REVIEW ARTICLE

Nanotherapy Technology Based Treatment and Drug Delivery Management for Osteoarthritis: A Review

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ABSTRACT

Osteoarthritis (OA) is a chronic disease that affects the cartilage in the joint owing to the cause of age factors, obesity deficiency, genetic disorder, and significantly it reduces the effect of motions in normal functional activities. Today, various treatment methods are followed to prevent this disease's adverse effects, such as exercise, surgery, topical and oral medications, steroidal injections, stem cell therapy, and viscosupplementation. Nevertheless, nonsteroidal anti-inflammatory drugs (NSAIDs) are suggested to overcome the intensity of pain, but it is still limited due to various side effects. Although there is no proper treatment adopted for the long term to permanently eradicate this disease, it is essential to know about the manifestation in both pharmacologic and non-pharmacologic treatments for OA. In spite of various treatments implemented there are many challenges that still remain unclear to completely rehabilitate from this disease, such as the origin of this disease and mechanism. This review aimed to discuss and summarize the significant progression in different treatment methods for OA, the importance of nano therapy, drug delivery systems for OA and highlighted the utilization of carbon nanotubes in OA therapy in order to bring out the noteworthy of nano therapy and demonstrating the importance of various therapeutic strategy followed for OA disease. Hence, a better understanding of treatment modalities for OA will pave the path to emerge new therapeutics in future clinical trials to control this disease and perspicuous view on choosing the treatment methods.

Keywords: Drug delivery system, Nanotherapy, Non-pharmacology, Osteoarthritis, Pharmacology.

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INTRODUCTION

Osteoarthritis (OA) is a chronic disease that occurs when cartilage in the skeletal system begins to crack and induces swelling in synovial membranes. These diseases are particularly found among aged people, and still, many factors associated with the disease need to be understood. The occurrence of OA was spotted to rise drastically due to obesity problems, genetics, and improper lifestyle.[1] The initial indication of osteoarthritis (OA) is pain. Consecutively excessive pain occurs when the cartilage becomes more worn out and showing less fruitful effects with medications or therapies.[2] Stiffness and swelling in the joint are also intermittent, particularly in the early morning. The feeling of breakage or crack over a joint during a normal gesture is usually identified in later stages.[3] The phenomenon and the growing prevalence of obesity among children are likely to contribute to higher OA rates in younger people. The approximate occurrence of diagnosed indication of knee OA was found highest among adults aged between 55 to 64 years, and approximately ranged from 0.37% per year for non-obesity men to 1.02% per year for obesity women. The lifespan occurrence of hand OA with obesity (47.1%, 95% CI 37.8-56.7%) was 11% greater than in people without obesity (36.1%, 95% CI 29.7- 42.9%).[4-5] Inhibitory efforts may need to concentrate highly on decreasing the adverse effect of obesity and on sarcopenic obesity to decrease the knee OA, which is more common.[6] Hand osteoarthritis has been related to the accomplishment of regular activity disability and partly intervene with pain.[7] The corresponding risk of knee OA was 35% for every 5 unit rise in Body Mass Index (BMI), with the effect of magnitude is considerably higher for women than men, as reported by many authors.[8] Recurrent pain in knees shows higher rates of longitudinal degradation of intermediate cartilage in comparison to knees often without pain. These might ultimately hasten the development of systematic disease due to elevated mechanical loading.[9] The consistency of the articular cartilage may be severely affected by enormous load, anxiety, and muscle imbalance.[10] At once, 1,500 mg of glucosamine sulfate taken orally daily is more effective than placebo in treating knee OA but less effective than non-

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steroidal anti-inflammatory drugs (NSAIDs) in OA pain management, particularly for patients with intermediate to severe pain.[11] Diacerein drug is highly effective for knee OA and safe to use for a long time compared with placebo. There were no substantial variations between the consequences of NSAIDs as well as those of diacerein. Also, the quick sign of OA symptoms occurs when the NSAIDs are stopped during the treatment period.[12] Treatment with diacerein substantially decreased the drastic morphologic changes in OA relative to placebo.[13] Chondroitin sulfate (CS) and glucosamine sulfate (GS) combination was not effective as placebo during 6 months of treatment in pain management and reduced physical function in knee OA patients.[14] When compared with placebo, 100μg dose of sprifermine showed less effect in a period of 12 months, and no substantial difference is reported in acute inflammatory reactions between sprifermine and placebo.[15] Celecoxib medication showed a fewer risk of cardiovascular, gastrointestinal, and renal malfunctioning in contrast with ibuprofen and naproxen drugs in patients suffering from osteoarthritis and rheumatoid arthritis.[16] Fulranumab treatment at 3 mg every 4 weeks exhibited reduced pain in a short time frame in connection with hip and knee OA, but at the same time, patients who had taken placebo medication stopped earlier as compared with fulranumab.[17] A single intra-articular of trans-capsaicin (CNTX-4975) 1.0 mg injection were found to be fruitful in providing a substantial reduction in pain that arises when walking in patients with medium to severe OA knee pain.[18] In treating patients with hand OA, chondroitin sulfate is efficient and stable.[19] Muscle building and aerobic workouts are widely prescribed exercise treatment modalities for hip OA.[20] Bones of lower limbs smaller by a minimum 2 cm are at an elevated risk of hip osteoarthritis (HOA) similar to knee osteoarthritis.[21] There is a need for further investigation on the appropriate form and duration of exercise in patients with various stages of the disease and the impact of an activity on disease progression, including consideration of the standard of living outcomes and the cost-benefit of treatment.[22] Bariatric surgery based on the complete weight reduction approach results in significant weight loss, relieves hip and knee discomfort, and also functional outcomes in obesity patients.[23] Increasing emphasis to post-treatment mental health, is required and can contribute to better surgery results, especially among patients with knee and spine osteoarthritis.[24] The challenge of therapeutics development in OA is an overwhelming task.[25] Various therapies are implemented to reduce the adverse effect of osteoarthritides, such as lifestyle modification, surgery, topical and oral medication, steroid injection, and exercise. However, there is no sign of long-term remedy associated with different treatment modalities for this chronic disease. In this review, the significant progression in different treatment methods for OA, importance of nano therapy treatment, drug delivery system for OA, and challenges in treatment methods for OA are discussed to bring out the momentousness of nano therapy and significant advancement in pharmacological effects by various implemented therapeutic management.

Current Therapy for Osteoarthritis Disease

The four key factors that encompass the option against a certain treatment method for osteoarthritis disease are treatment effect, cost, individual condition, guidance from patient's common circumstances.[26] Elderly patients suffering from the adverse effect of osteoarthritis must be equipped with drug free methods as the most important choice of treatment, whether or not including pharmaceutical therapies.[27] Patients who had experiences of chronic joint pain and self-health care prominence are advised to take part in physical activity programs or exercise and physiotherapy treatment to control the effect of pain.[28] Enhancement in self-reported knee uncertainty and a decrease in the anxiety of physical exercise are correlated to therapeutic responsiveness to treatment exercise programs.[29] Lanfeng Huang *et al.* reported that the joint discomfort and severe acute pain were adequately decreased and the knee joint flexibility enhanced with regular quadriceps isometric contraction exercise. Visual analog scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) results exhibited a substantial reduction in pain following 1 month of treatment ($p < 0.05$).[30] Andrea Dell'Isola *et al.* found that patients with knee osteoarthritis (KOA) who had taken home exercise (HE) illustrated a substantially reduced intensity of pain level in contrast with patients who attended education (ED) only.[31] An obvious sign was identified that 12-weeks of Tai Chi and physical therapy led to relatively extended development in pain intensity with negligible positive effects after 2 weeks and significant fruitful effects after 4 to 5 weeks.[32] Martijn F. Pisters *et al.* found that the effect of physical therapy or exercise in the management of chronic pain and functional optimization is not sustained for a long time in patients with hip and knee osteoarthritis.[33] Aerobic or advanced workout may be desirable for enhancing muscle strength and exhibited positive effects on normal functional activities.[34] Staja Booker *et al.* stated that a physical exercise workout exhibited a decrease in pain level and enhanced the normal functional activity with satisfaction in health condition of the patients. However, patients should undergo proper suggested training mode at an appropriate time, guidance, and encouragement to take part in treatment to amplify the health conditions in osteoarthritis pain control administration.[35] Nevertheless, particular exercise adopted to treat osteoarthritis will have remarkable benefits such as reducing the level of pain intensity. However, there is an ambiguity arises in types of exercise to be done and duration of the physical activities to avoid without injury the tissue system as stated by Judith C.Bautch *et al*.[36] There is a significant development in the quality of life for patients suffering from osteoarthritis on the hip following an exercise therapy (ET) for 8 weeks. The patient's gratification was relatively high, especially for people who attended ET.[37] As such, knee joint distraction (KJD) may be joint preservation considerably younger patients of advanced stage knee OA.[38] Doing exercise at home turned to be more effective for elderly peoples with osteoarthritis and stability abnormalities by enhancing the pose movement of the particular workout.[39]

Apart from this, the administration of stinging nettle leaf compared to placebo ($p = 0.026$ and $p = 0.0027$, respectively) has substantially decreased the intensity of pain level and impairment. Harpagophytum procumbens (generally recognized as a devil's claw) is generally sold as an herbal treatment for osteoarthritis as reported by Karen Walker-Bone.[27] Patients who had taken treatment with either ticagrelor or clopidogrel exhibited a 29% lower chance of experiencing OA was observed. A minimum occurrence of osteoarthritis (OA) in ticagrelor-treated patients was observed because of an increase in extracellular adenosine and a repercussion not shown in conjunction with clopidogrel.[40] The acceptable levels of high synovial fluid white cell count (SF-WCC) will distinguish people who are especially to take advantage through intra-articular steroid injection as well as other therapies adopted to treat severe joint pain.[41] Allan Gibofsky *et al.* stated that celecoxib 200 mg/day and rofecoxib 25 mg/day seem to be relatively efficacious in the treatment of osteoarthritis (OA), correspondent with the US drug delivery precautions.[42] Though many clinical studies have shown that intra-articular (IA) injection of hyaluronan (HA) minimizes the stiffness of joints in patients with knee OA, simultaneously indistinguishable outcomes are identified with placebo dissimilarity between hyaluronan and placebo are still ambiguous.[43] Jeanette Ezzo *et al.* suggested that there is a significant indication that real acupuncture is better successful than sham acupuncture in treating inflammation. There's been a lack of information to evaluate regarding acupuncture's effectiveness comparable to different therapies.[44] The inclusion of acupuncture therapy for patients with continuous pain related to knee or hip OA who had been getting general medical routine showed a meaningful and long-lasting improvement.[45] The intensity of osteoarthritis (OA) variations was decreased by calcitonin, and this type of therapy will have positive effects for people who have undergone severe wounding in the knee.[46] T. Pincus *et al.* found that diclofenac combined with misoprostol had significantly shown better enhancements than in patients who had taken acetaminophen at the end result. However, while patients with moderate pain level reported a considerable positive indication with both medications, there is a considerable positive indication.[47] At an advanced stage of osteoarthritis, the utilization of glucosamine and chondroitin as prescribed medications had not come out to minimize the adverse effect of the chronic illness.[48] The increased risk of nonsteroidal anti-inflammatory drugs (NSAIDs) reaction has a substantial adverse effect in mild conditions of osteoarthritis (OA) in comparison to extreme conditions of OA.[49] The extended period intake of NSAIDs has been correlated with progress in the patients' stiffness and physical activity and significant improvement in joint space width (JSW) levels.[50] Indistinguishable joint space width (JSW) impairment was noted in the combined medications (glucosamine and chondroitin sulfate) in comparison with placebo medication. However, joint space width impairment was found higher in patients who have received glucosamine or chondroitin sulphate exclusively as reported by Allen D. Sawitzke *et al*.[51] Patients who disappointed to get sufficient positive effect adequately through paracetamol or topical NSAIDs; chondroitin sulfate and intra-articular treatments are considered to be an appropriate treatment for osteoarthritis.[52] Owing to the application of naproxen, there is a substantial decrease in brain function of subsequent medications with naproxen and also found in regions of the brain typically correlated with the intensity of pain, along with the somatosensory cortex, thalamus, and amygdala.[53] Adult mesenchymal stem cells delivered locally to damaged joints showed significant meniscal tissue rejuvenation and delayed OA's continuous deterioration effects.[54] The gratification of stem cell injection was found to be good enough as reported by the patients with knee osteoarthritis and simultaneously there is an identification of inflammation sign occurrence owing to the effect of the injection.[55] Yancheng Song *et al* reported that mesenchymal stem cells (MSCs) are effectual in reducing the intensity of pain as well as maintaining normal functionality in patients with knee osteoarthritis (OA). The safeness and effectiveness need to be assessed in the view of long term to obtain a fruitful effect before the implementation of extensive use of MSCs therapy in medical application.[56] The utilization of paracetamol, oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs), opioids and intra-articular injections of corticosteroids or hyaluronic acid (HA) often provide concordance strength.[57] In a short period, the utilization of topical NSAIDs in hand and knee osteoarthritis is found to be secure and stable. Additional and supplemental drugs are used to treat osteoarthritis pain, such as S-adenosylmethionine (SAMe), methylsulfonyl-methane (MSM), dimethyl sulfoxide (DMSO), and green-lipped mussel (GLM).[58] Patients who suffered from hand osteoarthritis had a greater relief from pain and improved physical activities due to the application of diclofenac sodium 1% gel (DSG) and vehicle gel (placebo). Topical NSAIDs tend to have better therapeutic acceptability than oral NSAIDs.[59] However, to enhance maximal interincisal opening (MIO) as well as pain intensity in temporomandibular joint osteoarthritis (TMJOA) patients, platelet-rich plasma (PRP) is considered to be an excellent treatment when compared with chitosan. Although the clinical relevance of PRP is found to be indistinguishable as compared with chitosan to enhance joint sensation and condylar bone regeneration.[60] Intra-articular corticosteroid injection (ICI) can be an appropriate treatment for temporary relief from severe pain.[61] Alaa H. Salama *et al.* reported that intake of corticosteroids drug induces a severe adverse reaction in the normal functioning of the nervous system and osteoporosis deficiency. Therefore, etoricoxib injecting anti-inflammatory drugs could be a perfect option to prevent such side effects.[62] Depending upon the effectiveness and safety aspects, corticosteroids remain beneficial for intense about 1 to 2 weeks and perhaps a relatively short duration of reducing the inflammation in 4 to 6 weeks. Although hyaluronic acid is effective towards prolonging the period for positive therapeutic response.[63] A scaffold therapy may be applied for optimal osteoarthritis (OA) treatment by combining electrostatic

activity with cells or nanoscale technology, or cell proliferation. Exosomes therapies are not only an enzyme but also simple to manage as well as to develop for making it an appropriate solution for medical trials.[64] The decrease in pain level was considerably higher, prominent at 1% Hedera helix gel treatment in comparison with a placebo group. However, the reduction of pain level might not have been substantially different in comparison to diclofenac gel-treated patients. H.helix gel and diclofenac gel dramatically minimized the stiffness and activity in contrast to the placebo group as reported by Morteza Dehghan *et al.*[65] With the progression of treatment; injections are commonly utilized; however, the majority of individuals finally prefer total knee arthroplasty (TKA).[66] Current studies in osteoarthritis animal research conducted *in vitro* and *in vivo* investigation of antisense oligonucleotide (ASO) treatment found to be promising in clinical examination. Nevertheless, additional investigation is required in the controlled release of the drug.[67] However, treatment with bisphosphonates such as tiludronate, pamidronate, alendronate, and zoledronic acid has been shown to minimize subchondral bone attrition and bone degradation and retain articular cartilage in several animal model investigations. Although there is quite increment in remodeling, bisphosphonates could perhaps show fruitful effects in an earlier stage of OA.[68] Since the emotional parameters are considered as a major intervention in various treatment modalities, the patients with knee osteoarthritis who have undergone traditional therapy such as aerobic workout, ultrasound therapy, microwave therapy, muscle strengthening exercise, NSAIDs combined exercises demonstrated that the severity of pain is minimum with less adverse effect.[69] Jielai Yang *et al.* suggested that a novel intra-articular management preparation of kartogenin (KGN) loaded GelMA@ Lipo microgels (GelMA@Lipo@KGN) could decrease the mode of injection, thus preserving the effectiveness of KGN against side-effects, simultaneously offering an efficient OA therapeutic approach.[70] A popular herbal medicine, Qiang-Huo-Sheng-Shi Decoction (QHSSD), was found to be useful in treating rheumatoid arthritis (RA) and osteoarthritis (OA). However, biological data revealed that QHSSD can control the variance of osteoclast.[71] Isolated scaphotrapeziotrapezoid (STT) osteoarthritis is an operationally debilitating disease that, when conventional therapy is not effective, it should be treated surgically. Surgical management of isolated STT osteoarthritis that has refused to respond to appropriate therapy results in substantial functioning enhancement, notably in terms of discomfort, without affecting wrist mobility.[72] Nevertheless, 6 weeks of 10 mg prednisolone therapy contributed to a significant decrease in finger pain. In systematic reviews of pain intensity, prednisolone was significantly effective than placebo, with a substantial disparity in the comparison of Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) respondents among groups (72 % vs 33%).[73] Sharif Najafi *et al.* found that botulinum toxin type A was reported to be beneficial and harmless for the management of knee osteoarthritis. There is a considerable reduction in pain and stiffness was reported among elderly people. However, further research is needed to determine the positive effect of botulinum toxin injection for longer fruitful effects.[74] Arthroscopic therapy of elbow osteoarthritis offers acceptable physical results, improves defined functionality, and significantly reduces pain. Performance restoration was higher if the radial head had not been removed. Table 1 shows the strength, grip before and after surgery.[75]

Acetaminophen treatment does not sufficiently alleviate pain in several patients, although the regular consumption of acetaminophen is limited to 4 g. However, the optimistic features of tramadol were equivalent to ibuprofen. The inclusion of topical analgesics, namely capsaicin cream, is considered a supplementary treatment for patients with knee osteoarthritis disease.[76] Brian S. Winters *et al.* suggested that an osteochondral allograft surgical procedure is an alternative way for young patients suffering from adverse effects of arthritis in ankle joints compared with other nonsurgical treatments.[77] Arthroplasty replacement, an effective treatment for the elderly generation, is a challenging course of action in the younger generation and leads to increased inability. Cartilage reconstruction thus tends to be a viable approach to care for young age patients.[78] Inflammation, blood clot in the vein and wound tissue bonding are the main problems that may arise following articular cartilage reconstruction.[79] However, osteochondral allograft transplants surgery in chondral abnormalities contribute to consistent positive results and higher acceptance levels as suggested by Jaskarndip Chahal *et al.*[80] Osteochondral allograft transplantation (OAT) is an important method for preventing specific patellofemoral (PF) osteoarthritis (OA) development. Furthermore, the influence of graft processing on the functional knee movement is still ambiguous.[81] Wenham *et al.* conducted an accessible, clinical trial of 30 patients with knee osteoarthritis who had been using methotrexate for 6 months. Although, six-month results showed a 20% decrease in pain in 50% of patients and a 40% decrease in pain in 37% of patients. Unloader knee braces were utilized in osteoarthritis to attenuate the intensity of pressure in the joint.[82] Previous investigations revealed that following osteotomy procedures can enhance the joint space width. Joint alternation through surgery has increasingly become an important effective procedure among old age peoples, alleviating pain and aiding in the regeneration of activity.[83] C YU *et al.* suggested that microRNA (MiRNAs) could provide significant clinical practice ability and may also possess

Table 1: Variation and strength before and after surgery

Specification	*Before surgery Mean (range)*	*After surgery Mean (range)*	*Reference*
Flexion	119 (85–125)	132 (100–170)	75
Extension	-25 (-80 to 0)	-8 (-30 to 0)	
Overall grip strength, kg	33.1 (10–58)	42.1	
Elbow flexion strength, kg	8.8 (4–20)	15.3 (3–32)	

an innovative approach of managing OA.[84] Intra-articular injection of autologous conditioned serum (ACS) has been shown to be beneficial in reducing the adverse effect of knee OA in most investigations, with a relatively low rate of severe reactions and complications compared with surgery.[85] Also, intra-articular injections of hyaluronic acid manifest strong safety characteristics and have indicated more beneficial in treating knee osteoarthritis. NSAIDs and corticosteroid injections reduce pain for a short duration of time, while viscosupplementation injections alleviate pain for 26 weeks.[86] However, the pulsed electrical stimulation (PES) interface was widely accepted and could offer an efficient non-pharmaceutical to treat osteoarthritis of the knee for 16 weeks.[87] Previous studies have analyzed that S-adenosylmethionine (SAMe) as a possible effective therapy for osteoarthritis that can potentially rejuvenate cartilage.[88] Magnetic pulse treatment is fruitful for patients having knee osteoarthritis, feel less pain and have fewer limitations.[89] Cooled radiofrequency ablation (CRFA) treatment has offered effective pain control, functional improvement and reported beneficial effects over 24 months for patients with knee osteoarthritis.[90] Usage of opioids and antidepressant drugs need attentiveness.[91] Ceruso's procedure is a dermal laceration at a trapezium-phalange joint, somewhat arched in a longitudinal position. This technique provides better strength, firmness, and potential gripping to the first metacarpal. The patients reported no side effects and it is considered as an inexpensive surgery technique.[92] The clinical management of thumb carpometacarpal (CMC) joint osteoarthritis, the abductor pollicis longus (APL) suspension intervention arthroplasty is an effective and simpler alternative compared to certain illustrated techniques. It seems to be simple to incorporate the APL suspension procedure and also to prevent complicated bone excavation and surgical process of flexor carpi radialis (FCR) ligament.[93] Nortriptyline medication showed no improvement to suppress pain level for those affected with knee osteoarthritis. The most specific findings of patients who had taken nortriptyline are dry mouth (87% vs. 51% $p < 0.001$), constipation (69% vs. 30% $p < 0.001$) and perspire (31% vs. 21% $p = 0.033$).[94] The outcomes of ozone injection seem to have been quick and exhibited fruitful effects during two months, but after six months pharmacological effects tend to be are not effective. Platelet-rich plasma (PRP), plasma rich in growth factors (PRGF), and hyaluronic acid (HA) had improved positive effects than ozone injection after 6 months of monitoring. Table 2 shows the satisfaction level among the four groups.[95]

Platelet-rich plasma (PRP) therapy had a little adverse effect on the interleukin 1β (IL-1β) intermediation development of metalloprotease (particularly MMP1, MMP3, and MMP13) and nitric oxide. PRP can enhance the standard of living, particularly in patients suffering from severe condition of OA.[96] Specifically, the biologically active turmeric extraction is as effective paracetamol for enhancing joint functioning and mitigating joint pain in knee OA patients and reported to be secure and quite efficient in significant reduction of C-reactive protein (CRP) and tumor necrosis factor- alpha (TNF-α).[97] Hip lavage accompanied by triamcinolone injection enhances both short and long-term pain and functional capacity for patients with mild hip osteoarthritis (HOA); Hylan G-F20 also enhances the range of motion (ROM) up to one year.[98] Qiang-Qiang Li *et al.* reported that hydroxychloroquine might inhibit swelling and showed a good candidate in the treatment of hand osteoarthritis. It is already utilized effectively in the management of several inflammatory disorders.[99] Especially in comparison to specific cyclooxygenase-2 (COX-2) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, monoclonal nerve growth factor (NGF) antibody offer substantially superior pain control and physical performance in the management of OA. Monoclonal NGF antibodies did not show any extreme adverse events (AEs) such as headache and nausea.[100] An intra-articular injection of sodium hyaluronate and sodium chondroitin (HA-SC) was adequately regulated, and it is secure and reliable in the management of indicative hip OA. Hence, this therapy exhibited to a substantial reduction in the intensity of pain level (VAS) and activity (Lequesne's Index), which began instantly after following up with injection for a period of 6 months.[101] Ziqin Cao *et al.* reported that lutikizumab, the modern anti-interleukin-1α/β dual variable domain immunoglobulin, exhibited no progress in reduction of pain level or activity when compared to placebo. However, very secure and efficient medication for OA is found to be specific cyclooxygenase-2 (COX-2) antagonists and duloxetine. Duloxetine has paved the way for better results, while specific COX-2 inhibitors contribute to enhanced physical activities, and lutikizumab has fewer positive effects.[102] Intra-articular injection (IA) of hyaluronic acid and corticosteroid (HA+CS) in combination with duloxetine vs IA (HA+CS) can offer efficient strategies for alleviating pain and increase knee functionality in patients with KOA and providing effective direction on multidisciplinary pain relief.[103] Also, hyaluronic acid (HA) combined with triamcinolone IA showed a substantial reduction in pain level intensity.

Table 2: The level of appreciation in each of the four groups.

Specification	*PRP*	*PRGF*	*HA*	*Ozone*	*P Test*	*Reference*
Very little	4 (7.7%)	5 (9.8%)	7 (14.3%)	8 (16.7%)	0.06 kruskal-wallis	
Little	9 (17.3%)	8 (15.7%)	8 (16.3%)	7 (14.6%)		
Moderate	10 (19.2%)	9 (17.6%)	12 (24.5%)	19 (39.6%)		95
Much	15 (28.8%)	17 (33.3%)	13 (25.6%)	9 (18.8%)		
Very much	14 (26.9%)	12 (23.5%)	9 (18.4%)	5 (10.4%)		

Prescription-grade crystalline glucosamine sulfate (pCGS) resulted in considerable developments in physical activity.[104] The positive impact of collagen extracts has a certain ability to facilitate as an innovative and appropriate supplementation alternative for OA patients without considering its reliability.[105] In consideration of effectivenes, pelubiprofen CR 90 mg tablet was never subservient to aceclofenac 200 mg in the management of indicative knee osteoarthritis.[106] According to a report, patients who had received an increased dosage of glucocorticoid therapy (21 mg/day) had found dissipated of 27% lumbar spine bone thickness in the course of first-year therapy. Long-term consumption of glucocorticoids, on the other hand, is shown to exhibited severe side effects.[107]

Why Nano Therapy for Osteoarthritis Disease?

Nanoparticles (NPs) are probably the greatest creative biomaterials for osteoarthritis (OA) treatment. The capacity to formulate exceptional nanoparticles for the identification of the earlier stage of osteoarthritic variations in articular cartilage is one of the substantial advantages of nanomaterials.[108] Inclusion of a nanoparticle structure allows for major increases in joint preservation in corresponding to other medical treatments. Nanotechnologies in a medical application have achieved tremendous development and are very promising as an enforceable tool for the sustainable and effective infusion of drugs to OA treatment.[109] Targeted drug delivery to particular body tissues is among the key applications of modified NPs in medication. NPs from fascinating biomaterials are being utilized as a platform in the manufacture of bone tissue as they provide exceptional biological characteristics with encompassing tissues.[110] For a wide range of medical uses, magnetic nanoparticles (MNPs) have historically long been utilized, including cell separation, DNA extraction, gene focusing, drug delivery, and testing. A desirable technique for monitoring, managing, and regulating cells is the interaction of superparamagnetic iron oxide nanoparticles (SPIONs) with stem cells.[111] Magnetic nanoparticles were often utilized to validate chondrocytes in osteochondral deficiency reconstruction for control growth, separation, and rehabilitation.[112] Liu *et al.* reported a decrease in matrix metalloproteinase 3 (MMP-3) in the knee joints of rats followed with intra-articular hyaluronic acid reinforced graphene oxide injection, and considered fair that this consequence is secondary to the macrophages amplification. However, a previous study revealed that PEGylate carbon nanotubes equipped with anti-sense oligomers administered in the knee of osteoarthritis mice exhibited sustained retention of the joint cavity (exceeding 14 days).[113] Similarly, nano therapy inhibited nuclear factor kappa B (NF-κB) protein to minimize cartilage deterioration synovial inflammatory and to alleviate the functional effects of post-traumatic osteoarthritis (PTOA) chronic inflammation as reported by Huimin Yan *et al*.[114] Reza Mohammadinejad *et al.* reported that kartogenin (KGN) nanoparticles (NPPs), synthesized through wet milling and consequently filled with polymer microparticles (320 nm), showed elevated encapsulated drug (31.5 % w/w) and sustained release of drugs (62% for a period of 3 months). In comparison, the nanostructures equipped with p38 MAPK inhibitor (PH-797804) for OA administration (PH-NPPs) are impressive.[108] Ponnurangam *et al*. reported that by treating the defective chondrocytes with cerium oxide (CeO_2), nanoparticles exhibited the anti-inflammatory properties on prolonged chondrocyte inflammation.[115] Although some drugs are considered to exhibited severe consequences, such as methotrexate (MTX) and methylprednisolone, are explicitly applied to arthritis disorders. Carbon nanotubes (CNT) have often used to transmit genomes to chondrocytes when combined with poly (ethylene glycol) PEG (PEG-CNT) and polyethylene imine (PEI-coated).[116] Poly (lactic-co-glycolic acid) PLGA nanoparticles containing HA and ammonium bicarbonate (NH_4HCO_3) are considered fruitful medication for managing knee osteoarthritis. The nanoparticles are low enough, showed a homogeneous dispersion and innocuous both *in vitro* and *in vivo*.[117] Qiumei Lan *et al*. conducted a research and reported that MRC-poly(2-ethly-2oxazoline) - poly(ε-caprolactone)@Psoralidin (MRC-PPL@PSO) nano-micelle stimulated the cell expansion and suppressed inflammatory reactions and inactivating the tumor necrosis factor-α (TNF-α), MMP-3, and MMP-13 reduced the cartilage injuries and also with least OARSI value by a considerable amount after 2 to 6 weeks of post-treatment, demonstrating a cartilage protective and cartilage-targeting therapeutic consequence.[118] Metal-organic frameworks reformed hyaluronic acid charged with protocatechuic acid (MOF@HA@PCA) nanoparticles have the potential to extend the residency period of PCA in the joint space and thus enhance the therapeutic efficacy of OA. MOF@HA@PCA might release the drug according to the severity of disease in reaction to the acidic conditions of OA in joints.[119] Tian Jin *et al*. investigated and reported that hollow mesoporous silica nanomaterials were the perfect carrier for common insoluble drugs and were extremely biocompatible with intra articular injection. The intra-articular injection of celastrol - hollow mesoporous silica nanomaterials-chitosan (CSL@HMSNs-Cs) with enhanced emulsifiable offers a pH-responsive treatment approach targeting osteoarthritis.[120] Cationic polymeric hydrogel has been found to have a higher persistence duration of the drug carrier such as dextran after ionic bridge with nanoparticles in synovial fluid without affecting the characteristics of the fluid.[121] Barbara Crivelli *et al*. found that silk fibroin nanoparticles (SFN) loaded curcumin (CUR) had a synergic antioxidant impact, whereas celecoxib (CXB) were found to be certainly forbidden. There were no considerable variations in anti-inflammatory behavior among CUR-loaded SFNs and CXBs.[122] Feng Zhou *et al*. prepared zeolitic imidazolate framework-8 (ZIF-8) nanoparticles (NPs) and have been reported to conquer synovial M1 macrophages with enhanced persistence period in OA joints by changing the antigen to zeolitic imidazolate framework-8 (ZIF-8). Notably, reformed NPs inhibited the infiltration of M1 macrophages and stimulated M2 macrophages into synovial membrane, thereby impeding cartilage deterioration.[123] The drug release analysis demonstrated that the biodegradable mesoporous silica

nanoparticles reformed with poly(2-methacryloyloxxyethyl phosphocholine) (bMSNs–NH_2@PMPC) can release the pre-loaded drug in a consistent manner. The lubrication study revealed that the bMSNs–NH_2@PMPC had enhanced lubrication characteristics in comparison with the bMSNs.[124] Emine Alarcin *et al*. adopted W/O/W double-emulsion solvent evaporation process to successfully encapsulated oxaceprol into poly (lactic-co-glycolic acid) PLGA nanoparticles for intra-articular (IA) injection in OA management. Furthermore, significantly increased drug loading and wider particulates resulted in the quickest delivery of drugs. Pertaining to cell culture tests, nanoparticles equipped with oxaceprol had no cytotoxicity and showed enhanced bio-compatibility.[125] Dextran sulfate-Triamcinolone acetonide (DS-TA) nanoparticles have been proven to positively minimize the feasibility of functional macrophages (RAW 264.7 cells) and the output of proinflammatory cytokines, comprise such as interleukin 1β (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) in the cartilaginous tissues.[126] The *in vitro* and *in vivo* findings revealed that the designed photothermal-triggered nitric oxide (NO) nanogenerators (NO-Hb@siRNA@PLGA-PEG) (NHsPP) nanoparticles showed regulated NO escape not only in RAW 264.7 cells but also in alive OA mice. In conjunction with certain nano therapy methods, it can provide optical representation for certain inflammatory diseases.[127] Mesoporous silica nanoparticles and polyethyleneimine (MSN-CC-PEI) have effectively transmitted hyaluronan synthase type 2 (HAS2) into synovium and have stimulated endogenic hyaluronan development *in vitro* and *in vivo*. In particular, the higher HAS2 activation sustained for minimum 3 weeks and molecular mass of HA were substantially increased.[128] James McMasters *et al*. conducted a research and reported that sulfate-containing poly(N-isopropylacrylamide) (pNIPAM) nanoparticles have become an efficient medium for the processing and release of penetrated anti-inflammatory peptides with improved storage potential and extended drug release. *In vitro* studies showed that the nanoparticles are effectively absorbed into the endolysosomal chambers of RAW 264.7 cells, enabling the intracellular transmission of KAFAKLAARLYRKALARQLGVAA (KAFAK) loaded towards the particles and also reducing proinflammatory interleukin-6 (IL-6) production after interleukin-1 beta (IL-1β) activation.[129] The possibility of utilizing cationic nanoparticles is an exciting and innovative strategy to achieve improved persistence and continuous release of drug into the knee compartment to manage OA or other rheumatic diseases.[130] In mono-iodoacetate (MIA) - induced OA, nano curcumin may elevate functional modifications, improved cellularity, and boost matrix discoloration of articular cartilaginous. Nano curcumin can be significantly improving the chondro protective consequences of curcumin.[131] Rush L Bartlett II *et al*. conducted a transmission electron microscopy (TEM) study and found that particles comprising 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS) are more homogeneous and retain greater intraparticle size than N-isopropylacrylamide poly(NIPAm) itself. Hence, the inclusion of AMPS could be effectively utilized as a sulfated polymer chain to regulate thermal inflammation, colloidal retention, loading of drugs, and releases of the particulate peptide.[132] A distinguish administration of avidin conjugated drug allows for quick absorption and long-term release within cartilage at lower intertissued levels, thereby minimizing unintended drug access to certain joints tissues. Avidin-dexamethasone (DEX) single administration inhibited cytokine instigate sulfated-glucosaminoglycan (sGAG) deterioration across 3 weeks, retrieved cellular damage caused by cytokines (IL-1α), and preserved sGAG development rates.[133] Diacerein (DC) loaded solid lipid nanoparticles amended with chondroitin sulfate (ChS) (ChS-DC-SLN) composition was 396 ± 2.7 nm in dimension exhibited prolonged releasing of drug for 16 hours and enhanced the bioactivity of diacerein over 2.8 times. In the particular instance of ChS-DC-SLN, rhein concentrations were substantially larger (7.8 ± 1.23 μg/mL) than drug diffusion (2.9 ± 0.45 μg/mL).[134] The chondroitin sulfate (ChS) – chitosan (CS) nanoparticles loaded with fluorescein isothiocyanate combined bovine serum albumin (FITC–BSA) exhibited the better encapsulation efficacy and stable release of the drug.[135] A standard intra-articular injection of polyethylene glycol (PEG)-single-walled carbon nanotubes (SWCNTs) appeared to be effectively penetrated in the thick cartilage extracellular matrix (ECM). PEG-SWCNTs can remain in the joint compartment for a sustained period, penetrate the cartilage cells, and transmit chromosome modifiers to the chondrocytes in healthy and osteoarthritis-affected mice.[136] Rasika M Samarasinghe *et al*. reported that *in vivo* experiments with lakshadi guggul (LG) and alginate encased chitosan–calcium phosphate (LG NCs) showed cartilage regeneration in those provided by nano scale form. Nanocarriers (NCs) turn out to be harmless and no toxic indication to mice decreased joint inflammation and also suppressed matrix metalloproteinases (MMP) and cytokine gene activation.[137] *In vitro* experiments of fish oil protein (FP) and gold nano particles (GNP) integrated with dipalmitoylphosphatidylcholine (DPPC) (FP-GNP-DPPC) showed that FP was emancipated in prompted synovial fluid for an extended period of time. The hydrophilic nature for GNP was enhanced by FP, whereas the combined action of FP-GNP in liposomes escalated the hydrophobic nature.[138] Pranoprofen (PF) – nanostructured lipid carriers (NLCs) PF-NLCs F7 and F10 offered long-lasting exposure, excellent consistency, and optimum skin preservation and also preventing from adverse clinical impacts. Topical PF-NLCs F7 and F10 may provide novel therapeutic strategies for treating localized swelling and infection.[139] The chondrocyte affinity peptide modified PEGylated polyamidoamine conjugate (CAP-PEG-PAMAM) exhibited improved activity of cells and cartilage sensing capacity. CAP-PEG-PAMAM also lasted a considerable period in the joint space and had excellent biocompatibility. The CAP4-PP-RB showed significant efficacy of cell absorption than the PEG-PAMAM-RB.[140] Yan Zhou *et al*. conducted research and reported that an ionic cross-linking approach was used to produce novel berberine chloride (BBR) effectively loaded chitosan nanoparticles (CNs) and *in vitro* studies revealed that

the nanoparticles emitted BBR for a long time and were stable. Hence by using chitosan nanoparticles to load BBR can potentially maximize the efficacy of BBR implementation on anti-apoptosis behavior in rat anterior cruciate ligament transection (ALCT) in combination with medial menisci resection (MMx).[141] Xia Zhao *et al*. reported that chitosan enhanced green fluorescence protein (pEGFP) nanoparticles characteristic examined through fluorescence-activated cell sorting (FACS) study showed that transfection efficacy might achieve a quite higher level; therefore the number of healthy cells might surpass 50% under specific conditions.[142] Blanka Suto *et al*. conducted an *in vitro* testing and found that the ibuprofen loaded nanostructured lipid carrier (IBU-NLC) had greater drug permeability than that of the IBU suspensions. Hence IBU-NLC will be a good choice for treating inflammation joints.[143] Integrated hydrogen peroxide equipped with anti-inflammatory drug dexamethasone and cartilage-derived morphogenetic protein-1 (CDMP-1) showed that the drug-loaded micelle adequately secured the propagation of stimulated macrophage, macrophage apoptosis of antiphlogistic properties and also enabled the bone marrow mesenchymal stem cells (BMSCs) to distinguish within the chondrocytes.[144] Through the aid of collagen- II targeting peptide (WYRGRL), rapamycin and bilirubin loaded MPMW (RB@MPMW) was able to approach cartilage directly and had excellent MR image capabilities to control the treatment actions *in vivo*. Pertinently, the nanostructure exhibited improved chondrocyte vitality metabolic processes by stimulating the AMP-activated kinase–sirtuin 1-proliferator-activated receptor-γ coactivator-1α (AMPK-SIRT1-PGC-1α) signaling process. Moreover, it induces reduced cell apoptosis *in vitro*, also controls cartilage deterioration *in vivo*.[145] The collagen targeting lipid-polymer hybrid nanoparticles (ctLP-NPs) showed that drug delivery was maintained for 48 hr excluding exploding. Indeed while administered towards knee joints of mice with collagenase prompted OA, the drug-loaded nanoparticles significantly minimize cartilage degradation and perhaps relieve the intensity of the disorder.[146] Solid lipid nanoparticles (SLNs) – plasmid DNA (pDNA) facilitates cells development and prevents interleukin- 1β (IL-1β) induced apoptosis through up-regulating integrin β1 in chondrocytes. Compared to certain DNA transmission techniques such as lipofetamin 2000, the SLNs -pDNA structure is less harmful and has the same DNA transmission efficacy.[147] Tongming Chen *et al*. demonstrated that fullerene – molybdenum disulfide (F-MoS_2) nanoparticles had good abrasion resistance, and reduced friction capabilities were found to be substantially improved in the synovial fluid. In contrast to hyaluronic acid (HA), the liquid accompanied by F-MoS_2 nanoparticles had a greater welding load (P_D), reduced wear scar diameters (WSD), and lesser coefficient of friction (μ).[148] 4-arm-poly(ethylene glycol)-maleimide (PEG-4MAL) microgels comprising of poly (lactic-co-glycolic) acid (PLGA) nanoparticles were found to sustained throughout the joint region for minimum three weeks in a rat model afflicted with knee osteoarthritis, as assessed by equilibrium partitioning of an ionic contrast – microcomputed tomography (EPIC-μCT) and simultaneously not causing certain joint debilitating modifications.[149] Han *et al*. reported that when compared to sodium selenium and chondroitin sulphate respectively, the formulated selenium chondroitin sulphate nanoparticles showed higher selenium inducement ability, lower harmfulness towards chondrocytes, and quite efficient in minimizing undesirable cells in chondrocyte.[150] The finding of an *in vitro* osteoarthritis analysis indicates that cartilage deterioration was substantially reduced following intervention with cerium oxide nanoparticles (CeO_2), implying which cerium oxide nanoparticles would defend impaired chondrocytes from oxidative stress as stated by Yi-Wen Lin *et al*.[151] Deyu Zuo *et al*. conducted *in vitro* and *in vivo* study and found that the Prussian blue nanoparticles/low-intensity pulsed ultrasound (PBNPs/LIPUS) combined therapy has improved the protein rates in p-PI3K, p-Akt and p-mTOR, while decreasing protein rates in p-JINK and p-c-Jun and prevent ECM deterioration through decreasing MMPs activity.[152] Mesoporous silica nanoparticles (MSNs) - poly (3-sulfopropyl methacrylate potassium salt) (PMPK) - diclofenac sodium (DS) (MSNs-NH2 @ PSPMK-DS) can enhance the lubricating capacity, although the drug-releasing level is maintained when the thickness in the PSPMK polymer surface is enlarged. Furthermore, the findings of both *in vitro* and *in vivo* experiments showed the DS-loaded MSNs-NH_2@ PSPMK nanoparticles efficiently prevent chondrocytes from deteriorating.[153] The drug release analysis revealed that the poly[N-isopropylacrylamide-2-methacryloyloxyethyl phosphorylcholine] PNIPAM-PMPC nanospheres PNIPAM-PMPC nanospheres can effectively encompass anti-inflammatory drug of diclofenac sodium (DS) and obtained stable condition of delivery. *In vitro*, the PNIPAM-PMPC nanospheres have also been found to be bioactive and also to prevent chondrocytes against cytokine-induced degradation.[154]

Drug Delivery Systems (DDS) for Osteoarthritis

Different forms of intra-articular (IA) drug delivery methods have been established for OA management, particularly nanoparticles, microparticles, liposomes, hydrogels, and micelles.[155] Since osteoarthritis is considered a chronic disorder; nanoparticles have become an excellent medium for developing combinational drug treatments that activate or suppress particular functions in specified tissues.[156] Utilization of polymer-based nanoparticles, liposomes and micelles showed promising results in medical trials. Having certain tendency to promote drug aggregation in particular locations and inherent lubrication characteristics, nanoparticles activated with cartilage bounded peptides and liposomes indeed had desirable effects.[157] Drugs may be integrated into drug delivery systems using traditional compression, spray and dip coating, and encapsulation methods. While developing drug delivery systems, the inserted drug should be stable in the functional condition, biocompatibility, and the optimal release of drug period must be considered crucially.[158] The various methods adopted in drug delivery systems are auspicious if the period of drug delivery throughout the joint region is extended and lowers the necessary injection intensity.[159] According to

previous studies, a significant amount of delivery mechanisms has become refined; however certain issues persist, including drug dissemination without any particular region and drug supply to the bone. Nanomedicine can support drug delivery conditions and have good promise for managing osteoporosis (OP) and other bone disorders because of its capacity to amplify controlled drug activation.[160] However, utilizing an intra-articular regulated delivery method containing polymeric particles will result in longer drug delivery time, reduced toxic effects, and relaxation. Based on the previous investigations, different types of polymers were used to study microparticles and nanoparticle structured drug delivery systems effectively.[161] Intra-articular managed drug delivery systems exhibited desirable advantages such as decreased adverse reactions and toxic effects, minimal tissue susceptibility and regulated active pharmaceutical ingredient (API) activation in contradiction with oral management.[162] Besides this, the findings of the calcein-AM and MTT tests indicated that particle hyaluronic acid (HA) and particle + hyaluronic acid (HA), and diclofenac sodium (DS) preserved cells from hydrogen peroxide (H_2O_2) induced chondrocyte deterioration. Particle-HA and Particle-HA and DS batches displayed optimistic morphological improvements. The particle-HA and DS had more superior performance when compared to certain groups such as phosphate-buffered saline (PBS).[163] Ambika G. Bajpayee *et al*. found that the absorption capacity of avidin in ordinary cartilage was 400 times greater than that of neutravidin. Avidin is an effective illustration of a nanoparticle that can be used to activate and distribute lower molecule mass functionally medications. Secondly, significantly wider shaped particles can be utilized, which could bind within the marginal region of cartilage.[164] Zhen Li *et al*. carried cytotoxicity testing and revealed that the synthesized strontium-based metal-organic framework (Sr/PTA-MOF) had no harmful impact on OA chondrocytes. As a result, Sr/PTA-MOF-Ketoprofen should be regarded as a robust OA treatment process, as it is an effective agent for anti-inflammation, analgesia, and bone steadiness preservation.[165] Corticosteroids delivered through polymer circular frame exhibited that dynamic release motion was relatively slow. Corticosteroid discharge through cyclodextrin polymers showed prolonged retention over all other dextran groups with the maximum extended release for 10 days.[166] Yingyu Zhao *et al*. reported that the retention period of dexamethasone (DS) throughout joint space was considerably increased owing to the influence of molybdenum disulfide nanosheets-Chitosan-Dexamethasone MoS_2@CS@Dex (MCD). Intra-articular injection of MCD in conjunction with NIR radiation resulted in a substantial improvement in the clinical efficacy of DS towards lower consistent dose levels that reduced cartilage degradation induced through inflammation elements such as tumour necrosis factor α (TNF-α) and interleukin 1-β (IL-1β).[167] In comparison to kartogenin (KGN) loaded liposomes (Lipo@KGN), KGN-loaded gelatin methacryloyl (GelMA)@Lipo microgels (GelMA@Lipo@KGN) were able to prolong KGN activation lasting about three weeks and significantly enhance chondrocyte divergence of bone marrow mesenchymal stem cells (BMSCs) *in vitro*. According to the *in vivo* analysis in a rat DMM model, the GelMA@Lipo@KGN may strengthen cartilage rehabilitation and prevent OA development due to its improved presence in the joint as stated by Jielai Yang *et al*.[70] Hai-Yu Hu *et al*. conducted *in vivo* study and revealed that renovating the DOTAM (1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid amide) core including the collagen bonding WYRGRL peptide series will significantly increase the specific accessibility and persistence period of a DOTAM interconnected drug. Hence these drugs have the ability to substantially increase the drug retention period in the joints.[168] Polymer microparticles of 320 nm incorporated kartogenin (KGN) - nanocrystals-polymer particles (KGN-NPPs) have a higher drug load rate of 31.5% (w/w) and prolonged delivery of drugs with 62% for three months. KGN-NPPs could provide better joint preservation in comparison with KGN approach. Although, over dose levels ($100 \times EC_{50}$), KGN-NPPs seemed to not affect the cell feasibility of sophisticated OA human synovial membrane.[169] Ana Henriques Mota *et al*. conducted *in vitro* study and revealed that the discharge of hyaluronic acid (HA) through poly(lactic-co-glycolic acid) PLGA particles showed a consistent pattern. Accordingly, the HA correlation efficacy of PLGA particles with or without oleic acid were 73.6 and 86.2%. *In vivo* anti-inflammatory analysis revealed that HA charged PLGA particles exhibited significantly increased resistance in HA (78 vs 60%).[170] Chondrocyte affinity peptide (CAP) exosomes transmit miR-140 towards deeper cartilage areas by way of thick mesochondrium, suppress cartilage deteriorating proteinase, and slow down the development and adverse effect of osteoarthritis (OA) affected in a rat model, indicating an effective treatment in the progression of OA.[171] Mintao Xue *et al*. investigated and reported that *in vitro* release of rifampicin (RFP) incorporating gelatin hydrogel/tricalcium phosphate bioceramics (TSB) through ternary composites that can be efficiently maintained for an extended duration of span. Furthermore, these composites demonstrated strong biocompatibility for MC-3T3 cellular function *in vitro* and can be utilized for tissue reconstruction *in vivo* in a rabbit model.[172] Xianzhu Zhang *et al*. found that intraarticular injection of yes-associated protein (YAP) detected inhibitor, verteporfin charged chitosan microspheres substantially preserved cartilage equilibrium in OA affected mice model. Verteporfin are considered efficacious in preserving chondrocyte *in vitro* and implies conceivable administration for OA treatment.[173] Pengfei Chen *et al*. stated that *in vivo* analysis of sinomenium (SIN) prevents cartilage matrix deterioration through amplifying autophagy. SIN reduced matrix metallopeptidase 13 (MMP13) and a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS-5) manifestation, which helped to prevent cartilage deterioration.[174] According to the study of FX scanning in rats, the brucine charged PLGA nanoparticles in PLGA microparticles NiMs might remain throughout the articular compartment for about 11 days. *In vivo*, NiMs have the potential to reduce burst release rate and increase persistence with more stable as studied by

Zhipeng Chen *et al*.[175] Zhengxiao Ouyang *et al*. reported that *in vitro*, the synthesised Hesperetin (Hes)-Gadolinium carbonate ($Gd_2(CO_3)_3$) - Polydopamine (PDA)-Polyethylene glycol (PEG) - DWpeptide (HGdPDW) nanoparticles showed strong chondrocyte accordance, and anti-inflammation consequences in response to IL-1β activation by decreasing the expression of cartilage metabolic rate genes, which include Acan, Sox-9, MMP-13, Col2a1 and Col10a1 ensuing inhibiting chondrocyte progression and distinction.[176] Polyethylene glycol – manganese dioxide (PEG-MnO_2) nanoparticles may be able to minimize swelling instigated oxidative stress in cartilage, resulting in improved chondrocyte feasibility and extracellular matrix (ECM) conservation. Perhaps, when the intra-articular injection is stimulated into rat, the particles tend to be sustained in the joint region for one week, despite 75% of a preliminary sensation existing within a joint.[177] However, *in vitro* drug discharge characteristics of cartilage targeting and MMP-13/pH responsive ferritin nanocages (CMFn) - hydroxychloroquine (HCQ) revealed that persistent drug release was noticed and also it increases the drug retaining period to the extent of 14 days to reduce the synovial swelling in the OA joints significantly as stated by Haimin Chen *et al*.[178] The poly(d,l-lactide)-poly(ethylene glycol)-poly(d,l-lactide)-Platelet lysate (PLEL@PL-NPs) formations protected the chondrocytes from inflammatory reactions as well as excessive catabolism beneath interleukin 1β (IL-1β) activation. Such multipurpose composite structure avoids cartilage degradation mostly in initial stage of OA and even in the later stages.[179] Liposomes can be utilized for delivering as well as focusing carriers for anti-inflammatory drugs, allowing them to be administered at reduced levels with less toxic effects.[180] Liposomes have unique characteristics in applying effective drug delivery systems, particularly when made at the nanoparticle scale with innovative and complex strategies and methodologies like the SuperLip emerging technologies.[181] Due to the maximum load effectiveness, hydrogel is commonly employed in a drug delivery platform. For example, microspheres integrated along hydrogel are equipped with anti-inflammatory drugs and administered exactly on the knee joints of OA rabbits. The findings showed that the composite hydrogel have paved the way to discharge the drugs in a regulated way for about 7 days or even more.[182] Rachel H. Koh *et al*. reported that hyaluronic acid embedded with dextran – tyramine (HA-g-DX-TA) hydrogels increased the chondrocyte expansion and extracellular matrix (ECM) development after three weeks of *in vitro* evaluation, especially in comparison to DX-TA hydrogels. Platelet-rich plasma (PRP) carried gelatin-poly(ethylene glycol)-tyramine (GPT) hydrogels exhibited increased manifestation of cannabinoid receptors, CB1 and CB2 that were shown to provide anti-inflammatory characteristics and to reduce the intensity of pain in animal arthritis studies.[183] Efficient, micelle-guided recombinant adeno associated viral (rAAV) SOX9 increased levels improved the accumulation of extracellular matrix (ECM) elements and cell preservation rates, although also beneficially inverting the negative impact of OA cytokines on these pathways.[184] Cristiano Sacchetti *et al*. reported that a single IA injection of polyethylene glycol-single-walled carbon nanotubes (PEG-SWCNTs) were capable to effectively penetrate into the thick cartilage ECM, migrate towards cytoplasm of chondrocyte and produce gene inhibitors into OA affected mice as well as healthy mice.[136]

Challenges in Treatment of Osteoarthritis

The task of developing treatments for OA is overwhelming, including at minimum two purposes. Initially, OA pathogenesis incorporates mechanopathology and indeed the biochemical reaction to physically caused injuries, and these together tend to work to cause joint destruction and discomfort. If either or both of such essential explanatory factors were not approached, treatment will not give a positive approach and lead to dissatisfaction.[25] Nevertheless, to prevent gastrointestinal risks, NSAIDs must be used as minimum as possible. There is an insufficient study to support the utilization of opioid medication and a significant risk of impairment for long-term treatment with an opioid. While paracetamol seems to have better efficacy and security than NSAIDs, the possibility of liver problems is not insignificant at the prescribed limit of 4 g/day.[185] Health professionals prefer to use paracetamol because a certain pharmacological or non-pharmacological treatment, like topical NSAIDs and exercise, may have identical analgesic consequences with less adverse effects. A further challenge is that even though therapeutic options include details regarding treatments that should be administered, those are conspicuously ambiguous about whether particular interventions are necessary and whether different approaches can be combined in a holistic therapeutic strategy.[186] However, inadequate incorporation of multidiscipline programs through health care system environments is a significant impediment to appropriate control guidance adoption. Furthermore, the recommendations may not consider the impact of multiple diseases associated with choosing the treatment.[187] Diabetic patients with broader finger epiphyseal index may become significant harm of radiographic hand interphalangeal joint (IPJ) osteoarthritis development, although the proof is scarce and reports are subjective. Yet, there are no studies to evaluate the development of indicative IPJ osteoarthritis.[188] Standard treatment falls incapable of reaching the clinical needs, and therefore none of the appropriate pharmaceutical treatment is evidenced for the possibility of regenerating the originally formed pattern and functioning of OA cartilage as well as certain synovial tissues.[189]

CONCLUSION

In this review, the strategy of various treatments and their outcomes are highlighted and why nano therapy treatment plays a significant role in the management of OA are also discussed. The development of therapeutic strategies for OA is more challenging due to the disease's unknown origin and including mechanism. Based on previous studies, exercises, NSAIDs, viscosupplementation, injections, surgery, and other advanced therapies showed reduced intensity of pain to only a certain period. Platelet-rich plasma (PRP) is effective

in reducing inflammation, as reported in the previous investigation. Also, the utilization of nanoparticles for the treatment of OA shows improved persistence, continuous release of the drug into the knee compartment, and stable release of a drug. The application of carbon nanotubes in the treatment of OA exhibited excellent mechanical properties, stable release of drug, and restoration of bone both *in vivo* and *in vitro*. However, the toxicity study of carbon nanotubes is more needed in further studies. Many previous research works in different treatment modalities, and various pharmacologic medications have been extensively carried out to suppress OA, but the positive effect of well-established therapeutic platforms was sustained for a limited period only. The challenges remain in a way that there is inadequate evidence to promote the use of opioid medications, and there is a high risk of deterioration with long-term opioid treatment. Hence, future research work should focus on nanotherapy-based techniques in formulating a novel drug delivery system with bioinspired materials for effective management in suppressing osteoarthritis with combined treatment modalities.

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