OA model (Loffredo et al., 2014). Brett C Geiger (Geiger et al., 2018) et al loaded IGF-1 on positively charged PEGylated polyamidoamine (PAMAM) dendrimers and this dendrimer-IGF-1 presented prominent performance of drug absorption, cartilage penetration, drug retention and biocompatibility in vitro. The nanocarriers enhanced the treatment effects of alleviating cartilage degeneration and osteophyte formation in vivo. BMP2 is an important exctoanabolic factor in bone metabolism. BMP2 adsorbed onto graphene oxide (GO) flakes showed remarkable biocompatibility and sustained slow release in vitro. In the OA rat model, GO-adsorbed BMP2 had a better historical appearance after intra-articular intervention (Zhong et al., 2017). GO-loaded TGF-β3 3D nano-scaffold is a new progress of cartilage engineering. Culture of hMSCs encapsulated in 3D GO scaffold-adsorbed TGF-β3 hydrogel improved chondrogenesis and ECM production. This novel 3D GO scaffold demonstrated excellent drug delivery, low cytotoxicity and sustaining drug activity (Zhou et al., 2019).

Yung-Hsin Cheng (Cheng et al., 2017) et al developed a glutathione-loaded chitosan hydrogel and used it in Cisd2 deficiency-induced rat chondrocytes injury. The hydrogel showed thermosensitive and sustained drug release in chondrocytes without obvious cytotoxicity. Glutathione rescued the inflammation, apoptosis and oxidative stress in Cisd2−/− chondrocytes by restraining H2O2 activity.

Kartogenin (KGN) is found an important activator of the CBFβ-RUNX1 signaling pathway which promotes chondrogenesis and chondroprotection (Zhao et al., 2020). KGN was first conjugated to the head or end group of PEG-PAMAM to form KGN-PEG-PAMAM (KPP) or PEG-PAMAM-KGN (PPK) dendrimer. KPP showed the more prominent effect of CBFβ and chondrogenic markers activation. In vivo test showed prolonged retention of drug in a rat model (Hu et al., 2017). Pierre Maudens et al. (Maudens et al., 2018) introduced KGN nanocrystals acquiring by wet milling to PLA nanocrystal—polymer particles to form KGN-NPPs. The NPPs system presented commendable drug loading, sustained drug release and biocompatibility in vitro test. The KGN-loaded NPPs improved chondrohistology and osteophyte size in vivo test. In the past two years, tri-copolymer scaffolds structured by gelatin-chondroitin-hyaluronan and engineered exosomes were used to deliver KGN to chondrocytes and showed potential application future (Chen et al., 2021; Xu et al., 2021).

Nanoshaped liposomes conjugated to MAbCII were synthesized to encapsulate TPCA-1, a selective inhibitor of NF-κB pathway, and showed distinguished improvement of inflammation, oxidative stress and cell apoptosis in TNF-α-treated chondrocytes (Bhatti et al., 2019). The advantage of liposomes is the sustained drug release properties but once the release is activated, it does not extend the clearance time. Xiuling Liu (Liu et al., 2019) et al conjugated adenosine to biodegradable PLA-b-PEG NPs in different binding sites. In vitro studies showed that adenosine-loaded NPs can significantly increase intracellular cAMP and inhibit a variety of inflammatory factors. Early injection of adenosine-loaded NPs into rat joints can effectively prevent traumatic OA.

Haimin Chen (Chen et al., 2019) et al optimized the MMP/pH-responsive DDS by synthesizing ferritin nanocages (CMFn) loaded with hydroxychloroquine (HCQ). The fluorescence intensity of CMFn can reflect the severity of OA and HCQ can be sustained released for 14 days in an acidic pH microenvironment. This dual sensitive DDS has great application prospects for precision OA diagnosis and treatment.

### 4.5. Chinese herb extracts and targeted DDS

Curcumin is extracted from the Chinese herb Curcuma longa which is commonly used in OA for inflammation and pain relief. Combined injection of curcumin and bone marrow mesenchymal stem cells (BMSCs) into the OA rat model can enhance the migration and proliferation of chondrocytes, improve the level of anabolic factors and promote chondrogenesis (Zhang et al., 2021). Regardless of oral, direct joint injection or transdermal administration, Curcumin shows obvious anti-OA effects and the potential mechanism is related to inhibition of oxidative stress, promotion of anabolism, and anti-inflammatory apoptosis (Nicoliche et al., 2020; Zhou et al., 2020). However, the traditional administration still has drawbacks such as multiple dosing and gastrointestinal side effects, although the study showed better tolerance of curcumin than that of Dcf (Shep et al., 2019). Some studies used gelatin/silk fibroin MPs and synthetic NPs loaded with curcumin and showed good drug penetration and sustained release (Zhang et al., 2016; Ratanavaraporn et al., 2017).

Qiumei Lan (Lan et al., 2020) et al developed another MMP/pH-responsive DDS loading psoralidin (PSO) which is extracted from poralea corylifolia. The MRC-PPL NPs are designed to target cartilage and respond to MMP-13. MRC-PPL@PSO showed remarkable anti-inflammatory and cartilage repair effects in vitro and in vivo test by regulating PI3K/AKT, MAPK and NF-κB signaling. Zhengxiao Ouyang et al. (Ouyang et al., 2019) introduced hesperetin (extracted from citrus fruit) to Gd2(CO3)3-based NPs with a cartilage-targeting peptide. The NPs displayed excellent biocompatibility and magnetic resonance suitability. Hesperetin showed remarkable chondrocytes protection by inhibiting the TLR-2/NF-κB/Akt pathway.

Salvianolic acid A (SAA) is extracted from Salvia miltiorrhiza Bunge and it can inhibit chondrocyte apoptosis and ECM degradation in the OA rat model by restraining NF-κB signaling and activating TIMP-1 and TIMP-2 to inhibit MMPs (Xu et al., 2017; Wu et al., 2020). Artesunate (ART) is derived from artemisinin which is an extract of Chinese herb used to treat malaria. ART can relieve OA rat inflammation and improve cartilage pathological by regulating AK/STAT signaling (Zhao et al., 2017). Ethanol extract of Agkistrodon acutus
can alleviate the apoptosis of chondrocytes and correct the abnormal expression of MMPs and Col2a1 in OA rats (Wang et al., 2019). These Chinese herb extracts demonstrate remarkable effects in OA, and they have tremendous potential to work with appropriate DDS in the clinical application (Table 4).

4.6. Gene delivery system
Transferring exogenous nucleic acids to intracellular compartments is an effective method for OA treatment. Gene therapy includes DNA, RNA and no-coding RNA that are specific to different diseases and tissues. Nanomaterial non-viral vectors can avoid the immunogenicity, oncogenic effects and other lethality of traditional viral vectors and become a promising gene therapy DDS (Table 4). Cristiano Sacchetti et al. (Sacchetti et al., 2014) used single-walled carbon nanotubes (SWCNTs) to load morpholino antisense oligonucleotides (mASOs) modified by anti-green fluorescent protein (GFP). Intra-articular injection of PEG-SWCNT-anti-GFP mASOs can effectively penetrate the ECM, deliver drugs to the chondrocytes with a prolonged retention time and inhibit GFP expression.

Indian Hedgehog (Ihh) is a non-collagen related marker which is closely related to chondrocyte injury and the development of OA (Zhang et al., 2012; Thompson et al., 2015). Lipid NPs were used to load Ihh siRNA into chondrocytes with 100% transfection efficiency. Lipid NPs-Ihh siRNA was found to accumulate in the ECM instead of the synovium. In addition, it showed remarkable excito-anabolic and anti-catabolism effects and effectively alleviated cartilage degeneration in the OA rat model (Wang et al., 2018). The fibrin/HA hydrogel and self-assembling peptidic NPs were also used for carrying antimiR-221 and NF-κB p65 siRNA, respectively. These DDS showed excellent targeting delivery, gene silencing and OA therapeutic effects (Lolli et al., 2019; Yan et al., 2019).

4.7. Multidrug delivery system
Some formulations use targeted delivery of combination drugs, which makes the therapeutic effect more comprehensive. Mamta Bishnoi et al. (Bishnoi et al., 2014) conjugated aceclofenac-loaded CS to SLN and the SLNs showed sustained drug release over 24 hours in vitro test. When administered subcutaneously, SLNs presented high concentrations in the joints but no significant accumulation in vital organs and reduced edema induced by MIA. KGN and Dcf were conjugated to thermoresponse NPs outside and inside, respectively (Kang et al., 2016). The therapeutic effects of both drugs were fully demonstrated in the formula, and the drugs could be released with precise control in cold temperatures. Similarly, indomethacin and glucosamine were jointly loaded on PLGA nano-micelles and observably improved inflammatory response and histopathology in the OA rat model (Kamel et al., 2016).

Xu Chen (Chen et al., 2019) et al developed a photothermal-triggered nanogenerator which loaded NO and...
Notch1-siRNA on PLGA-PEG NPs. With the synergistic effect of phototherapy, this formula achieved NO anti-inflammatory effect, Notch1 gene silencing, and alleviation of cartilage erosion. The combination of multidrug delivery and physical factor therapy is a promising approach for OA treatment.

5. Conclusions and future prospects

The constant development of DDS displays a great avenue for targeted therapy of OA. Traditional drugs fully release the therapeutic potential and greatly reduce the drawbacks and side effects accompanied by systematic administration. Many emergent drug molecules present great therapeutic potential in vitro and in vivo studies, whether in inflammation suppression, chondrocyte protection, extracellular matrix generation, or the relief of corresponding symptoms. The future application of these drugs still needs more explorations to confirm and optimize the property, and help reveal the internal mechanism of the occurrence and development of OA.

Nano-DDS is an important optimization of OA topical administration, which realizes biological functions such as drug penetration, long-term retention and sustained release. By modulating DDS structure, the encapsulation efficiency of the drug is greatly improved, which avoid large dose or frequent administration. The penetration of chondrocyte ECM in DDS has made some progress, but it is still one of the difficult problems to be solved in the later period. Multi-structure integration of NPs can be loaded with different types of drugs, which can help enrich therapeutic strategies according to the specific condition of the disease. Responsive nano DDS opens a new horizon for the precise treatment of OA. Drug release controlled by joint microenvironment changes can help better grasp the disease progress, while the physical factor response system takes full advantage of physiotherapy on the basis of precision treatment.

Nanotechnology has revealed the great plasticity of new materials in the medical field and these findings will catalyze new breakthroughs of DDS. In future studies, it is necessary to more clearly reveal the pathogenesis of OA and find more drugs with definite efficacy to enrich treatment strategies. At present, many studies get remarkable results in vitro or ex vivo, but there is still a long way to go before clinical application. Each drug delivery strategy needs to be reevaluated for safety, consistency, and clinic efficiency over long-term clinical studies. The drug load is an important translation challenge due to the differences in drug requirements for human OA and animal studies. Biocompatibility, low biotoxicity, and biodegradability remain the primary concerns for the development of DDS. The nanomaterials need to be further optimized to achieve good human adaptability, and the pharmacokinetics of the drug loading system need to be clarified. In addition, the structure-function relationship between nanomaterials and different stages of OA (changes in synovial fluid, cartilage, subchondral bone, muscle, ligament and other tissues as well as the intraarticular environment) is also important challenge for clinical conversion.

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