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Recent Advances in Nanotechnology for Cartilage Regeneration in Osteoarthritis

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Abstract

Osteoarthritis (OA) is a progressive joint disorder that leads to cartilage degeneration, pain, and impaired mobility. Traditional treatments offer limited efficacy, often failing to provide sustained relief or reverse cartilage damage. In recent years, nanotechnology has emerged as a promising approach to improving OA management. This review focuses on various nanofomulations developed by researchers, such as liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLN), nanoemulsion and nano structured lipid carriers (NLC). These nanocarriers offer significant advantages, including enhanced drug delivery, improved bioavailability, and targeted release of therapeutic agents to the affected tissues. By enabling controlled and sustained release, these nanosystems can potentially improve cartilage repair and reduce inflammation, offering more effective treatment outcomes with fewer systemic side effects. Despite these advancements, key challenges remain, particularly in ensuring the long- term safety, biocompatibility, and scalability of nanomaterials for clinical use. Additionally, the complexity of OA calls for more personalized treatment approaches, combining nanotechnology with other therapeutic strategies. Although many nanofomulations have demonstrated promising preclinical results, extensive clinical trials are required to translate these innovations into approved therapies.

Keywords: Osteoarthritis; Nanoparticle; Nanotechnology; Cartilage repair.

1. Introduction

The most common chronic joint disease causing disability in adults is osteoarthritis (OA), which is characterized by stiffness, discomfort, and restricted movement in the joints [1]. Age, gender, obesity, joint damage, and other factors are associated with the incidence of OA [2]. People and society at large bear a significant financial burden from OA because of its high incidence [1]. The pathophysiological aspects of OA include the formation of osteophytes, inflammation of the

synovium, remodeling of the subchondral bone, sclerosis, and progressive and degenerative loss of articular cartilage. This illness is thought to be complicated, involving several different tissues and systems. The reasons are still not entirely known [3]. Many variables, including genetic predisposition, the biochemistry and biomechanics of the diseased joint, and the degree of inflammatory response, are linked to OA in contemporary views [4]. As such, pinpointing precise targets for treatment has proven challenging. Symptomatic therapy for pain relief, functional enhancement, and even mechanical joint replacement constitute the majority of current therapeutic practice; the underlying molecular causes of OA are not addressed [5].

Diagnostic imaging procedures like magnetic resonance imaging (MRI), computed tomography (CT), and plane radiographs are used to confirm the diagnosis of OA, which is based on clinical complaints such as pain, swelling, and reduced function. Sadly, imaging is skewed toward displaying the pathoanatomy of late-stage OA (i.e., loss of cartilage volume, edema in the bone marrow, thickening of the subchondral bone, development of cysts, and marginal osteophyttes) [6]. Hyaline cartilage has a limited capacity for self-healing, and permanent deterioration can place even before symptoms and radiographic indicators become apparent. Prognosis worsening and limited treatment choices result from late-stage diagnosis of OA, which occurs after macroscopic and microscopic alterations in tissue structure have occurred. OA is tough to treat and incurable. Reducing OA requires a comprehensive plan.

Three methods can be employed to address the mechanical causes that lead to chondrocyte injury and hyaline cartilage wear:

1. One possible approach is to stop the inflammatory cascade and neutralize the catabolic enzymes that degrade hyaline cartilage.
2. Replace end-stage chondral lesions or enhance component tissue elements.
3. A multidisciplinary field including physics, chemistry, biology, electronics, and engineering is nanotechnology.

Globally, there is a thriving nanotechnology research and development community. The scientific study and manipulation of atomic, molecular, or macromolecular particles—typically ranging in size from 1 to 100 nm—is known as nanotechnology [7]. Due to the particularity of the scale

structure, which gives birth to their distinctive features including size effects, interfacial phenomena, and quantum effects, among others, nanoparticles (NPs) exhibit many remarkable characteristics and novel capabilities [7]. The behavior of NPs is less predictable than that of microparticles. Therefore, by manipulating and modifying nanostructures, it may be possible to utilize the distinct chemical, physical, and biological characteristics of NPs in the future.

The structures of molecules at the microscopic level in the body, their large surface area relative to volume ratio, and the ideal size for catalysis have made nanotechnology increasingly significant [7]. Top-down and bottom-up approaches are commonly used in the fabrication of NPs using nanotechnology. Using methods for nanofabrication to reduce macro-sized structures to nanoscale particles is the top-down approach. However, the bottom-up strategy integrates atomic or molecular components into larger nanoscale particles by means of physical and chemical processes [8,9]. Numerous facets of our everyday life, such as sunscreen, cosmetics, textiles, and sporting goods, have demonstrated the outstanding application value of nanotechnology.

However, there isn't a clinical use of nanotechnology for OA treatment at this time. Nanotechnology has several benefits for the administration of OA therapies.

(1) More effective medication distribution and targeting;

(2) Increased drug solubility and consistency;

(3) Preventing and prolonging drug dispersion and breakdown in body fluids and increasing drug distribution and resorption time in the body;

(4) Enhanced therapeutic effectiveness and reduced adverse drug responses [10].

The recent fast advancements in pharmaceutical delivery methods facilitated by nanotechnology have opened up new treatment concepts and avenues for OA. In this review, the most recent developments and innovative applications of OA-related NP-based drug delivery, including as exosomes, polymers of nanoparticles (PNPs), liposomes, micelles, the dendrimers and inorganic NPs has been discussed.

2. LITERATURE REVIEW REGARDING NANOFORMULATIONS USED IN MANAGEMENT OF OA

Chang, et al. (2021) developed Hyaluronic acid (HA)-Liposomal (Lipo)-DIC/DEX formulation to

treat OA and relieve joint discomfort. HA was combined with diclofenac (DIC) and dexamethasone (DEX) to create the formulation for long-term OA use. These medications were subsequently put into and placed onto nanostructured lipid carriers (Lipo-DIC/DEX). The NPs showed an average size of 103.6 ± 0.3 nm, a zeta potential of −22.3 ± 4.6 mV, and an entrapment effectiveness of 90.5 ± 5.6%. The results showed that the DIC and DEX content were, respectively, 22.5 ± 4.1% and 2.5 ± 0.6%. HA-Lipo-DIC/DEX was shown to attain maximum efficacy in 4 hours and to continue the release of drugs for at least 168 hours. Increased cell counts were seen in co-culture with articular chondrocyte cells without appreciable toxicity. The reduction of knee joint inflammation in OA mice was validated by *in-vivo* imaging (IVIS) after four weeks of intra-articular injection with HA-Lipo-DIC/DEX. A single injection decreased the inflammation volume to 77.5 ± 5.1% of the starting level. These results point to the safety and efficacy of this innovative drug-releasing device, providing a viable means of managing OA pain [11].

Maestrelli F, et al. (2020) developed drug-in-cyclodextrin–double-loaded liposomes (DCL– DL). Curcumin (Cur) has anti-inflammatory and anti-osteoarthritic effects but suffers from low solubility. This issue was addressed with the development of drug-in-cyclodextrin–double- loaded liposomes (DCL–DL). The water compartment of these liposomes contains a drug– cyclodextrin combination, whereas the lipid bilayer contains free drug. Cur–DCL–DL formulations were evaluated for their effectiveness in treating OA using the monoiodoacetate (MIA) model for OA pain in rats. Three types of liposomes were injected intraarticularly: empty liposomes, ordinary liposomes, and Cur as DCL–DL. Assessments were conducted at 7 and 14 days for pain, balance, and gait; DCL–DL had significantly better results than SL. The ankle- joint tissue's histological examination showed that DCL–DL had protective effects against some forms of OA [12].

Jyothi VG, et al. (2022) aimed to assess how lipid characteristics such as chain length and functional groups affect meloxicam (MLX)-loaded SLNs (MLX-SLNs) in-vitro permeability. The manufactured MLX-SLNs had an entrapment effectiveness of between 89.13 ± 0.1% and 97.81 ± 0.01%, and their sizes varied from 152 ± 17 nm to 246 ± 5 nm with a polydispersity coefficient below 0.3. A parabolic connection between lipid chain width and permeation was found when these MLX-SLNs were incorporated into a chitin gel (MLX-SLNs-Gel) and tested for flow in ex

vivo skin permeation assays. After being examined in a Wistar rat model of OA caused by monosodium iodoacetate, stearylamine SLNs (MLX-SAM-SLNs-Gel) exhibited the greatest flow of 0.76 ± 0.03 μg/cm²/h across all the formulations. The findings demonstrated that the MLX-SAM-SLNs-Gel group's IL-1β and TNF-α levels were comparable to those of the oral MLX group and were considerably lower than those of the control groups. MLX-SAM-SLNs- Gel exhibited notably different TNF-α levels but similar IL-1β levels when compared to the MLX i.v. the solution group. Furthermore, the OA Research Society International, histology, and X-ray scores were all higher for the MLX-SAM-SLNs-Gel group. In general, MLX-SAM-SLNs- Gel seems to be a promising option for more clinical research [13].

González-Rodríguez ML, et al. (2017) employed cationic carriers to target the anionic cartilage matrix, establishing a reservoir of Rhein (RH), a dihydroxy-anthraquinone acid, which exhibits potential chondroprotective effects but suffers from poor oral bioavailability and gastrointestinal side effects within the tissue to enhance its therapeutic efficacy while minimizing adverse effects. The lipophilic properties of RH were improved using hydrophobic ion pairing (HIP), allowing for efficient loading into lipid NPs designed for slow release. The resultant RH-HIP solid lipid nanoparticles (RH-SLNs) were found in the joints of both healthy and arthritic rats, and they rapidly entered cartilage tissue. They also persisted in the joints for up to three weeks. Additionally, in rats with arthritis caused by MIA, RH-SLNs greatly reduced oxidative stress, inflammatory reactions, and cartilage deterioration. All things considered, intra-articular cationic RH-SLNs represent a potentially beneficial development in the management of OA [14].

Nagalakshmi S, et al. (2017) formulated sustained-release aceclofenac niosome formulation to improve its topical effectiveness and lessen gastrointestinal adverse effects. Various surfactant ratios were used to generate niosomes using the modified ether injection method. The niosomes were then adjusted based on in-vitro release and entrapment efficiency. The batch that was optimized was added to a niosomal gel and its vesicle size, shape, stability, and drug content were assessed. The entrapment efficiency of 88.68 ± 0.64% and 40% sustained drug release over 8 hours were demonstrated by the results, which outperformed commercial formulations in terms of effectiveness, bioavailability, and penetration [15].

Peng Y, et. al., (2024) investigated OA etiology and acknowledged it to be complex and closely related to joint tissue's oxidative stress response. In addition to producing reactive oxygen species, or ROS, and other oxidizing agents, oxidative stress (OS) in OA leads to decreased cartilage flexibility and strength as well as detrimental effects on chondrocytes. All of these factors hasten joint degradation. Antioxidant effects are important and should be considered while treating OA. Because of stability problems, several Traditional Chinese Medicine (TCM) components have not been widely applied despite having their antioxidant and anti-inflammatory qualities scientifically proven. The use of nanotechnology in conjunction with TCM components has improved treatment efficacy and overcome these issues [16].

Lee CK, et al. (2022) delivered berberine, a naturally occurring anti-inflammatory chemical, using proniosome gels to demonstrate the viability of the therapy of OA. The main component of proniosome gel is non-ionic surfactant; this was created so that berberine could be released without the need for mechanical effort. *Ex vivo* studies on skin penetration revealed that the utilization of sorbitan stearate (S60), sorbitan oleate (S80), and polyethylene glycol sorbitan monolaurate (T20) together ensured efficient skin delivery. Experiments carried out in-vitro on OA models demonstrated that chondrocytes could once more synthesize sulphated glycosaminoglycan (sGAG) at modest concentrations (1 μg/mL) without damaging keratinocytes. The mixture reduced cartilage deterioration, pain, and inflammation in a mouse model of OA. This information supports the use of proniosome gels for the administration of active medications in the management of OA [17].

Corciulo, et al. (2020) fabricated nanostructured lipid carriers (NLC) of lornoxicam (LRX) to overcome is gastrointestinal adverse effects, short half-life, and low solubility when taken orally for OA. LRX-NLCs were optimized and produced via hot homogenization, yielding particles with the following characteristics: size of 172.1 ± 2.0 nm, a polydispersity coefficient of 0.293 ± 0.01, zeta potential of −15.5 ± 1.21 mV, and entrapment efficiency of 92.85 ± 0.25%. Throughout the course of 24 hours, a consistent drug release pattern was seen. pH, spreadability, drug content, skin penetration, and retention were among the characteristics assessed when LRX- NLCs were added to a gel based on carbopol (LRX-NLCs-Gel). When monosodium iodoacetate was used to generate OA in rats, pharmacodynamic investigations showed a considerable decrease in pain and

inflammation as well as better radiographic and histological characteristics. COX-2, TNF-α, and IL-1β levels of cytokines that promote inflammation decreased substantially, and cartilage structure was improved by the gel. Emu oil, which is supplemented with omega-3, omega-6, and omega-9 fatty acids, also gave LRX synergistic effects by inhibiting the proteolytic functions of MMP-2 and MMP-9. Therapeutically viable dose forms such as LRX-NLCs-Gel appear promising in treating OA [18].

Table 1: Application of Nanoparticles for intra-articular medication delivery in OA treatment

Study/NP Type	Model	Treatment	Key Findings	Reference
Liposomes	Obesity-induced (mice)	Adenosine, CGS21680	Favorable histology; prevention of OA progression	[19]
Liposomes	Post-traumatic (rats)	Rapamycin	Decreased IL-6, MMP-13; increased collagen II; lower OARSI scores; improved histology	[20]
Fish oil protein + GNPs + DPPC	Collagenase-induced (rats)	Intra-articular injection	Increased GSH, SOD, catalase; decreased pro-inflammatory cytokines; increased anti-apoptotic activity; reduced NFκB levels	[21]
Clodronate	Post-traumatic (rats)	Intra-articular injection	Decreased M1 macrophages; lowered collagen X levels; positive histology	[22]
Micelles (MRC-PPL/Psoralidin)	Papain-induced (mice)	Intra-articular treatment	Lowered TNF-α, NFκB, MMP-13; positive histology	[23]

Micelles (Curcumin + PAE)	MIA-induced (mice)	Intra-articular treatment	Decreased TNF-α, IL-1β; improved histology	[24]
Dendrimers	Post-traumatic (rats)	PAMAM/IGF-1	Decreased synovial inflammation and deteriorated cartilage; improved histology and micro-CT results	[25]
Dendritic polyglycerol sulfates	Post-traumatic (rats)	dPGS	Decreased Mankin and Glasson scores; enhanced cartilage integrity	[26]
Polymeric NPs	MIA-induced (rats)	p66shc si-PLGA	Improved histology; reduced TNF-α, IL-1β, COX2 levels	[27]
Polymeric NPs	MIA-induced (rats)	p47phox si-PLGA	Enhanced histology; reduced ROS	[28]
PLGA NPs	Post-traumatic (rats)	Etoricoxib/PLGA-PEG-PLGA	Improved OARSI scores; positive histology; decreased COX2, iNOS, MMP-13, ADAMTS-5	[29]
PLGA NPs	Post-traumatic (rats)	PLA-PEG-adenosine	Decreased NFκB levels and OARSI scores; positive histology results	[30]

Abbreviations: HA: Hyaluronic acid; i.a.: intra-articular; PEG: poly (ethylene glycol); KGN: Kartogenin; BDMC: bisdemethoxycurcumin; CNPs: Chitosan nanoparticles; COLBP: Collagen binding peptide; dPGS: Dendritic polyglycerol sulfates; DPPC: dipalmitoyl phosphatidylcholine; BBR: Berberine chloride; SOD: Superoxide dismutase; FP: Fish oil protein; GSH: Glutathione reductase; HABP: Hyaluronic acid-binding peptide; IGF-1: Insulin-like growth factor 1; MIA: Monoidoacetic acid; OARSI: Osteoarthritis Research Society International; PAMAM: polyamidoamine; PNPs: Polymeric nanoparticles; PPL: Poly (2-ethyl-2-oxazoline)-poly (ε-

caprolactone); s.c.: subcutaneous; HA/CS-CrmA: Hyaluronic acid-chitosan nanoparticles containing plasmid DNA encoding CrmA; MRC: MMP-13 responsive/Coll-II α1 chain-binding peptide–CollB; PAE: Poly(β-amino ester); GNPs: Gold nanoparticles; In a post-traumatic OA rat model, polyurethane-KGN decreased OARSI scores and produced favorable histology outcomes (31). Reductions in OARSI scores and positive histology were also observed in another investigation that used KGN-PLA in post-traumatic OA animals [32].

Novel pairings between biomolecules and carriers have also been investigated. Collagen-binding peptide HABP-PEG-COLBP decreased MMP-13, IL-1β, and IL-6 in a post-traumatic OA model in rats, but improved histology and OARSI scores (33). When injected intraperitoneally (i.p.) to post-traumatic OA rats, berberine chloride nanoparticles (BBR-CNPs) exhibited good histology, decreased expression of bax and caspase-3, and enhanced Bcl-2 levels [34].

Curcumin-based NPs, namely curcuminoid-hyaluronic acid (HA)-CNPs, showed anti-inflammatory benefits in a post-traumatic OA rat model. They increased collagen II expression and showed good histology while reducing NFκB, MMP-1, and MMP-13 levels [35]. In addition to better OARSI scores and histological results, a different research using CrmA-HA-CNPs in post-traumatic OA rats also revealed decreased levels of IL-1β, MMP-3, and MMP-13 [36].

These investigations demonstrate the potential of NPs for intra-articular medication administration, exhibiting encouraging outcomes in lowering inflammation, cartilage deterioration, and the overall course of OA in a range of animal models.

3. Conclusion

In conclusion, the exploration of various nanofomulations for the management of OA has underscored the significant potential of nanotechnology in enhancing therapeutic outcomes. Through the innovative work of numerous scientists, nanocarriers such as liposomes, SLNs, polymeric NPs, and show on have been developed, each offering distinct advantages in drug delivery, bioavailability, and targeting of osteoarthritic tissues. These formulations provide more controlled and sustained release of therapeutic agents, minimize systemic side effects, and enhance cartilage repair processes.

Despite the encouraging progress, certain challenges remain, including optimizing the biocompatibility, long-term safety, and large-scale production of these nanocarriers. Variability in

patient response and the complexity of OA also call for more personalized and multi-targeted treatment strategies. Furthermore, while preclinical studies have demonstrated promising results, translating these nanofomulations into clinically approved therapies will require extensive trials to ensure their efficacy and safety in humans. Overall, the advances in nanotechnology-based formulations offer a promising future for the effective management of OA, potentially transforming current therapeutic approaches and improving patient quality of life. As research progresses, these innovative strategies may become integral components of OA treatment, providing more efficient, targeted, and patient-centered solutions.

References

1. Murphy, L.; Helmick, C.G. The impact of osteoarthritis in the United States: A population-health perspective. Am. J. Nurs. 2012, 112, S13–S19.
2. Heidari, B. Knee osteoarthritis prevalence, risk factors, pathogenesis and features: Part I. Caspian J. Intern. Med. 2011, 2, 205–212.
3. Fang, H.; Beier, F. Mouse models of osteoarthritis: Modelling risk factors and assessing outcomes. Nat. Rev. Rheumatol. 2014, 10, 413–421.
4. Glyn-Jones, S.; Palmer, A.J.; Agricola, R.; Price, A.J.; Vincent, T.L.; Weinans, H.; Carr, A.J. Osteoarthritis. Lancet 2015, 386, 376–387.
5. Bijlsma, J.W.; Berenbaum, F.; Lafeber, F.P. Osteoarthritis: An update with relevance for clinical practice. Lancet 2011, 377, 2115–2126.
6. Hayashi D, Roemer FW, Guermazi A. Imaging for osteoarthritis. Ann Phys Rehabil Med Elsevier Masson SAS. 2016:161-169
7. Jeevanandam, J.; Barhoum, A.; Chan, Y.S.; Dufresne, A.; Danquah, M.K. Review on nanoparticles and nanostructured materials: History, sources, toxicity and regulations. Beilstein J. Nanotechnol. 2018, 9, 1050–1074.
8. Biswas, A.; Bayer, I.S.; Biris, A.S.; Wang, T.; Dervishi, E.; Faupel, F. Advances in top- down and bottom-up surface nanofabrication: Techniques, applications & future prospects. Adv. Colloid. Interface Sci. 2012, 170, 2–27.
9. Lawson, T.B.; Mäkelä, J.T.A.; Klein, T.; Snyder, B.D.; Grinstaff, M.W. Nanotechnology and osteoarthritis; part 1: Clinical landscape and opportunities for advanced diagnostics. J. Orthop. Res. 2020.
10. Gu, W.; Wu, C.; Chen, J.; Xiao, Y. Nanotechnology in the targeted drug delivery for bone diseases and bone regeneration. Int. J. Nanomed. 2013, 8, 2305–2317.
11. Chang, Ming-Cheng, Ping-Fang Chiang, Yu-Jen Kuo, Cheng-Liang Peng, Kuan-Yin Chen, and Ying-Cheng Chiang. 2021. "Hyaluronan-Loaded Liposomal Dexamethasone– Diclofenac Nanoparticles for Local Osteoarthritis Treatment" *International Journal of Molecular Sciences*

22, no. 2: 665. https://doi.org/10.3390/ijms22020665

12. Maestrelli F, González-Rodríguez ML, Fernández-Romero AM, Mura PA, Rabasco AM, Micheli L, Mannelli LD, Ghelardini C. Curcumin-in-cyclodextrins-in-liposomes: an alternative for osteoarthritis treatment. InProceedings 2020 Dec 1 (Vol. 78, No. 1, p. 52). MDPI.
13. Jyothi VG, Katta CB, Singothu S, Preeti K, Bhandari V, Singh SB, Madan J. Analysis of the therapeutic efficacy of meloxicam-loaded solid lipid nanoparticles topical gel in Wistar rats knee osteoarthritis. Journal of Drug Delivery Science and Technology. 2022 Nov 1;77:103914.
14. González-Rodríguez ML, Fernandez-Romero AM, Rabasco AM. Towards the antioxidant therapy in Osteoarthritis: Contribution of nanotechnology. Journal of Drug Delivery Science and Technology. 2017 Dec 1;42:94-106.
15. Nagalakshmi S, Sandeep T, Shanmuganathan S. Fabrication of Vesicular Drug Delivery of Niosomal Topical Formulation for the Effective Treatment of Osteoarthritis. Nano Hybrids and Composites. 2017 Jan 17;12:1-8.
16. Peng Y, Yang Z, Li J, Liu S. Research progress on nanotechnology of traditional Chinese medicine to enhance the therapeutic effect of osteoarthritis. Drug Delivery and Translational Research. 2024 Jun;14(6):1517-34.
17. Lee CK, Zhang S, Venkatesan G, Chong SY, Wang JW, Goh WJ, Panczyk T, Tay YZ, Hu J, Ng WK, Wacker MG. Enhanced skin penetration of berberine from proniosome gel attenuates pain and inflammation in a mouse model of osteoarthritis. Biomaterials Science. 2022;10(7):1752-64.
18. Liu, L., Tang, H., & Wang, Y. (2023). Nanotechnology-Boosted Biomaterials for Osteoarthritis Treatment: Current Status and Future Perspectives. *International Journal of Nanomedicine*, *18*, 4969–4983. https://doi.org/10.2147/IJN.S423737
19. Corciulo, C.; Castro, C.M.; Coughlin, T.; Jacob, S.; Li, Z.; Fenyö, D.; Rifkin, D.B.; Kennedy, O.D.; Cronstein, B.N. Intraarticular injection of liposomal adenosine reduces cartilage damage in established murine and rat models of osteoarthritis. Sci. Rep. 2020, 10, 13477.
20. Chen, C.H.; Kuo, S.M.; Tien, Y.C.; Shen, P.C.; Kuo, Y.W.; Huang, H.H. Steady Augmentation of Anti-Osteoarthritic Actions of Rapamycin by Liposome-Encapsulation in Collaboration with Low-Intensity Pulsed Ultrasound. Int. J. Nanomed. 2020, 15, 3771– 3790.
21. Sarkar, A.; Carvalho, E.; D'souza, A.A.; Banerjee, R. Liposome-encapsulated fish oil protein-tagged gold nanoparticles for intra-articular therapy in osteoarthritis. Nanomedicine 2019, 14, 871–887.
22. Sun, A.R.; Wu, X.; Liu, B.; Chen, Y.; Armitage, C.W.; Kollipara, A.; Crawford, R.; Beagley, K.W.; Mao, X.; Xiao, Y.; et al. Pro-resolving lipid mediator ameliorates obesity induced osteoarthritis by regulating synovial macrophage polarisation. Sci. Rep. 2019, 9, 426.
23. Lan, Q.; Lu, R.; Chen, H.; Pang, Y.; Xiong, F.; Shen, C.; Qin, Z.; Zheng, L.; Xu, G.; Zhao, J. MMP-13 enzyme and pH responsive theranostic nanoplatform for osteoarthritis. J. Nanobiotechnol. 2020, 18, 117.
24. Kang, C.; Jung, E.; Hyeon, H.; Seon, S.; Lee, D. Acid-activatable polymeric curcumin

nanoparticles as therapeutic agents for osteoarthritis. Nanomedicine 2020, 23, 102104. [CrossRef] Nanomaterials 2020, 10, 2368 15 of 20

25. Geiger, B.C.; Wang, S.; Padera, R.F., Jr.; Grodzinsky, A.J.; Hammond, P.T. Cartilage-penetrating nanocarriers improve delivery and efficacy of growth factor treatment of osteoarthritis. Sci. Transl. Med. 2018, 10, eaat8800.
26. Schneider, T.; Welker, P.; Licha, K.; Haag, R.; Schulze-Tanzil, G. Influence of dendritic polyglycerol sulfates on knee osteoarthritis: An experimental study in the rat osteoarthritis model. BMC Musculoskelet. Disord. 2015, 16, 387.
27. Shin, H.J.; Park, H.; Shin, N.; Shin, J.; Gwon, D.H.; Kwon, H.H.; Yin, Y.; Hwang, J.A.; Hong, J.; Heo, J.Y.; et al. p66shc siRNA Nanoparticles Ameliorate Chondrocytic Mitochondrial Dysfunction in Osteoarthritis. Int. J. Nanomed. 2020, 15, 2379–2390.
28. Shin, H.J.; Park, H.; Shin, N.; Kwon, H.H.; Yin, Y.; Hwang, J.A.; Kim, S.I.; Kim, S.R.;

    Kim, S.; Joo, Y.; et al. p47phox siRNA-Loaded PLGA Nanoparticles Suppress ROS/Oxidative Stress-Induced Chondrocyte Damage in Osteoarthritis. Polymers 2020, 12, 443.
29. Liu, P.; Gu, L.; Ren, L.; Chen, J.; Li, T.; Wang, X.; Yang, J.; Chen, C.; Sun, L. Intra- articular injection of etoricoxib-loaded PLGA-PEG-PLGA triblock copolymeric nanoparticles attenuates osteoarthritis progression. Am. J. Transl. Res. 2019, 11, 6775– 6789.
30. Liu, X.; Corciulo, C.; Arabagian, S.; Ulman, A.; Cronstein, B.N. Adenosine- Functionalized Biodegradable PLA-b-PEG Nanoparticles Ameliorate Osteoarthritis in Rats. Sci. Rep. 2019, 9, 7430.
31. Fan, W.; Li, J.; Yuan, L.; Chen, J.; Wang, Z.; Wang, Y.; Guo, C.; Mo, X.; Yan, Z. Intra-articular injection of kartogenin-conjugated polyurethane nanoparticles attenuates the progression of osteoarthritis. Drug Deliv. 2018, 25, 1004–1012.
32. Maudens, P.; Seemayer, C.A.; Thauvin, C.; Gabay, C.; Jordan, O.; Allémann, E. Nanocrystal-Polymer Particles: Extended Delivery Carriers for Osteoarthritis Treatment. Small 2018, 14, 1703108.
33. Faust, H.J.; Sommerfeld, S.D.; Rathod, S.; Rittenbach, A.; Ray Banerjee, S.; Tsui, B.M.W.; Pomper, M.; Amzel, M.L.; Singh, A.; Elisseeff, J.H. A hyaluronic acid binding peptide-polymer system for treating osteoarthritis. Biomaterials 2018, 183, 93–101.
34. Zhou, Y.; Liu, S.Q.; Peng, H.; Yu, L.; He, B.; Zhao, Q. In vivo anti-apoptosis activity of novel berberine-loaded chitosan nanoparticles effectively ameliorates osteoarthritis. Int. Immunopharmacol. 2015, 28, 34–43.
35. Wang, J.; Wang, X.; Cao, Y.; Huang, T.; Song, D.X.; Tao, H.R. Therapeutic potential of hyaluronic acid/chitosan nanoparticles for the delivery of curcuminoid in knee osteoarthritis and an in vitro evaluation in chondrocytes. Int. J. Mol. Med. 2018, 42, 2604–2614.
36. Zhou, P.H.; Qiu, B.; Deng, R.H.; Li, H.J.; Xu, X.F.; Shang, X.F. Chondroprotective Effects of Hyaluronic Acid-Chitosan Nanoparticles Containing Plasmid DNA Encoding Cytokine Response Modifier A in a Rat Knee Osteoarthritis Model. Cell Physiol. Biochem. 2018, 47, 1207–1216.