



Effectiveness of phytoconstituents and potential of phyto-nanomedicines combination to treat osteoarthritis

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ABSTRACT

Osteoarthritis (OA) is a well-known degenerative joint disease recognized by the deterioration of cartilage in the joints, leading to pain and reduced mobility. Traditional treatments for OA include pain management, physical therapy, and in severe cases, joint replacement surgery. In recent years, there has been growing interest in exploring the potential of phytoconstituents and nanomedicines combined for treating OA. Furthermore, with the increasing amount of study in this field, now is the opportune time for the widespread use of plant-derived medications as complementary and alternative medical therapies to be acknowledged and used for more efficient treatment of human ailments like OA. Combining phytoconstituents with nanomedicine technology (phyto-nanomedicine) can potentially enhance their effectiveness in treating OA. The phyto-nanomedicines has many advantages, including enhanced permeability, increased bioavailability, and sustained/controlled drug release at the joint site, decreased adverse effects, and possible use in combination treatment. It's important to note that while there is promising preclinical and some clinical evidence regarding the effectiveness of phyto-nanomedicine in OA treatment, further research is needed to establish their safety and efficacy conclusively. In this review, the effectiveness of phytoconstituents to treat OA and the potential of combining phytomedicines with nanoparticulate drug delivery to enhance the former therapeutic effectiveness is discussed in detail. Furthermore, we have also described briefly on the application of organ-on-chip and/or joint on-chip models to accelerate the identification of novel phytoconstituents and evaluate the potency of phyto-nanomedicines to treat OA.

1. Introduction

By 2023, the prevalence of osteoarthritis (OA) in North America and Western Europe was expected to reach around 20 %. Pro-inflammatory

cytokines are key factors that contribute to the increased generation of inflammatory mediators at the joints [1]. This, in turn, leads to an increase in the production of enzymes that degrade the matrix of the articular cartilage. As a consequence, the cartilage deteriorates further,

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resulting chronic OA [2,3]. It is a challenging pathological condition to treat, since joint cartilage has a limited capacity to rebuild itself. Despite the potential of developing treatment techniques, such as the use of mesenchymal stem cells (MSCs) and tissue engineering (TE) for regeneration of cartilage tissue, these approaches are often expensive and do not effectively replace the joint cartilage. Therefore, there is a growing demand for new, secure, and better options to encourage TE and cartilage joint repair in OA. Long ago, plants were employed as a source of medications, and as of now, some 70,000 species have been examined for their potential as therapeutics [4]. Using bioactivity-based fractionation procedures, various anticancer medicines have been produced from plants in recent years, including paclitaxel, docetaxel, etoposide, and camptothecin [5]. Currently, 8 out of 10 medications used to treat infections, malignancies, cardiovascular diseases, or immunosuppressants are either derived directly from plants or have some connection to them. Notably, 155 anticancer medicines were authorized between 1981 and 2006, with about half coming from natural sources [6]. On the other hand, regulators have finally established that just one in 10,000 examined chemicals is safe and effective to be used in human. There are several instances where pharmaceuticals introduced to the market were withdrawn within a few weeks, months, or even years because of unfavourable side effects. Thus, emphasis on plant-based compounds for drug development has arisen because of the high level of uncertainty, particularly since they are thought to be safer and more potent than synthetic chemicals [4,4,7].

Natural phytochemicals (herbal medicines) have received a lot of interest as innovative therapeutic techniques to treat inflammatory illnesses, such as avoiding OA and age-related cartilage deterioration. Several medicinal plant extract and their single compounds have been reported to have potent anti-inflammatory and antioxidant properties, as well as anabolic potential [8–11]. Moreover, numerous studies have demonstrated the powerful pharmacological characteristics of several plants, including their ability to inhibit inflammation and the catabolic and anti-apoptotic effects of pro-cytokines. These characteristics can be utilized to shield cartilage from these pro-cytokine effects like inflammation, including tumor necrosis factor alpha (TNF- α), interleukin-1 (IL-1), and damaging enzymes, such matrix metalloproteinases (MMPs), as well as the inflammatory mediator, cyclooxygenase-2 (COX-2) [12]. Nowadays, various anti-inflammatory and analgesic drugs are used to treat the pain and symptoms of OA and RA; however, some patients may find it challenging to take these medications for prolonged durations due to their side effects. In addition, the long-term treatment of arthritis with non-steroidal anti-inflammatory drugs (NSAIDs) is not a preferred choice due to its propensity for gastrointestinal, cardiovascular, and nephrotoxic adverse effects. [13,14]. Hepatotoxicity may be brought on by acetaminophen [15]. The central nervous system and gastrointestinal tract may be affected by tramadol [16]. Intra-articular (IA) corticosteroids may not be as effective as advertised in treating OA and can even cause more harm to tissues and joints [17]. Hyaluronic acid injections provide good safety and OA pain alleviation, although they are costly [17]. On the other hand, disease modifying-OA drugs (DMOADs) are very effective as well in treating early rheumatoid arthritis (RA) with modest disease activity. Using them also increases the risk of gastrointestinal, liver, kidney, and blood issues [18]. Although they have poor tolerability and raise the risk of major infection, malignancy, and heart failure, DMOADs are still found to be effective in treating moderate to severe OA [10,18 19,21]. Crucially, several studies have demonstrated that the cytokines, pro-inflammatory, and degradation mediators mentioned are all directly regulated by the major master pro-inflammatory transcription factor NF- κ B. Even more fascinating is the possibility that phytochemicals might effectively stop cytokine-induced extracellular matrix (ECM) degradation in cartilage tissue by suppressing the transcription factor NF- κ B signalling pathway. Using botanical products for therapeutic treatment and prevention has several advantages, not the least: affordability, accessibility to a broad range of people, safety, and lack of adverse effects. Even if it is challenging to carry

out a reliable scientific assessment of herbal medical products, several procedures reported in modern delivery systems have looked at the use of herbal medicines in biotechnology to treat OA and RA more effectively [8,11,22,23]. The results depend critically on how the herbs are prepared, used, and delivered. Tinctures, fatty oils, and other herbal medications are made from powdered, extracted, fractionated, refined, concentrated, or treated for other physical or biological procedures. Studies on the appropriate use of herbal medicines and herbal substances in TE must be considered as a vital and appropriate strategy for the articular cartilage's regeneration and repair. [8,22,24].

Phytoconstituents can provide considerable difficulties while formulating them because of their varied and intricate physicochemical characteristics [25]. These problems can also impact the process of extracting, isolating, characterizing, formulating, and enhancing the bioavailability of the substances. A significant number of phytoconstituents exhibit low solubility in water, which poses challenges in their extraction and formulation into aqueous solutions [26,27]. Factors such as poor absorption, fast metabolism, and quick removal from the body usually limit the bioavailability of phytoconstituents [26,27]. Certain chemicals serve as substrates for efflux transporters, such as P-glycoprotein, which actively remove them from cells, therefore diminishing their efficacy [28,29]. In context of OA, the elimination of a drug after it is injected into a joint area, known as intra-articular (IA) injection, is a vital aspect in determining the drug's and/or phytomedicine effectiveness, and how long it remains active in the joint [30]. Several variables, including the drug pharmacokinetics and pharmacodynamics, as well as the patient's physiological and pathological circumstances, could influence the rapid removal of drug from joints. The production and drainage of synovial fluid, which serves to lubricate the joints, occur in a continuous manner [31]. The frequent fluid renewal can rapidly eliminate the presence of drugs in the synovial fluid. Synovial joints, in particular, provide a robust blood supply that enables efficient elimination of medicines from the joint region and their return to the systemic circulation [32]. Smaller chemicals that can dissolve in water may move more readily from the joint area into circulation. On the other hand, highly lipophilic molecules tends to rapidly absorb into nearby tissues and eliminate themselves from the joint. In addition, the synovial fluid expedites the elimination of drugs with weak protein binding [33]. Notably, OA and other inflammatory conditions can enhance blood flow and vascular permeability in the joints, facilitating the elimination of drugs more quickly compared to the healthy joints. In addition, inflammation may also enhance the flow of lymphatic fluid from the joint area, accelerating the elimination rate of medicines [34]. Thus, creating extended-release formulations that deliver the medication gradually and consistently into the joint are considered to be beneficial in the context of OA. Next, studies frequently reports using nanoparticles, liposomes, or other encapsulating techniques to prolong medication release and improve its permeation and retention within the joint. The process involves modifying the therapeutic molecule to increase its affinity with synovial proteins or decrease its metabolic breakdown. Administering drugs in conjunction with substances or polymers that impede their quick breakdown or improve their accumulation in the joint are highly desirable [35]. In this regard, the utilization of nanoparticles to augment the persistence of medication inside joints is a developing and encouraging methodology in the realm of drug delivery to treat OA. This technique seeks to tackle the problem of sustaining optimal drug levels in the synovial fluid and tissues of joints for extended durations, a crucial aspect in the treatment of disorders including OA, RA, and other inflammatory joint diseases. Therefore, combination of phytomedicine and nanomedicine presents a hopeful approach for treating OA. Through the integration of the inherent healing characteristics of plant-based chemicals with cutting-edge nanotechnology, it becomes feasible to create therapies that are both more potent and less risky for this incapacitating ailment. Herein, we have reviewed recent research on the use of herbal extracts and phytochemicals for OA therapy. Furthermore, the objective of this review is

to elucidate the therapeutic efficacy of established herbal phytoconstituents following their incorporation into various types of nanoparticles, which may serve as an extremely efficient vehicle for delivering former for effectively managing OA.

2. Systemic survey of literature

Two major search engine, PubMed and Scopus were employed to write this comprehensive review. The research, review, and clinical trial-based papers were used combined to prepare the contents for this work. As we searched phytomedicine to treat OA in these search platforms, 50 articles were found from the year 2000–2023, wherein 13 articles were from clinical trial studies. Next, we wanted to search for phytomedicine used for effective articular cartilage regeneration. Four research paper was found from the year 2018–2023. Next, we looked for phytomedicine with anti-inflammatory activities. Notably, 1,428 articles popped up from 1994 to 2023. Similarly, as we typed phytomedicine with analgesic activities, 610 research articles appeared in the search. The results strongly pointed toward two things. First, investigation of phytoconstituents anti-OA has begun in recent years. However, the database is still insufficient to present strong arguments in support phytomedicine for treating OA. Secondly, enough anti-inflammatory, and analgesic activities of herbal medicine have been investigated, and it could be utilized to initiate the study of anti-OA potential of herbal medications. In upcoming years, it can be expected that various plant-based scaffolds could be reported to treat OA.

3. Therapeutic classification of phytoconstituents based on its mechanism of action to manage arthritis

3.1. Anti-inflammatory herbal medicines

Anti-inflammatory herbs have been shown to be useful in fighting inflammatory reactions that cause significant abnormalities in physiological systems [4,4,7,8]. Beneficial features of medicinal plants or their components include sufficient potency, convenience of availability, low cost, few or no adverse effects, and being safer and more efficient than synthetic alternatives [36–38]. These therapeutic plants include phytoconstituents that may prevent and treat unwanted inflammatory conditions [39–42]. Common phytoconstituents in these plants include steroids, glycosides, phenolics, flavonoids, alkaloids, polysaccharides, terpenoids, cannabinoids, and fatty acids [6]. Different mechanisms for anti-inflammatory activity of these active compounds have been investigated. They may synergize or interfere with anti-inflammatory pathway enzymes, factors, and proteins such as lipoxygenases, COX, TNF- α , ILs, PGs, nitric oxide, mitogen-activated protein kinases, and nuclear factor kappa B. Considering all the elements, molecular cellular studies will allow for a deeper understanding of the processes. *Zingiber montanum*, *Juglans regia*, *Aegle marmelos*, *Nelumbo nucifera*, *Curcuma longa*, *Urtica dioica*, *Terminalia chebula*, *Eriobotrya japonica*, *Camellia japonica*, *Vaccinium myrtillus*, and many more are common anti-inflammatory herbal medicinal plants [43–51]. They are thought to be free of adverse effects, in contrast to their chemical equivalents or synthetic anti-inflammatory medications, such as steroids, nonsteroid anti-inflammatory pharmaceuticals, and immunosuppressants used to regulate and suppress inflammatory crises. A thorough phytochemical, pharmacological, and physiological study will allow them to be used safely and effectively in inflammatory situations. Many anti-inflammatory drugs and herbal formulations have been patented, and others are being considered. Because of the high activity of individual bioactive components or the synergistic influence of numerous potent phytochemicals, medicinal plant extracts have substantial pharmacological action, including anti-inflammatory activity [52]. Table 1 lists major phytochemicals and medicinal plants with anti-inflammatory therapeutic potential against arthritis.

Table 1

List of various herbal medicinal plants with potent anti-inflammatory properties.

Herbs	Activity	Reference
<i>Curcuma longa</i> (Turmeric)	In contrast to phenylbutazone, which is employed as an active control measure, the results implied that curcumin may be helpful in lowering clinical signs of RA, such as joint swelling and morning stiffness.	[4,6,53–55]
<i>Zingiber officinale</i> (Zinger)	Compared to ibuprofen and indomethacin, ginger extract showed an equivalent improvement in pain levels in individuals with OA.	[56–60]
<i>Rosmarinus officinalis</i> (Rosemary)	During a 4-week open-label trial, the effects of rosemary extract were evaluated in patients with OA, RA, and fibromyalgia; hs-CRP, an index for the presence of inflammation, was significantly lower in patients who had demonstrated augmentation in this index; incidentally, treatment resulted in a reduction in inflammation related to pain score but not in remission in fibromyalgia scores.	[55,61,62]
<i>Borago officinalis</i> (Borage)	In the first experiment, individuals with RA were given 1.4 g of borage seed oil as a capsule daily or placebo. By the end of six months, the treatment group had improved by 36.8 %. For six months, patients in the consecutive trial received 2.8 g/day of borage seed oil; after therapy, RA symptoms improved in the treatment group by 64 %, compared to 21 % in the control group.	[55,63,64]
<i>Oenothera biennis</i> (Evening Primrose)	Because of sterols like campesterol and sitosterol in this oil, evening primrose oil has stronger reported anti-inflammatory properties than borage oil.	[55,65–67]
<i>Harpagophytum procumbens</i> (Devil's Claw)	Devil's claw root extract is thought to restrict arachidonic acid production and inhibit NO, inflammatory cytokines, PGE2, and eicosanoids, which suppress COX-2 and lessen inflammation.	[55,68–70]
<i>Boswellia serrata</i> (Indian frankincense)	It has been shown that <i>Boswellia serrata</i> extract is beneficial for treating OA. After treatment, there was a notable decrease in the frequency of joint discomfort and swelling, along with an improvement in joint flexibility and walking distance.	[55,71,72]
<i>Rosa canina</i> (Dog rose)	Following treatment with this herb, patients with OA reported decreased pain, stiffness, and the need for rescue drugs to be reduced. CRP levels were also dramatically lowered. Two clinical studies conducted on individuals with OA supported the latter claim. Rosehip powder may be used as a supplement in addition to conventional RA therapies since it has also been demonstrated to lower ESR and enhance the quality of life in RA patients.	[14,55,73,74]
<i>Urtica dioica</i> (Common nettle)	Nettle leaf was investigated in a pilot study to show its anti-inflammatory properties. Individuals diagnosed with acute arthritis were given an oral infusion of <i>Urtica dioica</i> (50 mg) and 50 mg of diclofenac daily. These findings indicate that <i>U. dioica</i> has a remarkable synergistic impact when taken with NSAIDs. It has been	[55,75–78]

(continued on next page)

Table 1 (continued)

Herbs	Activity	Reference
<i>Uncaria tomentosa</i> (Cat's claw)	demonstrated that in chondrocytes, along with nettle leaf, rosehip, and willow bark suppress COX-2 and IL-1. In a 24-week, double-blind, placebo-controlled trial, a highly purified extract of <i>U. tomentosa</i> was administered with sulfasalazine or hydroxychloroquine to evaluate its effects in RA patients; a small benefit of this herb in reducing joint pain, swelling, and tenderness was seen in the treatment group in contrast to the placebo group.	[55,76,79–81]
<i>Salvia officinalis</i> (Common sage)	Carnosol and Carnosic acid have been found to have potent anti-inflammatory activities. By inhibiting microsomal PGE2 synthase-1, these two medicines may have stopped PGE2 production.	[55,82–87]
<i>Ribes nigrum</i> (Black currant)	In a six-week clinical trial involving RA patients, researchers studied the effects of blackcurrant oil (BCO) on patients; the results included a decrease in morning stiffness in the experimental group and a decrease in proinflammatory mediators like IL-1 and TNF- α in peripheral blood monocytes.	[55,88–91]
<i>Persea americana</i> Avocado)/Glycine max (Soybean)	153 OA patients participated in a prospective multicenter, 3-month randomized control study and underwent NSAID and avocado/soybean unsaponifiable (ASU) treatment; after 45 days of therapy, the requirement for NSAID decreased, but there were no substantial improvements in the patients' pain levels.	[55,92–95]
<i>Elaeagnus angustifolia</i> (Russian olive)	Oleaster effectiveness in the treating oral lichen planus (OLP) lesions was evaluated in a randomized controlled trial with 28 patients. There was a 75 % reduction in pain and a 50–75 % reduction in lesion size in the case group. Another randomized clinical trial including 90 female patients with knee OA discovered that the active treatment group dramatically lowered levels of TNF- α and matrix metalloproteinase-1 (MMP-1) (proinflammatory mediators) as well as IL-10 (an anti-inflammatory cytokine).	[40,55,96,97]
<i>Vaccinium myrtillus</i> (European blueberry)	The patient's group's circulating lipopolysaccharide (LPS) concentration reduced, as did hs-CRP, IL-6, and IL-12 levels, according to a randomized clinical investigation on 27 patients with metabolic syndrome who received 400 g of fresh bilberry daily. After six weeks, bilberry resulted in remission in 63.4 % of 13 patients with ulcerative colitis, and a significant decrease in Mayo score and fecal protection level. No changes in anti-inflammatory peptides (monocyte chemotactic protein-1) were seen when people with diabetics were given one capsule of concentrated bilberry extract (36 % w/w anthocyanins) daily.	[55,98–100]
<i>Olea europaea</i> (Olive)	Extra virgin olive oil (EVOO) has been demonstrated to have beneficial effects on postprandial plasma lipopolysaccharide, proinflammatory cytokines, TXB2 and LTB4, and a	[55,101–103]

Table 1 (continued)

Herbs	Activity	Reference
	lower risk of coronary heart disease in healthy and metabolic syndrome patients.	

3.2. Phytoconstituents as analgesic pain medicine

Many chronic pain sufferers turn to alternative therapies that are not covered by the medical system now. These alternative therapies are being scrutinized rigorously as any other evidence-based medical therapy (Table 2). Research conducted across 16 nations found that 67 % of individuals with chronic pain sought therapies other than synthetic allopathic medication [104]. In traditional Chinese medicine (TCM) and other traditional medical systems around the globe, herbal remedies are

Table 2

List of herbal medicinal plants with potent analgesic effect.

Herbs	Activity	Reference
<i>Hypericum perforatum</i> (St John's Wort (SJW))	Serotonin, norepinephrine, dopamine reuptake, monoamine oxidases (MAOs) A and B, and gamma-aminobutyric acid (GABA) receptors strongly have an affinity to the crude extracts of hypericin. It can therefore be utilized for sedative, anxiolytic, analgesic, and antidepressant activity.	[108,109]
<i>Zingiber officinale</i> (Zinger)	Due to its antioxidant function, it may be used to treat bacterial and viral infections as well as colds and muscular pain and swelling, arthritis, headaches, digestive and appetite issues.	[108,110–112]
Capsaicin	Capsaicin is a recognized therapy for several pain problems. Capsaicin causes a reversible and selective loss of nociceptive nerve terminals after prolonged or intense exposure.	[113–116]
<i>Tripterygium wilfordii</i> (Thunder God Vine)	It prevents lymphocytes, macrophages, synovial chondrocytes, and fibroblasts from expressing proinflammatory cytokines, proinflammatory mediators, adhesion molecules, and matrix metalloproteinases.	[117,118]
<i>Petasites hybridus</i> (Butterbur)	The sesquiterpenes in it, notably petasin and isopetasin, are probably the active ingredients. Transient receptor potential ankyrin 1 (TRPA1) channel may be activated by isopetasin, which causes neuropeptide-containing nociceptor stimulation and, therefore, heterologous neuronal desensitization.	[119–121]
<i>Tanacetum parthenium</i> (Feverfew)	Many centuries ago, it was used to cure inflammation, headaches, and, fever. In the latter half of the 20th century, it was rediscovered to treat migraines. The parthenolide found in the leaves is its active ingredient. It may stop platelet aggregation and the release of serotonin from platelets and white blood cells. By preventing the production of prostaglandins and phospholipase A, it may also have anti-inflammatory effects.	[118]
<i>Salix</i> sp (Willow Bark)	Salix is often standardized to salicin, although it also contains flavonoids, polyphenols, and other salicylates. It has been used for its antipyretic, analgesic, and anti-inflammatory properties for countless years. The active ingredients in willow bark extract prevent tumor necrosis factor- α , interleukin 1 β , and prostaglandin E2 from being released by COX-2.	[122–124]

the most often utilized form of pain relief. Tetrahydropalmatine, aloperine, oxysophocarpine, matrine, sinomenine, ligustrazine, evodi-amine, brucine, tetrandrine, stapholidine, and lappaconitine are among the analgesic alkaloids from TCM that are the subject of Jiang et al. study on the mechanism and potential therapeutic applications [105]. Drug-cloud (dCloud) theory was employed by Jiang et al. to provide a clearer picture of these alkaloid mechanisms. dCloud demonstrated the full therapeutic range of multi-target analgesics in two dimensions: “background efficacy,” which includes reducing neuronal inflammation/oxidative stress, inhibiting glial cell activation, re-establishing the balance between excitatory and inhibitory neurotransmission, and curing chronic pain, and “direct efficacy,” which includes blocking ion channels, activating gamma-aminobutyric acid/opioid receptors, and directly inhibiting the pain signal [105]. Empirical studies show that between 30–50 % of people with chronic pain benefit from pharmaceutical combinations. Afterwards, Jiang et al. discussed the potential benefits of analgesic compositions using analgesic alkaloids originating from Chinese medicine for alternative drug discovery models. Compared to opioids, TCM analgesic alkaloids are less harmful over the long term despite their moderate effectiveness as natural compounds [106], making them suitable medication candidates. In South Africa, traditional medicine continues to be the predominant approach for treating inflammatory diseases and pain. Several scientific databases, as well as widely available ethnobotanical literature were used in an extensive search focused on South African ethnobotany. Using 38 sources, the systematic analysis produced a list of 495 plants from 99 families that were hypothesized to be effective treatments for inflammatory-related pain and diseases (such as headache, toothache, backache, menstrual pain, and rheumatism) among South African populations of varied racial backgrounds [107]. Traditional medicine continues to be the focus for treating inflammatory diseases and pain in South Africa [107]. Given its acceptability across all age groups, the expanding global market for herbal medicine, and clinical trials and scientific data to back it, some alternative therapies, like herbal medicine, is suggested to be classified as conventional medicine. However, little is known about how they function, and their use is unreported to medical professionals often and without supervision. Therefore purpose of this section is to provide a list of widely accessible herbal remedies that can be used to treat OA or RA instead of or in addition to prescription painkillers and is enlisted in Table 2 [108].

3.3. Phytomedicine in cartilage tissue engineering

Three essential requirements must be met for tissue construction and regenerative medicine to be viable, *i.e.*, scaffolds, effector stem cells, and signals from the body’s tissues and organs. Scaffolds function in conjunction with organic components of body to assess, heal, improve, or replace bodily tissues or functions, including mature bone stem cells, cartilage, skin, brain, and nerve cells. These platforms aims to correct or alter cell stage and behaviour, *i.e.*, how cells respond to developing forms such as shape arrangement. Additionally, scaffolds serve as blueprints, guiding the development of contemporary tissues by showing them how to be taken care of and ensuring that cells receive the nourishment they need. However, most biomaterials in clinical settings don’t tick all these boxes. Restorative plants have long been fundamental part in numerous societies [8]. Their part in tissue designing builds remains largely unexplored. But since therapeutic plants have proven useful in wound recuperating, pharmaceutical, and anti-aging medicines, it stands to reason that they might also be valuable in OA field. A research group from South Africa investigated two plants *i.e.*, *Eucomis autumnalis*, commonly known as Pineapple Lily, and *Pterocarpus angolensis*, or wild teak. The class *Eucomis autumnalis* has been utilized for centuries to treat bone fractures. It’s widely used as a home remedy for wound healing and post-operative recovery [125]. *Pterocarpus angolensis*, for its part, promotes the organization of cartilage and regulates collagen, which is extensively present in human bones and

cartilage. These plants were mixed with scaffolds and fat cells by the researcher. They found that the two plants enhanced bone production and stimulated the body’s cells. Moreover, they are excellent in healing wounds *in vitro* and do a better job of scaffolding when paired with pertinent signals and stem cells [126]. Table 3 summarizes the medicinal plant with potent cartilage re-engineering capabilities.

Nanofibers have become a viable tool for treating OA because of their distinctive characteristics, such as a large surface area, adjustable mechanical properties, and the capacity to administer medicinal substances [127]. Biomedical engineers can customize nanofibers that look like cartilage’s ECM. This helps chondrocytes stick to the nanofibers, grow, and specialize. Materials commonly used include polycaprolactone (PCL), polylactic acid (PLA), collagen, chitosan, and hyaluronic acid [128]. Further, researchers have found that nanofibers can also hold anti-inflammatory drugs (like NSAIDs and corticosteroids), growth factors (like TGF- β and BMPs), and herbal extracts that are known to protect cartilage [129]. Notably, investigator can control the release of these therapies by fabricating the nanofiber’s content and structure, ensuring their continuous release only in the damaged cartilage area. Additionally, incorporating magnetic nanoparticles into nanofibers allows for precise delivery of healing substances to the injured joint using external magnetic fields [130,131]. These nanofibers have the ability to react to particular stimuli, such as changes in pH or temperature, in order to deliver their therapeutic payload at the exact moment it is required. Nanofibers have the capacity to include extracts derived from herbs such as turmeric (curcumin), green tea (EGCG), and *Boswellia* (boswellic acid), which are renowned for their anti-inflammatory and antioxidant characteristics [132]. The integration of several herbal extracts into nanofibers are expected to augment their overall therapeutic effectiveness, offering a versatile strategy to addressing OA. On the other hand, nanofibers can be designed to provide mechanical reinforcement to the injured cartilage, thereby facilitating the inherent healing process under normal load conditions [133]. Nanofiber-based scaffolds that are well-designed may send mechanical signals that boost chondrocytes activities and ECM synthesis, which will help cartilage heal faster. Nanofiber-based interventions have shown encouraging outcomes even in animal models of OA, showcasing enhanced cartilage regeneration and decreased inflammation [134]. The subsequent stage involves extrapolating these discoveries to human clinical trials, with a specific emphasis on ensuring safety, effectiveness, and long-term results. Next, the integration of nanofiber scaffolds with stem cells, such as MSCs, may accelerate the process of cartilage regeneration [135]. Thus, nanofibers provide a diverse and efficient method for treating OA through structural reinforcement, controlled drug administration, and tissue regeneration stimulation. As research progresses, these technologies have the potential to greatly improve OA therapy management and results.

Hydrogels are networks of highly hydrated polymers that can act like cartilage’s natural ECM [136]. These properties makes them a good choice for treating OA. They can retain a large amount of water, similar to natural cartilage, providing a conducive environment for chondrocyte survival and function. In addition, the mechanical properties of hydrogels can be tuned or adjusted to match those of native cartilage, providing necessary support while allowing for normal joint movement [137]. Hyaluronic acid, collagen, and alginate are commonly used due to their biocompatibility and bioactivity [138]. Formulation Scientist can engineer polyethylene glycol (PEG), polyvinyl alcohol (PVA), and polyacrylamide (PAM) to have specific mechanical and degradation properties [139]. Hydrogels loaded with anti-inflammatory drugs, growth factors, and herbal extracts, are expected to gradually release the therapeutic payload to provide sustained therapeutic benefits [140]. Moreover, modifying the hydrogel’s cross-linking density, polymer composition, and degradation rate can adjust or fine-tune the release profile as desired [141]. When injectable hydrogels are directly administered into the joint space, an *in situ* gel is formed that precisely delivers therapeutic agents. Notably, embedding drug-loaded nanoparticles in hydrogels can improve drug release in a more controlled and

Table 3

List of herbal phytoconstituents with reported cartilage engineering capabilities.

Application of phytochemical in cartilage engineering	Studies and finding
Curcumin	<p>I. It acts as a naturally occurring anti-inflammatory drug for the treatment of OA [154].</p> <p>II. Curcumin-inhibited action of cytokines can be used to maintain the chondrogenic potential of chondrocytes [155].</p> <p>III. Curcumin has anti-apoptotic and anti-catabolic properties. For the treatment of OA and similar osteoarticular conditions, curcumin can potentially be an additional nutraceutical chondroprotective agent [156].</p> <p>IV. A scaffold made of curcumin and silk fibroin was revealed to be an excellent therapeutic option for injured cartilage. The scaffolds were designed with enough mechanical strength and pore size to support cartilage repair. The biocompatibility of the curcumin/silk scaffold was demonstrated, creating an excellent environment for <i>in vivo</i> cartilage repair following transplantation. A functional silk/curcumin composite scaffold may be used as a possible substrate for cartilage healing in cartilage-tissue engineering (TE) [157].</p>
Ginger	<p>I. Ginger significantly decreased pain and OA symptoms compared to the placebo control group and was well tolerated by most OA patients [158]. In chondrocytes and cartilage explants, ginger extract significantly reduced the generation of the pro-inflammatory mediator nitric oxide (NO) and prostaglandin E2 (PGE2) [159,160].</p> <p>II. Zingerone inhibited cartilage inflammation and degradation by lowering TNF-α, IL-6, and IL-8 mRNA expression and decreasing p38-MAPK and c-Jun n-terminal kinase phosphorylation [161].</p> <p>III. Chondrocytes were pre-treated with ginger extract before being co-treated with IL-1. Ginger extract prevented IL-1-induced oxidative stress, mitochondrial changes, and chondrocytes mortality [162].</p>
Icariin	<p>I. Natural extracellular matrix (ECM)/PLLA scaffolds comprising Ica (icariin) and Ica-2-hydroxypropyl-cyclodextrin were created using phase separation, solvent replacement, and freeze-drying. PLLA scaffolds with an inclusion complex of ica-2-hydroxypropyl-cyclodextrin was found suitable for cartilage TE [163,164].</p> <p>II. Ica was added to the chondrogenic medium of bone marrow MSC cells. Ica increases chondrogenesis of bone marrow MSCs, which induces cartilage TE growth factors but not hypertrophy [165]. Ica was used to produce isolated rabbit chondrocytes at various concentrations. Former increases the expression of aggrecan (AGC), COL2A1 and SOX9 genes, which speeds up chondrogenesis. Ica-loaded biomaterials might benefit cartilage TE [166].</p> <p>III. LPS-treated murine chondrocytes were co-cultured with different dosages of Ica. It is a safe chondrocyte anabolic medication that inhibits NO and MMP production and may have protective effects by reducing NO and MMP synthesis, which reduces ECM deterioration [167,168].</p> <p>IV. A porous sodium alginate and gelatin 3D scaffold was created via 3D printing. The cells were treated with Ica. It significantly boosted chondrocyte proliferation, indicating a possible use for cartilage TE [169].</p>
Avocado/soybean unsaponifiables	I HPLC and mass spectrometry examined chondrocytes cultivated for 72 h with/without IL-1 and co-treated with avocado/soybean

Table 3 (continued)

Application of phytochemical in cartilage engineering	Studies and finding
	<p>unsaponifiable (ASUs). Anti-inflammatory and anabolic properties were looked at. ASU enhanced COL2A1 and AGC gene expression, as well as cell proliferation. ASU partly reversed the effects of IL-1 on chondrocytes. The reduction of IL-1 effects corresponded to chondroprotective action [170].</p> <p>II. The capacity of ASU to increase TGF-expression stimulated ECM production. ASU enhanced plasminogen activator inhibitor (PAI-1) production, inhibited MMP, and activated matrix repair pathways in chondrocytes [171].</p> <p>III. The effects of ASU/-lipoic acid (LA) on PGE2 synthesis in horse chondrocytes stimulated with LPS, IL-1, or H₂O₂ for 24 h and supernatants immunoassayed for PGE2. ASU/LA suppressed chondrocyte PGE2 synthesis more efficiently than either alone, related to the reduction of NF-κB translocation. The effect of ASU/LA on PGE2 synthesis can be used as an anti-inflammatory/antioxidant strategy in OA [172].</p>
<i>Punica granatum</i> (Pomegranate)	<p>I. OA chondrocytes or cartilage explants were pre-treated with pomegranate fruit extract (PFE) and co-treated with IL-1. A colorimetric test was performed to determine the level of prostaglandins (PG). The expression of NF-κB was ascertained using EMSA, whereas the expression of MMPs, plkB, and MAPKs was detected using WB. PFE inhibited PG breakdown, MMP protein and mRNA synthesis, p38-MAPK, phosphorylation of inhibitor of kappa B alpha (IκB), and NF-κB binding to DNA in OA cartilage explants [173].</p> <p>II. PFE-fed rabbits showed higher levels of AGC and COL2A1 mRNA expression and lower levels of IL-6, MMP-13, and PGE2 in their synovial fluid/plasma. The injection of PFE significantly suppressed the formation of PGE2 and IL-1-induced MAPK and NF-κB inhibitors, highlighting PFE's chondroprotective significance in the treatment of OA [174].</p> <p>III. PFE enhances the growth of cartilage and bones. After being grown and exposed to PFE, MSCs from fetal limb buds produced more viable cells than in control conditions. PFE-treated cells had more cartilage nodules overall, both in quantity and diameter [175].</p>
Resveratrol	<p>I. To investigate the potential synergistic effects of resveratrol and/or curcumin on IL-1-stimulated human PCH, western blot and electron microscopy (EM) were employed. Both medications obstructed the MAPK and NF-κB signalling pathways. Resveratrol inhibits the proteasome, but curcumin alters the inhibition of MAPK and upstream kinases [176,177]. PCH cultures were grown in 3D-alginate cultures, and resveratrol was produced in ethanol and diluted in the medium. TNF-α, or T-lymphocytes were used to treat PCH alginate cultures, which were then co-treated with resveratrol. TNF-α suppression by resveratrol/histone deacetylase sirtuin-1 (SIRT1), comparable to TNF-α or T-lymphocytes-induced inflammatory milieu in PCH, might be a potential therapeutic method for addressing inflammation during OA/RA [178].</p> <p>II. Osteochondral defects were completely repaired by the collagen/resveratrol scaffold, and the neo-cartilage integrated well with the surrounding tissue [179].</p> <p>III. Resveratrol decreased the synthesis of VEGF, MMP-3, MMP-9, and COX-2 in PCH that had been stimulated by IL-1. By inhibiting IL-1, ROS, p53 production, and apoptosis through</p>

(continued on next page)

Table 3 (continued)

Application of phytochemical in cartilage engineering	Studies and finding
Quercetin (QCN)	NF- κ B downregulation, resveratrol has a chondroprotective effect [180,181]. I. QCN prevents OA formation and progression by preserving the homeostasis of the inflammatory cascade. QCN may thus be a useful treatment drug to stop the development of OA in high-risk individuals [182]. II. According to Hu et al., QCN has chondroprotective effects by reducing apoptosis and inflammation of chondrocytes, altering synovial macrophage polarization to M2 macrophages, and creating an environment that is pro-chondrogenic for chondrocytes to enhance cartilage regeneration in OA patients [183].

sustained manner. Next, incorporating different herbal compounds into a hydrogel matrix can help them work better together as medicines, allowing for a more targeted approach to treating OA [142,143]. Hydrogels that mimic the viscoelastic properties of cartilage can enhance the natural repair processes by providing appropriate mechanical cues. Numerous research based investigations in animal models of OA have shown that hydrogel-based treatments can enhance cartilage regeneration and reduce inflammation [136–138]. Overall, hydrogels loaded with phytomedicines represent a promising therapeutic approach for OA. This plan combines the natural healing properties of plant-based compounds with the advanced features of hydrogel systems to provide targeted, long-lasting, and effective treatment for OA, which leads to better patient outcomes and quality of life.

The integration of phytomedicine with cartilaginous organoids is an innovative method for addressing OA [144]. This technique exploits the regeneration powers of organoids in combination with the anti-inflammatory and chondroprotective qualities of phytomedicines [145]. Cartilaginous organoids are compact and simplified replicas of organs, formed from stem cells or progenitor cells that spontaneously arrange themselves into fully functioning structures. Cartilaginous organoids are often generated by differentiating MSCs or induced pluripotent stem cells (iPSCs) into chondrocytes. The cells are cultivated under circumstances that facilitate the development of cartilage tissue. They closely imitate the structure and functionality of real cartilage. It offers a more biologically accurate setting in comparison to conventional 2D cell cultures. Researchers report either direct loading or a co-culture method to incorporate phytomedicine into the cartilaginous organoids and in direct loading method former is conditioned with phytomedicines or drug of choice before directly loading them for implantation [146]. This entails cultivating organoids in a solution containing phytomedicines in order to enhance their medicinal properties. The co-culture approach involves the cultivation of organoids and phytomedicines together in bioreactors, enabling direct contact and increased therapeutic synergy [147]. Moreover, phytomedicines have the ability to stimulate the transformation of stem cells into chondrocytes in organoids, which aids in cartilage development. Organoids and phytomedicines based unified platform can both increase the production of ECM components like collagen and proteoglycans. These are important for keeping cartilage in good shape. Therefore, the combination of plant-based medication with artificial cartilage structures presents a new and hopeful method for treating OA. This approach aims to revolutionize OA treatment by utilizing organoids' regeneration capacities and phytomedicines' anti-inflammatory and chondroprotective properties.

3.4. Senolytic phytoconstituents to treat osteoarthritis

Cellular senescence is also considered as a crucial factor in the

advancement of OA. Senescent chondrocytes, which are the cells present in cartilage, build up in osteoarthritic cartilage as per the increasing age [148]. These cells after undergoing senescence experience a decline in their capacity to sustain and restore the cartilage matrix, resulting in its deterioration and eventual onset of chronic OA. Moreover, senescent cells can also build up in the synovial membrane, leading to inflammation and deterioration of the joints [149]. To tackle this condition, senolytic medicines that specifically trigger the demise of senescent cells are utilized. These treatments attempt to reduce inflammation and enhance tissue healing by lowering the load of senescent cells in the joint. Preclinical investigations have shown encouraging outcomes with senolytic substances including fisetin, quercetin, and dasatinib in diminishing symptoms of OA and enhancing the condition of joints [150]. Senolytic drugs, which specifically trigger the apoptosis of senescent cells, have attracted attention due to their potential in the treatment of age-related disorders such as OA [151]. Phytoconstituents, which are natural chemicals present in plants, have shown potential as senolytic agents. Quercetin, fisetin, curcumin, epigallocatechin gallate, and resveratrol are some commonly used senolytic drug from plant based sources and these have been frequently reported for treating OA [152,153]. In conclusion, since they can target senescent cells, lower inflammation, and preserve cartilage, phytoconstituents have potential as senolytic drugs in the treatment of OA. To completely comprehend their workings and maximize their use in therapeutic contexts, further investigation is needed.

4. Phyto-nanomedicine and drug delivery confluence to enhance therapeutic effectiveness

The pharmacokinetics of a medication delivered *via* IA route, meaning directly into a joint, requires careful study owing to the unique characteristics of the joint area [33]. Further, injecting a drug or phytomedicines directly into the IA cavity bypasses the need for systemic absorption, resulting in an instantaneous and high local concentration within the joint [30]. Formulations like gels or sustained-release particles can be used to for this purpose. Initially, the drug diffuses into the synovial fluid, which serves to lubricate and provide nutrients to the cartilage and joint structures. Subsequently, the medication is able to infiltrate the synovial membrane and cartilage [31]. The drug's molecular dimensions, lipophilicity, and propensity for binding to joint tissues determine the depth of infiltration. However, enzymes in the synovial fluid are reported to digest drugs. Hyaluronidase, for example, has the ability to break down medications that are based on hyaluronic acid [184]. In addition, the cells that cover the joint capsule have the ability to break down drugs *via* cellular enzymes, which might possibly impact the length and strength of the drug's effects [185]. On the other hand, the lymphatic system eliminates any surplus fluid and solutes, including medications, from the synovial fluid through constant production and drainage. Therefore, drug formulation in the nanoparticulate size ranges are usually designed to increase the system's circulation time, area under the curve (AUC) pharmacokinetics, dissolution/bioavailability, and targeting of phytomedicines or synthetic drugs (Fig. 1). Many of these drug-loaded nanoparticulate vehicles are being investigated to enhance the targeting. Passive targeting prolongs circulation time by disguising the nanoparticle with a coating, such as polyethylene glycol (PEG). By changing its surface, *i.e.*, adding ligands to target particular receptor, active targeting enables a nanoparticle to recognize and stick to certain bodily parts—like cancerous tumors—while avoiding healthy tissue. Notably, cell-specific ligands can be anchored to the nanoparticle's surface to enable it to attach precisely to complement receptors. Furthermore, nanoparticulate vehicles loaded into the formulations like carbohydrate-based polymers or hydrogels are reported provide a longer duration of action by gradually releasing the drug over time. The above-mentioned technologies for medication and/or phyto-nanomedicine delivery are expected to be beneficial in resolving issues with OA therapy. This section will describe the potential

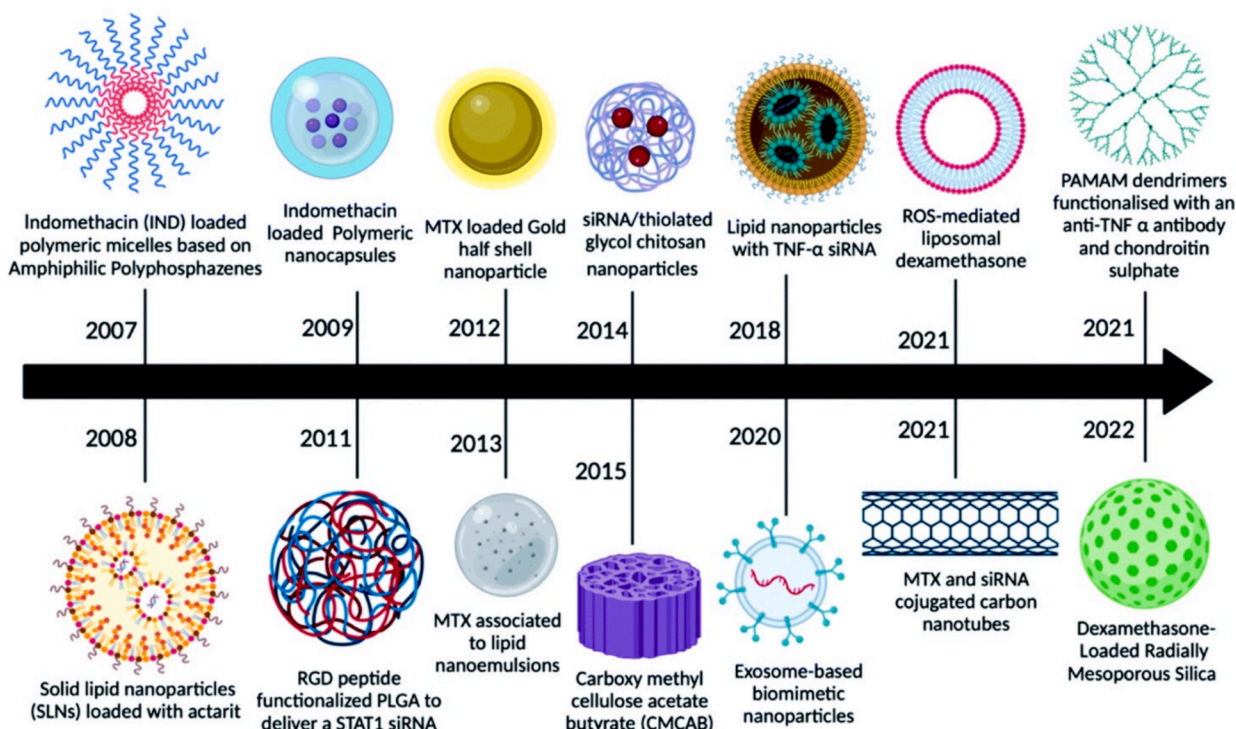


Fig. 1. Several nanoparticles have been developed and used during the last two decades for the treatment or management of several ailments. Figure reproduced with permission and without modification from Nasra et al. [187].

for drug delivery technologies, specifically nanomedicine, to enhance the therapeutic effectiveness of phytoconstituents treating OA [186].

4.1. Parameters to be considered for designing effective phytoconstituent-incorporated nanoparticles to treat osteoarthritis

Articular cartilage has an overall negative charge because it contains glycosaminoglycans, such as chondroitin sulfate and keratan sulfate, which have negatively charged sulfate and carboxyl groups [35]. Moreover, utilizing biocompatible cationic polymers such as chitosan, polyethyleneimine (PEI), or cationic poly(lactic-co-glycolic acid) (PLGA) to induce a positive charge in nanoparticles are reported to facilitate drug penetration into the articular cartilage [188]. Additionally, cationic lipids can also be used to fabricate liposomes or solid lipid nanoparticles (SLNs) that possess a positively charged on the exterior surface. Similarly, the application of cationic surfactants such as cetyltrimethylammonium bromide (CTAB) or polymers to nanoparticles will result in an increase in their positive charge [189]. For further precision, investigator can also consider attaching particular ligands such as antibodies, peptides, or aptamers that have the capability to preferentially bind to cartilage components or OA biomarkers [190]. This can be a unique approach when personalizing the delivery vehicles. In order to get the best possible outcomes, it is advisable to focus on a size range between 50–200 nm. This range enables efficient infiltration into the deep layers of cartilage while also guaranteeing durable preservation [191]. Next, formulation scientists often choose spherical nanoparticles due to their capacity to distribute uniformly and be absorbed effectively by cells. The development of nanoparticles that can selectively release compounds in a controlled way is achieved by using biodegradable polymers or materials that are responsive to changes in pH or temperature, and can adapt suitably to the specific environment [192]. In order to provide strong electrostatic interaction with negatively charged cartilage and avoid clumping, it is vital to maintain a zeta potential within the range of +20 to +40 mV [35]. Moreover, it is advantageous to maintain the stability of nanoparticles under physiological conditions

by limiting rapid aggregation or clearance. Further, it is equally important to choose biocompatible materials and undertake thorough cytotoxicity studies to ensure former safety. By using these specific design principles, it is possible to customize positively charged nanoparticles in order to efficiently treat OA.

4.2. Types of nanoparticles that can be used to improvise delivery of phytoconstituents

Nanomedicine encompasses a diverse range of small-scale materials and technologies specifically designed to diagnose, treat, and prevent illnesses and diseases. Many characteristics, such as the type of nanomaterials used, their specific use, and their functional properties, can categorize them [193]. This section has classified the various nanoparticulate drug delivery vehicles that can be utilized to deliver therapeutically active phytoconstituents to manage OA in detail. Furthermore, in Table 4, the phytoconstituent incorporated nanoparticulate drug delivery vehicles for treating OA and RA has been summarized.

4.2.1. Polymeric nanoparticles

Polymeric nanoparticles are a kind of nanomedicine composed of biodegradable and biocompatible polymers. They usually have a size between 10–1000 nm [194]. Chitosan, gelatin, alginate, albumin, polylactic acid (PLA), polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and polyethylene glycol (PEG) are often utilized to create these nanoparticles [195]. Polymeric nanoparticles can regulate and prolong drug release, thereby increasing therapeutic effectiveness and reducing dosage frequency. It can preserve and protect medications against environmental variables and enzymatic deterioration [188]. In addition, surface modification using targeting ligands (e.g., antibodies and peptides) enables the delivery of specific medications to target tissues or cells. This approach is suitable for a wide range of pharmaceuticals, including proteins, peptides, nucleic acids, and both hydrophobic and hydrophilic chemicals. The common surface

Table 4

The table displays the summary of the reported studies on incorporation of various phytoconstituents in different types of nanoparticulate drug delivery vehicles (phyto-nanomedicine) to treat arthritis [249].

Nanoparticle type	Active Phytoconstituents	Method of formulation	Average Particle diameter	Encapsulation efficiency	Application	References
Polymeric nanoparticles	Triptolide	Ultracentrifugation	98.0 nm	48.6 %	Reduced the cytotoxic effects of the Triptolide	[250,251]
	Curcumin	Ultracentrifugation	79.0 nm	48.6 %		
Nanoemulsion	Curcumin	high-pressure homogenization	150.0 nm	90.0 %	Improved drug permeability and absorption	[252]
	Quercetin	Self-emulsifying	41.1 nm	42.9 %	Improved penetration of curcumin using nanoemulsion	[253]
Lipid core nanocapsule	Resveratrol and curcumin	interfacial deposition of preformed polymer	200 nm		Enhanced physicochemical stability, satisfactory mechanical characteristics, and increased skin permeability	[182]
	Solid lipid nanoparticle	Microemulsification technique	134.6 nm	81.9 %	Reduced toxicity, improved stability and bioavailability	[254]
Liposome	Quercetin	Film hydration and extrusion method	122.3 nm		Enhanced surface area resulted in heightened bioadhesion, thus leading to amplified and sustained cellular absorption, as well as improved bioavailability.	[255]
	Liquiritin	Solvent evaporation method	91 nm	57 %	Enhanced antioxidation	[211]
Microsphere	Quercetin	Solvent evaporation method	91 nm	57 %	These results suggest that optimised quercetin-loaded polycaprolactone microspheres may be the viable strategy for controlled release of quercetin in the joint cavity for more than 30 days by intra-articular injection to treat rheumatoid arthritis.	[256]
	Curcumin	High-pressure homogenization	105.99 μ m		Can be used in OA and RA	[238]
	Quercetin	Thin-film hydration technique and ultrasonication	<400 nm			[239]
Nanocrystals	Resveratrol	Wet media milling technique	270 nm			[240]
	Quercetin		<100 nm		Potent anti-inflammatory efficacy in carrageenan-induced paw edema mode and can also be utilized in OA.	[183]

modification technique improves polymeric nanoparticles' functioning and targeting abilities. The next step is to anchor PEG chains to extend circulation duration by reducing immune system clearance and opsonisation [196,197]. Further, we could incorporate cationic or anionic groups to enhance their interactions with specific cellular constituents or cell membranes [198]. Thus, in nanomedicine, polymeric nanoparticles are a flexible and potent platform that provide a number of benefits for therapeutic and drug delivery uses. The goal of ongoing research and technology developments is to get beyond present obstacles and reach their full capacity in therapeutic environments.

4.2.2. Lipid nanoparticles

Lipid nanoparticles (LNPs) are a kind of nanocarrier that finds widespread usage in drug delivery and other biomedical applications because of their targeted delivery capabilities, biocompatibility, and capacity to encapsulate both hydrophilic and hydrophobic medicines [199]. Usually made of lipids that resemble biological membranes, these nanoparticles are more physiologically compatible with the human body. Types of LNPs are discussed below.

I Solid lipid nanoparticles

One kind of lipid-based nanocarrier that is employed for medication delivery is called solid lipid nanoparticles, or SLNs. Solid lipid cores stabilized by surfactants give them a number of benefits over conventional drug delivery methods [200,201]. The ability of SLNs to encapsulate and safeguard medications, enhance their stability, and provide regulated release is very noteworthy. Lipids such as glyceryl monostearate, glyceryl behenate, stearic acid, and triglycerides; solid at both body temperature and room temperature, form the basis of SLNs [202,203]. On the other hand, stabilizers such as lecithin, poloxamers, and polysorbates prevent nanoparticles in suspension from aggregating, caking, and agglomeration [204]. They can encapsulate drugs that are either hydrophilic or hydrophobic, either on the surface or within the

lipid matrix, and are commonly formulated by high-pressure homogenization, solvent evaporation, solvent injection, and the double emulsion method [205] (Table 4).

II Micelles

Micelles are aggregated colloids formed in solution by the self-assembly of amphiphilic polymers, provide a novel strategy to overcome numerous drug delivery challenges, such as limited water solubility and poor drug permeability through biological barriers (Fig. 2) [206,207]. Moreover, polymeric micelles have a smaller size, faster preparation, and sterilization procedures, and high solubilization capabilities compared to other nanocarriers; yet, they have inferior stability in biological fluids and are more challenging to characterize. Further, studying of their interaction with the biological environment, is essential to predict former true *in vivo* behaviour after therapy, is very difficult [208]. Micelles develops when the concentration of the polymer in solution exceeds a specified threshold concentration known as the critical micellar concentration (CMC). These micelles could be effectively tailored to deliver hydrophobic phytoconstituents adequately to the site of abnormalities and are very easy to produce in commercial settings.

III Liposomes

Liposomes are vesicular structures consisting of bilayers that form on their own when phospholipids are dispersed in aqueous solutions (Fig. 3, Table 4). These are minuscule vesicles entirely encased in an aqueous layer of lipid bilayer membrane. These colloidal spheres called liposomes may hold cholesterol, long-chain fatty acids, sphingolipids, glycolipids, non-toxic surfactants, membrane proteins, and therapeutic compounds in a single nanoparticulate drug delivery platform. Depending on the hydrophilicity of the active pharmaceutical ingredient (API) or phytoconstituents, it is often introduced into the liposome either into the hydrophilic pocket or sandwiched between the hydrophobic bilayers. Moreover, for effective targeting, surface modification

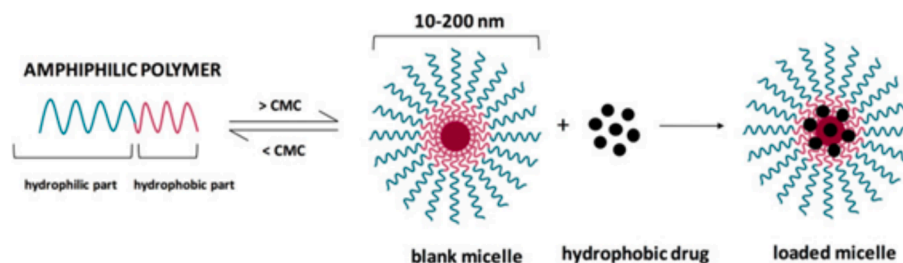


Fig. 2. Graphical illustration of polymeric nanoparticles that can be employed to load phytomedicine to treat osteoarthritis. Figure reproduced without modification and with permission from Ghezzi et al. [208].

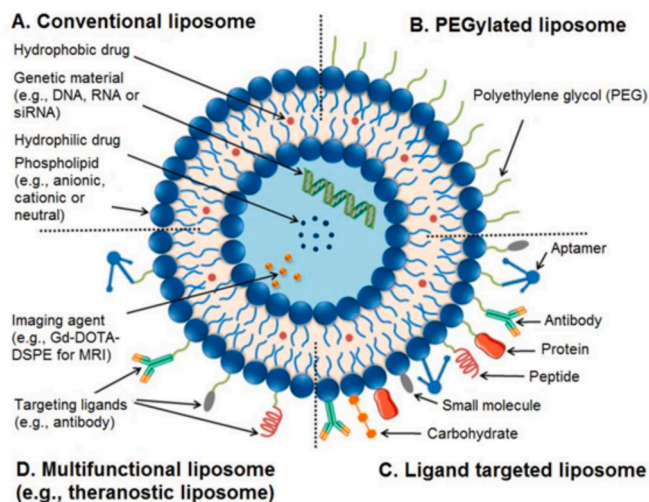


Fig. 3. Conventional and functionalized liposome structures (A) phospholipid-based conventional liposomes; (B) PEGylated/stealth liposomes with a layer of polyethylene glycol (PEG); (C) targeted liposomes with a specific ligand to target a cancer site; and (D) multifunctional liposomes that can be used for solid tumor diagnosis and treatment. Figure reproduced with permission and without modification Olusanya et al. [213].

with different ligands can be done [209]. Li et al. developed injectable liposome-anchored teriparatide incorporated gallic acid-grafted gelatin hydrogel for OA treatment and showed good therapeutic potential of former [210]. Notably He et al. reported photo-cross-linkable methacryloyl groups (ChsMA) microgels anchored liposomes with liquiritin (LQ)-loaded liposomes (ChsMA@Lipo) to delay the progression of OA by dual antioxidation [211]. Similarly, to address joint discomfort, Chang et al. developed a new OA therapeutic formulation called hyaluronic acid (HA)-Liposomal (Lipo)-DIC/DEX. Hyaluronic acid (HA) and DEX-loaded nanostructured lipid carriers Lipo-DIC/DEX were combined to create the formulation for long-term OA use. The nanoparticles had average size of 103.6 ± 0.3 nm, a zeta potential of -22.3 ± 4.6 mV, an entrapment efficiency of 90.5 ± 5.6 %, and DIC and DEX contents of 22.5 ± 4.1 and 2.5 ± 0.6 %, respectively. Research showed that HA-Lipo-DIC/DEX could release the medication for at least 168 h while maintaining an effective working concentration in 4 h. Co-culturing HA-Lipo-DIC/DEX with articular chondrocyte cells resulted in no discernible toxicities but did enhance the number of cells [212].

IV Nanoemulsion

Nanoemulsion formulations offer several benefits, such as administering of biological agents, medications, and diagnostics (Fig. 4, Table 4) [214–217]. This advanced medicine delivery system was developed to address many significant issues with conventional drug administration techniques, such as solubility, permeability and bioavailability. In addition, nanoemulsion are most frequently used to cover up the unpleasant taste of fatty liquids. Further, they can protect drugs or

molecules that are susceptible to oxidation and hydrolysis and also enhances the solubility and permeability of BCS class II and IV drugs. Mohammadifar et al. demonstrated that nanoemulsion containing essential oils of peppermint and rosemary reduces OA pain via increasing antioxidant capacity and improving the histopathological features of the rats' knee joint [218]. Similarly, Rivera-Pérez et al., reported that incorporation of curcumin into nanoemulsion followed by microencapsulation enhanced its absorption and therapeutic benefits in OA. Next, Faheem et al. developed naproxen and gaultheria oil based nanoemulsion to treat OA, and suggested nanoemulsion to be better option for delivering the former [219]. Future studies and development pertaining to the application of phytomedicine in nanoemulsion for OA treatment are anticipated to increase greatly in near the future [136].

4.2.3. Metallic nanoparticles (MNPs)

Metal nanoparticles (MNPs) are nanoscale particles made of metals, usually with sizes between 1–100 nm [221]. Their distinctive physical, chemical, and biological characteristics render them advantageous for a range of biomedical uses, such as medication administration, treatment, and diagnosis. MNPs may be synthesized in a variety of forms and sizes, such as cubes, spheres, and rods, which will affect their characteristics and uses. With a variety of biological uses, the MNPs include gold (Au), silver (Ag), iron oxide (IO), platinum (Pt), copper, zinc, titanium, and cerium nanoparticles [222]. When it comes to treating OA, MNPs have a great deal of promise. MNPs' unique qualities, such as their large surface area, reactivity, and capacity for functionalization, enable a variety of applications in the treatment of OA. It is reported that, AuNPs modify inflammatory pathways in osteoarthritic joints, and subsequently they produce pro-inflammatory cytokines and mediators less frequently [223]. AgNPs have anti-inflammatory qualities and have the ability to lower oxidative stress, which can halt the advancement of OA [224,225]. Nevertheless, iron oxide nanoparticles (IONPs) can aid in cartilage regeneration and repair by delivering growth factors or stem cells. The antioxidative qualities of platinum nanoparticles (PtNPs) may protect cartilage cells, or chondrocytes, from oxidative stress-induced damage [226]. Therefore, phytomedicine-incorporated MNPs must be evaluated systematically both *in vitro* and *in vivo* studies, to establish former in OA and RA treatment.

4.2.4. Nanotubes and nanofibers

Long, cylindrical nanostructures with distinct mechanical, electrical, and thermal characteristics are known as nanotubes and nanofibers [227]. Because of their potential for tissue engineering, regenerative medicine, and drug delivery, they have attracted a lot of attention in a variety of sectors, including biomedical applications. Carbon atoms organized in a hexagonal lattice form the cylindrical nanostructures known as carbon nanotubes (CNTs). Their distinct mechanical, electrical, and thermal characteristics render them immensely advantageous in several domains, including the biological and medical arena. In tissue engineering, CNTs are utilized to strengthen scaffolds by giving them mechanical strength and encouraging cell adhesion, proliferation, and differentiation. The electrical conductivity of CNTs is advantageous for

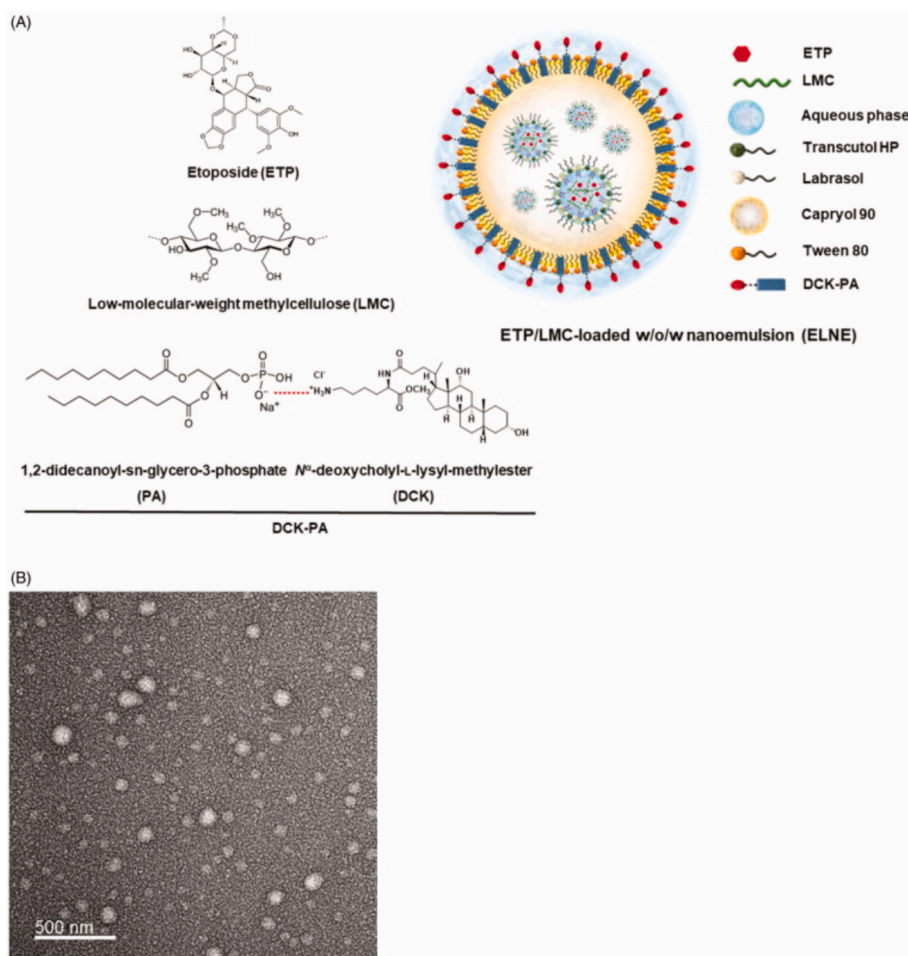


Fig. 4. The graphical illustration of incorporating plant-based anticancer drug i.e., etoposide into the nanoemulsion. Figure reproduced with permission and without modification from Jha et al. [220].

the tissue engineering of electrically active tissues, including heart or brain tissues [228]. Drugs or phytoconstituents could be incorporated into or placed onto CNTs for regulated, long-term release that prolongs therapeutic benefits and lowers administration frequency. By directly delivering painkillers to the injured joints, CNTs can increase patient comfort and range of motion. Scaffolds for cartilage tissue engineering can also include CNTs and their surface could be functionalized to encourage chondrocyte (cartilage cell) cell adhesion, proliferation, and differentiation, while their mechanical strength maintains the scaffold's structural integrity. By electrically stimulating chondrocytes, CNTs' electrical conductivity could promote their proliferation and matrix synthesis, both of which are advantageous for cartilage regeneration [229]. In addition, stem cells can also be administered to the injured cartilage using CNTs. By enhancing stem cell survival and integration in the joint environment, they are expected to encourage cartilage regeneration and repair [230].

Nanofibers are elongated nanostructures that may have lengths ranging from micrometres to centimetres with diameters generally ranging from 10–100 nm. They are made from a variety of materials, including as metals, ceramics, and polymers. Because of their special qualities and wide range of uses in a variety of industries, such as materials science, biomedicine, and the environment, nanofibers have attracted a lot of attention. Moreover, due to their very high surface area-to-volume ratio, nanofibers may be used in filtration, sensing, and drug delivery—applications that need strong surface contacts [231]. Former tiny diameter gives them special optical, mechanical, and electrical qualities that set them apart from their bulk counterparts. High

porosity and linked pores are common features of nanofibrous materials, which may be useful for processes like tissue engineering and filtration. In addition, it is possible to load nanofibers with pharmaceuticals or bioactive compounds to provide targeted and controlled release [232]. Notably, when compared to conventional dressings, wound dressings based on nanofibers provide improved breathability, moisture retention, and biocompatibility. Anti-inflammatory drugs or phytoconstituents can be encapsulated in nanofibers and delivered straight, over time, to the injured joints. Moreover, to preserve and regenerate cartilage, nanofibers may transport medications that alter disease progression, such as matrix metalloproteinase inhibitors or growth hormones. On the other hand, drugs or phytoconstituents can be kept at therapeutic concentrations in the joint area for longer periods of time by controlled release from nanofibers, which improves the therapeutic effectiveness [233]. Next, by imitating the ECM found naturally in cartilage, nanofibrous scaffolds provide chondrocytes a favourable environment in which they can develop and differentiate well. Apart from these, for load-bearing applications in joints, nanofibers can also be reinforced with ceramics or polymers to increase mechanical strength and stability. Notably, MSCs and other cell types can also be transported *via* nanofibers, which improves their survival and retention in the joint environment [234]. Overall, because of their special qualities and capacities in medication administration, tissue engineering, pain management, and diagnostics, CNTs and nanofibers have intriguing prospects for the treatment of OA. The treatment results and quality of life for patients with OA might be greatly enhanced by CNTs and nanofibers by resolving issues with biocompatibility, drug loading, and regulatory approval. To achieve

these nanomaterials' full therapeutic potential in OA treatment, further *in vivo* investigation and advancement are necessary.

4.2.5. Nanocrystals

Because of a higher surface-to-volume ratio, crystalline nanoparticles or nanocrystals may increase bioavailability, permeability, and solubility (Fig. 5). All the frequently utilized administration routes, including oral, injectable, pulmonary, ophthalmic, and topical administration, include crystalline nanoparticles as a viable delivery method. Moreover, nanoparticle aqueous dispersions may be made into tablets, capsules, fast melts, and lyophilized products for use in sterile applications [54,235]. Pharmacokinetic characteristics of nanocrystals can vary from being quickly soluble in blood to slowly dissolving; in the latter case, drug delivery is prolonged, while peak height is limited by macrophage absorption and subsequent drug release. This increases efficacy in several drug types, permits greater dosages, and enhances safety. Nanocrystals can concentrate therapeutic substances in certain areas through surface and size modification. This section focuses on formulations based on nanocrystals that are meant to be administered by various routes, such as liquid nanosuspensions and, upon additional processing, as solid dosage forms. The literature suggests the medicinal uses of pharmaceutical nanocrystals, emphasizing their applicability as a formulation methods for poorly soluble drugs [236,237]. Another delivery technique that may increase the bioavailability of both hydrophobic and hydrophilic medications is lipid-based liquid crystalline nanoparticles (LCNPs). These are self-assembled structures formed by spreading a nonlamellar liquid crystalline matrix at high shear energy into the water phase. Curcumin, a constituent derived from turmeric, has limited solubility in water and demonstrates low levels of bioavailability [238]. Nanocrystals have boosted curcumin's solubility and improved its medicinal benefits. Similarly, quercetin, present in several fruits and vegetables, has antioxidant and anti-inflammatory characteristics. Researchers have created Quercetin nanocrystals to improve its solubility and bioavailability [239]. Additionally, researchers have also reported that nanocrystals enhance the stability and

bioavailability of resveratrol, which is present in grapes and berries and has anti-aging and cardioprotective properties [240]. Thus, nanocrystals provide a potential approach to improve the delivery of phytochemicals by resolving issues related to their solubility, stability, and bioavailability. Although there are notable benefits, this technique also encounters challenges linked to manufacturing, regulations, and costs. Further investigation and innovation in this field have the potential to result in enhanced and readily available phytochemical treatments for managing OA.

4.2.6. Dendrimer

Dendrimers are molecules with many branches radiating from a central core. The name comes from the Greek words dendron, meaning "tree", and meros, meaning "part". Dendrimers are polymers, but they are not the same as the linear network of monomers that make up all these plastics (Fig. 6, Table 4) [242,243]. To make polyethylene and other related materials, monomers are linked by forming "cross-links" between long molecular chains. Dendrimers may seem simple and attractive, but they are huge, intricate, and time-consuming. It must be constructed step by step, beginning with the proper monomers and gradually adding additional components. A dendrimer is made up of three main components: The core lies at the centre, with branches flowing from it and terminating in end groups. These abilities include modifying components, particularly end groups, to produce polymers with sophisticated physical and chemical characteristics [242,243]. Because of their special qualities and many uses in drug administration, imaging, diagnostics, anti-inflammatory therapy, and tissue engineering, dendrimers offer great promise for the management and treatment of OA. In addition, dendrimers can be used in biosensor systems to identify OA biomarkers in biological fluids such as blood or synovial fluid. This enables disease activity and treatment responses to be tracked [244]. Due to their excellent sensitivity and specificity, dendrimer-based biosensors make it possible to precisely quantify OA biomarkers in clinical samples. Using dendrimers, pro-inflammatory cytokines (such as TNF- α and IL-1 β) may be targeted using siRNA or small-molecule

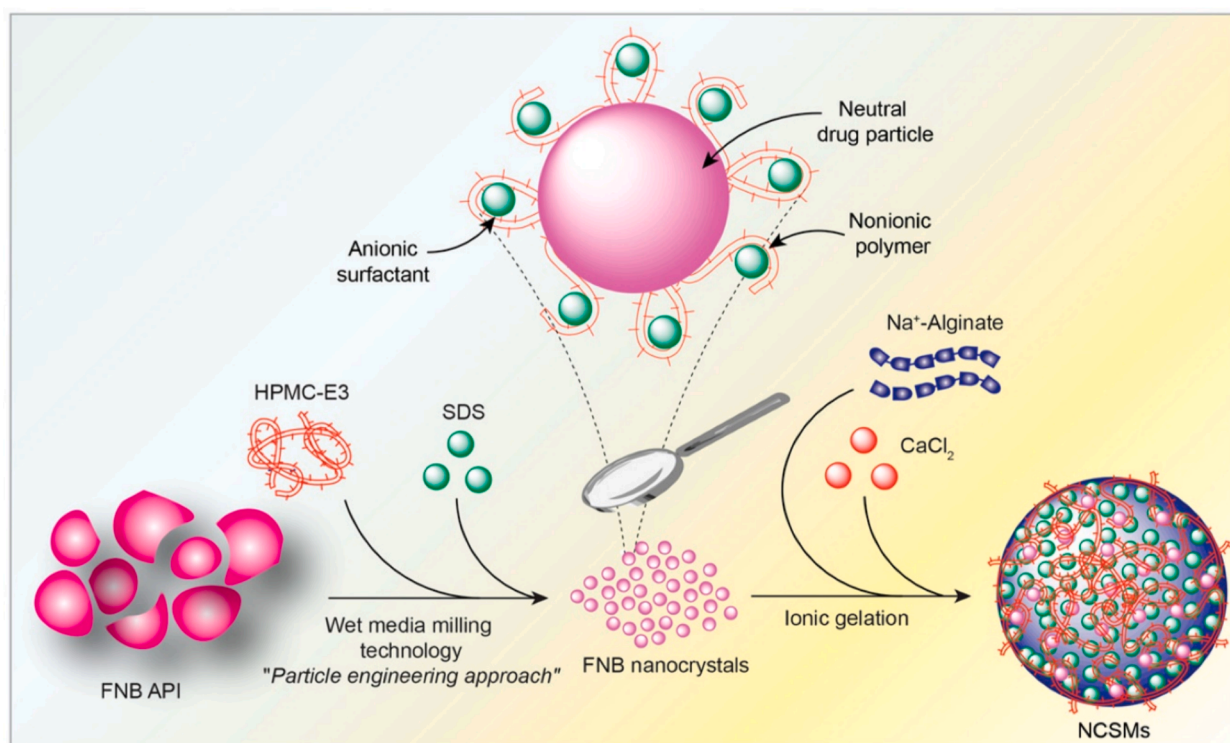


Fig. 5. Fenofibrate nanocrystals (FNB-NCs) are encapsulated, and this causes nanocrystals to develop in composite spherical microparticles (NCSMs). Figure taken from Kevadiya et al. with permission and without alteration [241].

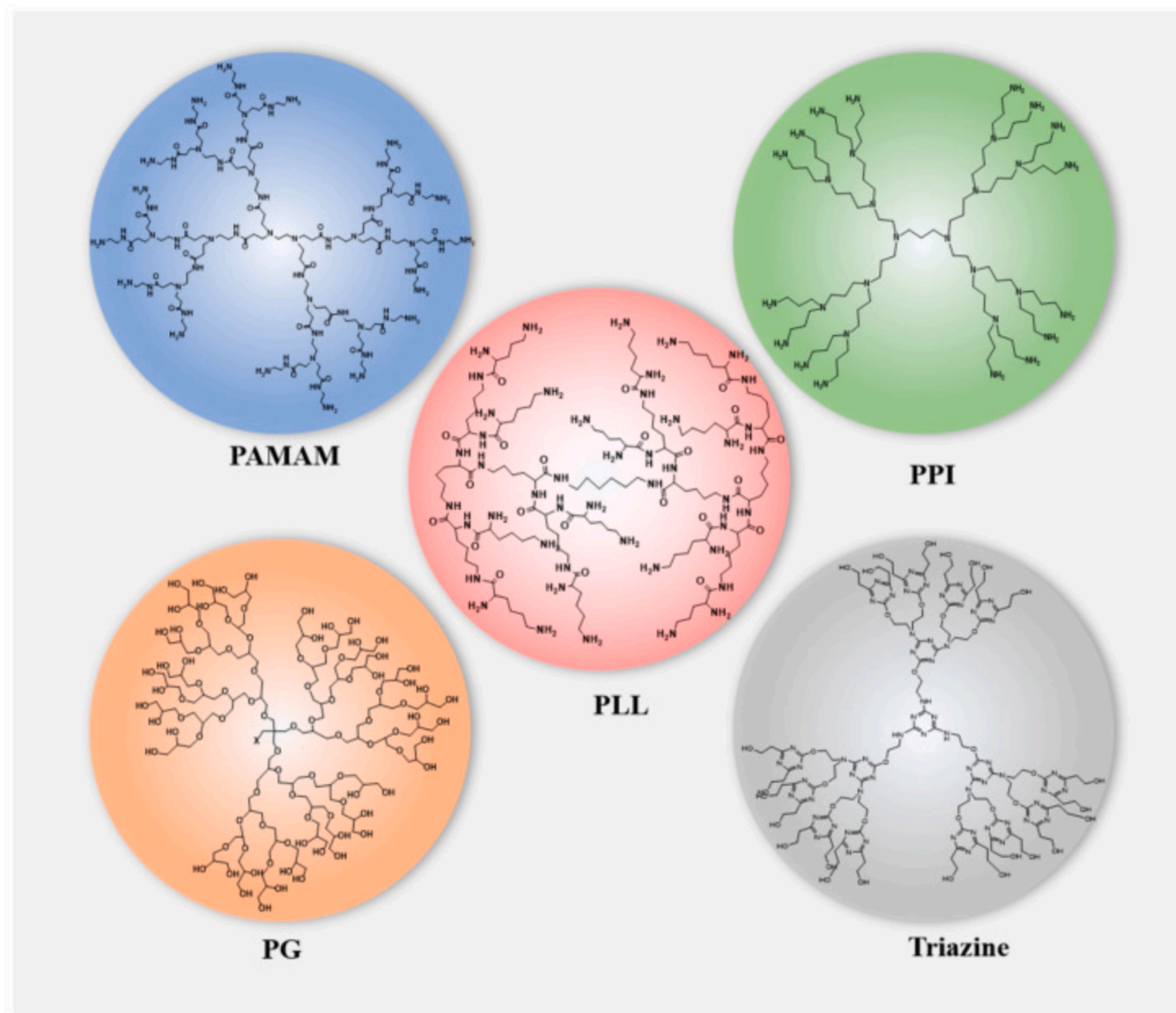


Fig. 6. The graphical representation of various dendrimers. Phytomedicine can be incorporated into the dendrimers and delivered at the joint site via intra-articular (IA) injection. Figure reproduced with permission and without modification from An et al. [242].

inhibitors to lessen joint inflammation, relieve pain, and delay the course of illness [245]. Dendrimers containing siRNA molecules have the ability to specifically silence genes linked to inflammatory pathways, offering an OA treatment strategy that is more focused on reducing inflammation [246]. In cartilage tissue engineering applications, dendrimers can enhance the mechanical strength, biocompatibility, and cell adhesion of scaffold materials. The incorporation of growth factors or cell-adhesive peptides onto the surface of dendrimer-based scaffolds may promote ECM formation and chondrogenic differentiation in encapsulated cells [247]. Oliveira et al. aimed to develop poly(amidoamine) dendrimers (PAMAM), functionalised with chondroitin sulphate (CS), lined with anti-TNF α antibodies (Abs) to provide anti-inflammatory properties. Physicochemical characterisation demonstrated that anti-TNF α Abs-CS/PAMAM dendrimer nanoparticles were successfully produced. The *in vitro* studies revealed that CS/PAMAM dendrimer nanoparticles did not affect the ATDC5 and THP-1 cell lines' metabolic activity and proliferation, presenting good cytocompatibility and hemocompatibility. Moreover, anti-TNF α Abs-CS/PAMAM dendrimer nanoparticles showed suitable TNF α capture capacity, making them appealing for new immunotherapies in RA patients [248].

4.3. Advantages of nanoparticles for the delivery of phytomedicines

(I). Enhanced Bioavailability: Phytoconstituents often exhibit low absorption levels when taken orally. Nanomedicine has the potential to enhance the solubility and stability of these drugs, hence promoting improved absorption and bioavailability. Ensuring precise administration of therapeutic dosages to the afflicted joint is of utmost importance (Fig. 7) [257,258].

(II). Targeted Delivery: Nanoparticles could be engineered to selectively target the damaged joint tissue. This focused delivery method reduces the amount of contact with healthy tissues and increases the concentration of phytoconstituents specifically at the location of OA pathology. It mitigates the likelihood of systemic adverse effects [257,258].

(III). Sustained Release: Controlled-release nanoparticles might have an extended therapeutic impact. OA is a long-lasting disease, and continuous drug release may help maintain a steady amount of phytoconstituents at the joint, hence minimizing the need for frequent administration of drugs [141255,258].

(IV). Reduced Side Effects: Nanomedicine can mitigate the overall negative effects caused by phytoconstituents by targeting the

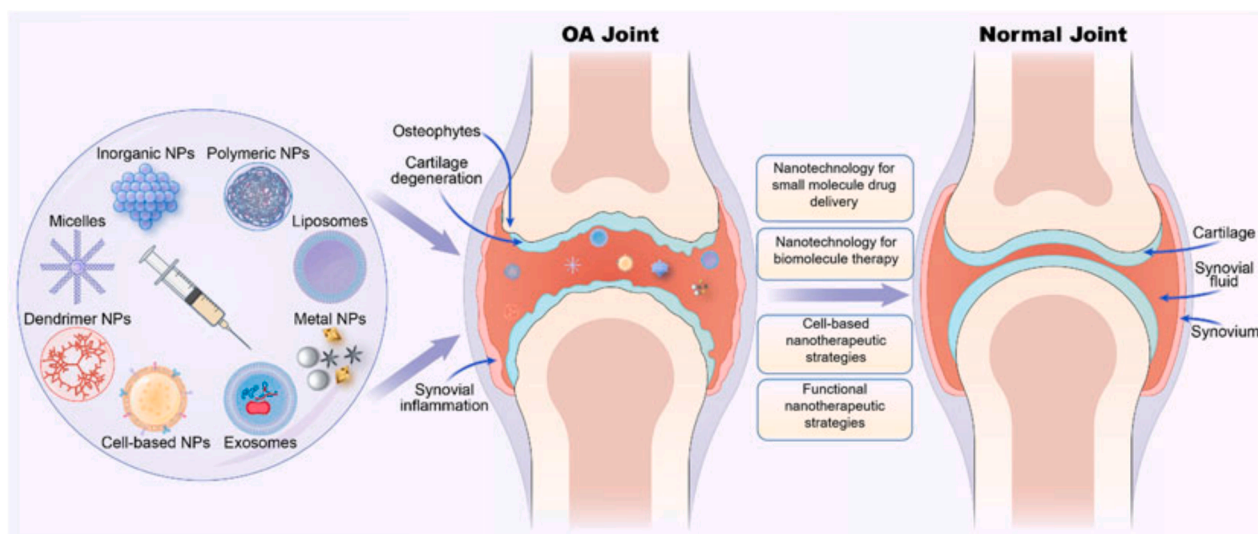


Fig. 7. Advantages of nanoparticulate drug delivery systems to treat osteoarthritis. Figure reproduced with permission and without modification from Guo et al. [259].

medicament specifically at the joint. This is especially important for people with OA who have other health issues or are on multiple medications [257,258].

(V). Combination Therapy: Nanomedicine enables the incorporation of various phytoconstituents or medicines with complimentary modes of action into a single formulation. This collaborative approach has the potential to enhance the treatment of symptoms associated with OA [257,258].

(VI). Improved Disease Modifying Potential: Some nanomedicine formulations can provide symptom relief and potentially slow down OA progression by delivering disease-modifying agents to the joint [257,258].

(VII). Non-Invasive Routes: Nanomedicine can be administered through various routes, including intra-articular (directly into the joint), oral, or transdermal, depending on the formulation. This flexibility enhances patient comfort and adherence to treatment [257,258].

(VIII). Imaging and Monitoring: Advanced nanomedicine systems can incorporate imaging agents, allowing healthcare providers to visualize the drug's distribution within the joint and monitor treatment progress [257,258].

4.4. Enhanced bioavailability

The drug delivery vehicles must disperse the active component at the proper pace and dosage to accomplish the intended therapeutic goal. Depending on the desired therapeutic aim, an appropriate biopharmaceutical design can alter the rate and degree of drug absorption (also known as bioavailability) or the systemic administration of pharmaceuticals to the body [260]. The spectrum of absorption rates varies from rapid and total to slow and continuous. By decreasing particle size, altering the surface, and attaching or entrapping the phytomedicine with different kinds of micro or nano materials, the application of nanoparticulate drug delivery systems raises the penetration, bioavailability, and bioactivity of phytomedicine [260]. Furthermore, the nanomedicine can be administered through various routes, including IA, oral, or transdermal, depending on the formulation. This flexibility enhances patient comfort and adherence to treatment. Interestingly, advanced nanomedicine systems can incorporate imaging agents, allowing healthcare providers to visualize the drug's distribution within the joint and monitor treatment progress. However, it's important to note that while the potential benefits of phyto-nanomedicine in OA treatment are promising, there is ongoing research to optimize these

delivery systems and establish their safety and efficacy. Patient-specific factors, disease severity, and the choice of phytoconstituents must all be considered when developing and prescribing these therapies. Collaborative efforts among researchers, clinicians, and pharmaceutical companies are essential further to advance the field of phyto-drug delivery for OA management.

4.5. Targeted drug delivery to treat osteoarthritis via IA injection

IA injections are often utilized in musculoskeletal disorders such as OA and RA to provide large concentrations of medicines to the joint area directly. Current IA-injected drugs are promptly cleared and have no substantial effect on the course of joint illness (Figs. 7, 8, 9). In this section, we highlighted recent advances in IA therapy, focusing on present and upcoming therapeutic carriers and their potential to offer disease-modifying treatment modalities for arthritis. Recent progress in IA techniques have mostly emphasized the development of safe platforms, improved tissue penetration capabilities, and enhanced translatability for the controlled and sustained delivery of pharmaceuticals or phytomedicine. In addition, gene therapy given by viral or non-viral vectors, and cell-based treatment, are being researched extensively for cartilage preservation and regeneration [33]. Phyto-nanomedicine delivered via IA injection offers an innovative approach to treating conditions like OA by enhancing the permeability of therapeutic agents within the joint space. Nevertheless, nanoparticles can be engineered as microspheres, hydrogel, nanoparticles, and liposomes to enhance targeting, ensuring that phytoconstituents or other drugs reach the specific area needed [261]. Controlled-release nanoparticles via IA-injection can maintain therapeutic levels of phytoconstituents within the joint over an extended period. This can provide long-lasting relief from pain and inflammation associated with OA, reducing the need for frequent injections. Fewer injections can improve patient compliance and is convenience for medical professional as well. It's important to note that while the concept of phyto-nanomedicine and IA drug delivery holds promise for OA treatment, research is ongoing to optimize these delivery systems and ensure their safety and efficacy. The choice of phytoconstituents, nanoparticle materials, and formulation design should be carefully considered based on the specific needs of OA patients and the desired therapeutic outcomes. Collaboration between researchers, clinicians, and pharmaceutical companies is essential to advance the development and clinical application of these innovative approaches for OA and other joint-related conditions [262].

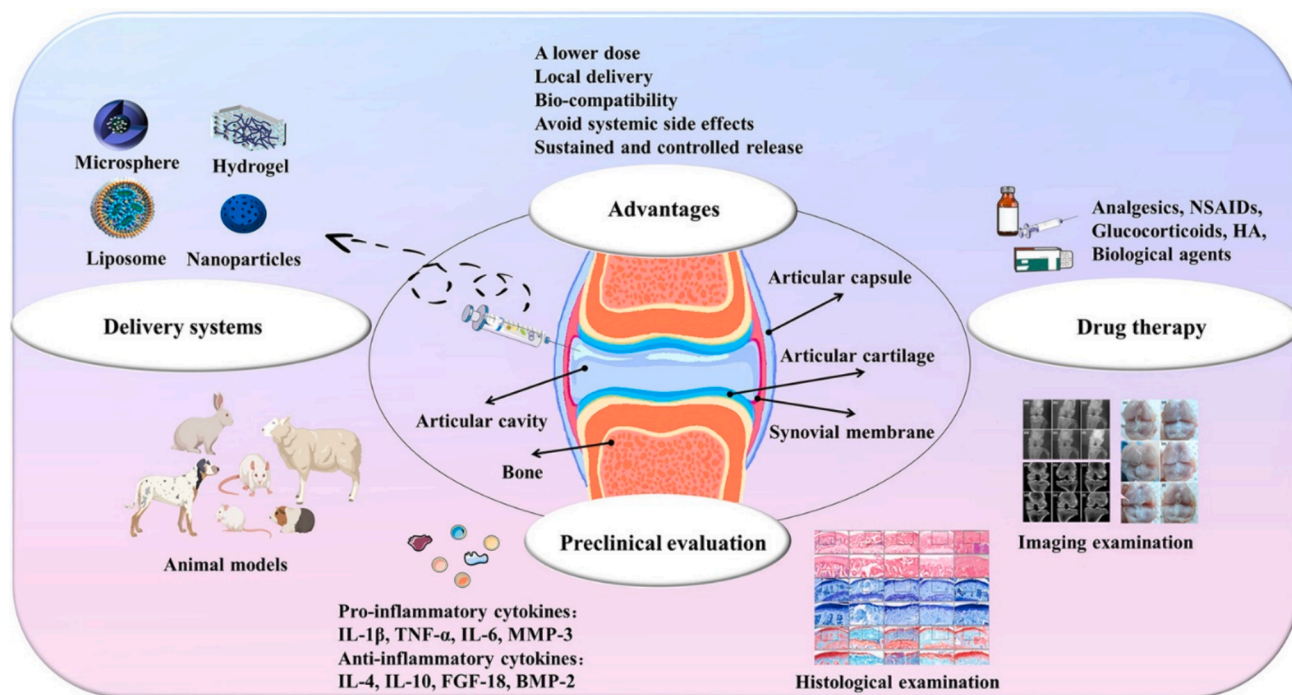


Fig. 8. The graphic illustration represents the application and prospects of intra-articular drug delivery systems in arthritis. Figure reproduced with permission and without modification from Song, Cui and Hu [261].

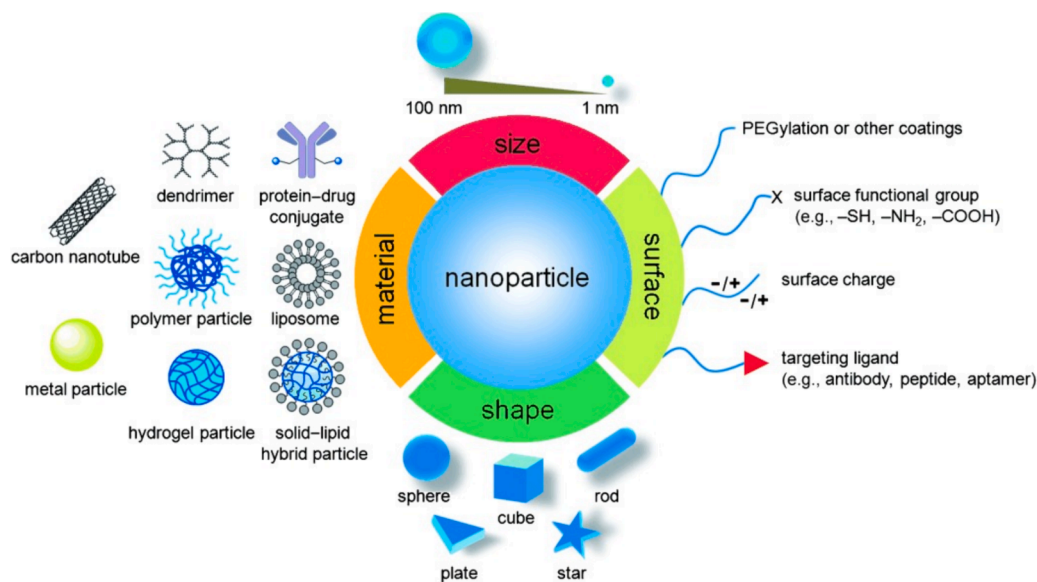


Fig. 9. Figure illustrates various drug delivery systems that can be employed to load phyto-medicines for enhanced bioavailability and targeting ability. Figure reproduced with permission and without modification from Sun et al. [263].

4.6. Sustained release concept of phyto-nanomedicine to treat osteoarthritis

According to Moghimi et al. [264], sustained release enables the distribution of a particular medicine at a predetermined pace, resulting in extended drug delivery (Fig. 10). This drug release profile is beneficial for drugs that are digested too quickly and leave the body soon after taking them. Moreover, drug concentration in the blood or target tissue can be maintained at a consistent level by sustained release via modifying the pace of drug release [263]. For instance, the treatment of cancer benefits from a consistent medication dose inside the therapeutic window [265,264 265]. According to several studies, blocking drug

molecules from fully interacting with the aqueous environment for a reasonable amount of time is one way to achieve prolonged drug release [263]. The concept of sustained release in phyto-nanomedicine entails using nanotechnology-based approaches to deliver phytochemicals or natural compounds extracted from plants in a controlled and extended manner [263]. This approach addresses some of the limitations associated with traditional drug delivery methods for phytochemicals, such as rapid clearance from the body, limited bioavailability, and the need for frequent dosing. Various materials, such as lipids, polymers, or inorganic substances, can form these nanoparticles. The choice of nanoparticle material depends on factors such as the phytochemical's physicochemical properties and the desired release profile. Various

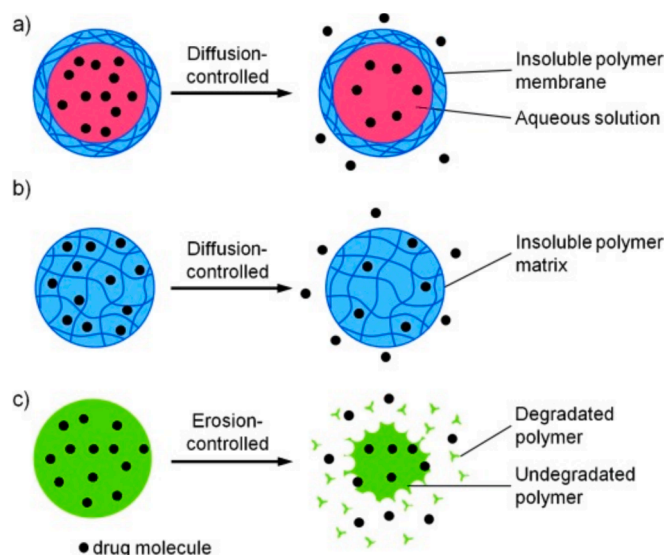


Fig. 10. An illustration of the three main methods for obtaining sustained drug release is shown in figures a, b, and c. These methods include diffusion through an insoluble polymer shell or matrix and matrix erosion. Figure reproduced with permission and without modification from Sun et al. [263].

mechanisms, such as diffusion through nanoparticle pores, degradation of the nanoparticle matrix, or responsive behaviours triggered by environmental factors like pH or temperature, can achieve this controlled release [263]. This allows for precise delivery of phytochemicals to the intended site of action, reducing off-target effects and minimizing systemic exposure. Sustained release in phyto-nanomedicine holds promise for various applications, including the treatment of chronic diseases, cancer, inflammatory conditions like OA and RA, and more [263]. However, it's important to note that developing these formulations requires careful consideration of factors such as nanoparticle design, release kinetics, and safety profiles. Before sustained-release phyto-nanomedicine formulations can be used in clinical practice, extensive preclinical and clinical testing is typically required to validate their effectiveness and safety.

5. Microfluidic organ-on-chips model for effective identification and evaluation of novel phyto-nanomedicine based anti-osteoarthritic drugs

Microfluidic organ-on-chips (OoC) or joint-on-a chip (JOC) models provide a sophisticated, biomimetic method for *in vitro* investigation of different drugs, phytoconstituents and nanomedicine in various disease [268] (Fig. 11). These models combine the biological intricacy of live tissues with the exact control of microfluidics to provide a potent platform for a range of applications, including the phytoconstituent identification process. Because plant extracts are complex and high-throughput screening is required, it might be difficult to identify and characterize these chemicals using conventional approaches. In this case, microfluidic OoC and/or JOC models provide several benefits [269]. The screening procedure may be greatly accelerated by testing many phytoconstituents in considerably shorter duration of time than *in vivo* by this technology. Notably, microfluidic devices are tiny in size, only minimal volumes of plant extracts are required, which preserves priceless samples. When comparing OoC or JOC models to conventional cell culture or animal models, the data they provide are more indicative of human reactions. They make it possible to investigate in-depth the mechanisms of action of phytoconstituents by examining their interactions with certain cell types and tissues. After successfully identifying a valuable phytoconstituent that demonstrates great efficacy, characterized by promising *in vitro* outcomes, the next step is to perform

in vivo experiments with phytoconstituents incorporated nanoparticles to validate the findings [270]. Therefore, with the ability to simulate the whole range between healthy and OA joints, a highly adaptable and adjustable OoC or JOC platform can provide insight into the early start of OA in people, which is difficult to get in clinical practice. Further, JOCs can also replicate the long-term course of OA if the settings of the cell culture are set up to maximize cell survival for extended research. Undoubtedly, JOCs will improve and speed up the traditional drug development methods' speed, efficacy, and safety.

6. Conclusion

Current pharmacological therapy options for OA and RA have varying efficacy and safety, particularly when managing chronic pain and inflammation. According to the literature, phytoconstituents have high *in-vitro* bioactivity; however, limited water solubility, increased molecular size, disintegration during stomach emptying, and extensive metabolism are some of the difficulties that limit its *in-vivo* usefulness. Certain herbal remedies can be used as a supplementary treatment to supplement or replace pharmaceutical drugs. Herbal medicine treatment also provides a safer option with similar or higher effectiveness. Herbs commonly reported anti-arthritis mechanisms include the suppression of pro-inflammatory and pro-catabolic mediators, such as cytokines, PGE2, MMPs, ROS, and apoptotic proteins through signalling pathways like NF- κ B, RANKL, and PI3K/Akt. Phytoconstituents could be used to target these mechanisms and help reduce joint pain, inflammation, edema, structural damage, and functional impairment caused by OA and RA, with little or no adverse effects. On the other hand, nanotechnology promotes phytoconstituent permeability, bioavailability and bioactivity by reducing particle size, altering the surface, and attaching or entrapping the phytoconstituent with different polymers of micro or nanomaterials. In addition, nanomaterials aid with targeted and sustained delivery, and the diffusion of drugs or phytoconstituents into multiple organs by crossing barriers such as the skin, gastrointestinal, and blood-brain barrier. Current research should concentrate on the design and development of multifunctional nanomaterials, as well as *in-vivo* clinical examinations of their formulations. Focused and evidence-based research is needed in the future to investigate the clinical safety and therapeutic efficacy of herbal treatment in arthritis and other chronic pain conditions. Moreover, research-based investigations on the chemical constituents of herbal plants and their extraction might contribute to the development of tailored therapeutic treatments. Ultimately, it will be essential to develop natural product formulations that possess suitable solubility, permeability, bioavailability, and release kinetics in order to optimize therapy outcomes and reduce the toxic effects in OA. This can be effectively achieved by using nanoparticulate drug delivery technologies.

CRediT authorship contribution statement

Laxmi Akhileshwar Jha: Conceptualization, Writing – original draft, Writing – review & edit. **Mohammad Imran:** Writing – original draft. **Jesus Shrestha:** Writing – original draft. **Hari Prasad Devkota:** Writing – original draft. **Kunal Bhattacharya:** Writing – original draft. **Abdulrhman Alsayari:** Writing – original draft. **Shadma Wahab:** Writing – original draft. **Saurav Kumar Jha:** Writing – original draft. **Keshav Raj Paudel:** Writing – review & editing, Supervision. **Prashant Kesharwani:** Supervision, Writing – review & editing.

Declaration of competing interest

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

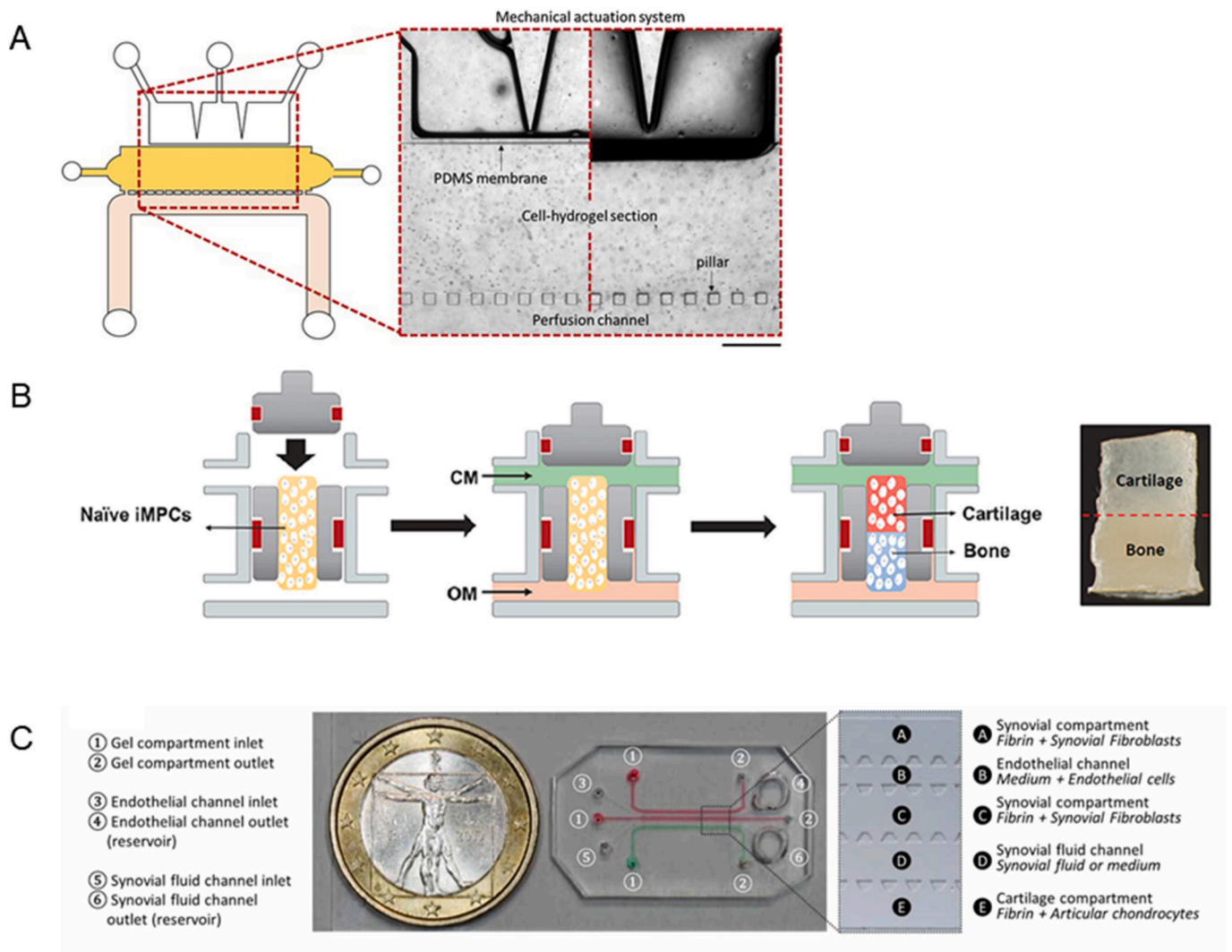


Fig. 11. A summary of reported joint-on-a-chips (JOCs) is shown in Figure. (A) Paggi et al.'s monolithic PDMS-based platform for applying mechanical stimulation to a 3D manufactured tissue [271]. (B) Dual-flow bioreactor with biphasic osteochondral tissue for Lin et al.'s microJoint platform [272]. (C) Mondadori et al. created a vascularized synovium and articular cartilage JOC model to study the mechanism of monocyte extravasation in OA joints [273]. Figures are reproduced with permission and without modification from the original and their use is permitted under the Creative Commons Attribution 4.0 license. The compiled figure in current form (A, B, and C) is reproduced with permission and without modification from Banh et al. Source [268].

Data availability

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

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