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Review Article

Plant-derived Anti-arthritic Nanomedicines for Effective Therapy in the Management of Inflammatory Diseases

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ABSTRACT

Arthritis comes under the bandwagon of one of the most menacing diseases that are known to mankind and the more concerning matter is unavailability of permanent cure for this condition. The conditions of severe joint inflammation are being treated with conventional therapeutics that imparts a range of adverse effects, which prompted the researchers to look for safer options in the form of herbal medicines. Numerous plants, their parts, extracts, and their phyto-isolates have been explored till date for their anti-arthritic potential. However, there are risks of stability and delivery issues with these plant products, hence limiting their utility for effective therapy in the management of inflammatory diseases. Nanotechnology based herbal medicines may overcome the delivery limitation of various natural products utilizing the multi and versatile properties of various nanoparticles. This review reports the herbal anti-arthritic drugs, challenges associated with them, and pharmacodynamics/ pharmacokinetics of anti-arthritic herbal nanomedicines.

Keywords: Arthritis, Phytomolecules, Medicinal plants, Nanotechnology, Nanoparticles, Herbal nanomedicines.

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INTRODUCTION

Arthritis is a collective form of gravely inflammatory diseases and is characterised by low to severe degree of inflammation and degeneration in the joints and the auxiliary parts like bones and cartilages. The manifestation of inflammation is demonstrated in the common arthritic symptoms where a single or multiple joints displays swelling, stiffness, leading to pain and discomfort at great lengths.[1,2] This not only affects the physical well-being but also creates a huge economic burden for the affected individuals and their family. Several existing variation of arthritis includes rheumatoid arthritis, osteo-arthritis, infectious arthritis, psoriatic arthritis, lupus arthritis, fibromyalgia, ankylosing spondylitis, gout, and juvenile arthritis.[3] Of which, the cases of osteo-arthritis (OA), rheumatoid arthritis (RA), and gout dominates the majority of arthritis-related cases.[1] However, this paper will have its primary focus oriented towards the former two types i.e. OA and RA. Both these conditions have similar pathological manifestation however RA is an autoimmune condition whereas, OA gradually develops with age.[4,5] The exact etiology of RA is uncertain, however the correlation between the autoimmune response and the joint inflammation has been established and the contributing causing factors are mainly genetic and some environmental factors like smoking and infectious diseases.[6,7] About 0.5-2% of the world's populations is affected by RA and women are found to be more prone to developing RA.[8] Whereas OA is a condition in which almost all the parts of joint like cartilage, bones, and ligaments starts deteriorating with inflammation which results in stiffness thereby, causing aches and pain in flexing joints. The condition is found to progress as individuals grow older.[9] Both these arthritic conditions persists for long time hence are categorised as chronic condition and the most dismaying thing backed by literature is that no permanent cure has been found till date.[2] Till now, these debilitating diseases are being mitigated with non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs), glucocorticoids, and some biological agents.[10] But prolonged use of these agents comes with multiple setbacks like first past metabolism, hepatotoxicity, renal toxicity, cardiotoxicity, gastric bleeding, immunosuppression, hyperglycaemia, and so on.[11] Apart from these, biological agents arises the risk of developing bacterial infections in addition to being low responsive and highly expensive.[12] Invasive surgical procedures like joint replacement surgery, osteotomy, resection-arthroplasty, arthrodesis, etc. present many drawbacks like high cost, painful, and risky.[13] It can be said that none of these therapy options completely eliminates arthritis and provide full recovery. Moreover, these available

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synthetic anti-rheumatic drugs also impart drug resistance upon prolonged use in addition to causing side effects.[14] This prompted the scientists and researchers to divert their attention towards a safer alternative of herbal source which are being traditionally used and overtime as Ayurveda, Siddha, Unani, Traditional Chinese medicine, etc.[15] Herbal source of medicine presents a broad scope of developing new lead molecule as they are abundantly blessed with various phytoconstituents and are relatively safer than synthetic options and surgical interventions.[16] There are myriad of papers in the literature reported about the herbs and phytoactives having potential anti-arthritic activity. The herbs are either being explored in the form of plant parts, extracts, essential oils, fixed oils, or isolated phytoconstituents such as, glycosides, alkaloids, terpenes, flavonoids, fatty acids, etc.[17,18] Although, it is evident that herbal drugs have several advantages but the predicament lies in their delivery due to their large sizes and another issue being the less stability as plant products are highly susceptible to microbial growth, hydrolysis, and oxidation. For any formulation to be suitable for human application it is necessary to pass certain stability and safety criteria and the formulation must in fact be able to deliver the actives at the desired site in the desired form. There comes the role of nanoformulation where these plant extracts and actives are either entrapped, coated, or encapsulated, depending on the type of the nanocarriers.[19] The nanotechnology based novel drug delivery ensures the delivery of herbal drugs at the desired site of action along with providing prolonged and sustained delivery at desirable doses. The nano-based herbal formulations have comparatively increased shelf life, bioavailability, solubility, in addition to providing protection from degradation which enhances the stability of the formulation thereby increasing the therapeutic efficacy as well.[20] Similarly many of the herbal drugs having anti-arthritic potency have been subjected to nanotechnology where these phytoactives are used for the preparations of polymeric nanoparticles, lipid nanoparticles, metallic nanoparticles, nanovesicles, nanogel, etc.[21] An attempt has been made to comprehensively canvas the herbal anti-arthritic drugs as well as nano-based herbal anti-arthritic formulations for the treatment of RA and OA specifically. The overview of the review has been vaguely represented in Figure 1.

Plants and their preparations having potential anti-arthritic properties

With more advancement, the world has started realising the goods' and benefits of the old ways and hence is going back to the ancient ways in every field of life. It can be said same for pharmaceutical field too. So, whenever one associates the term herbal in any formulation, this develops conscious feeling of safety, even for the laymen people who has not an iota of idea about the composition and manufacturing procedures of pharmaceuticals. This has led to the development of plant based

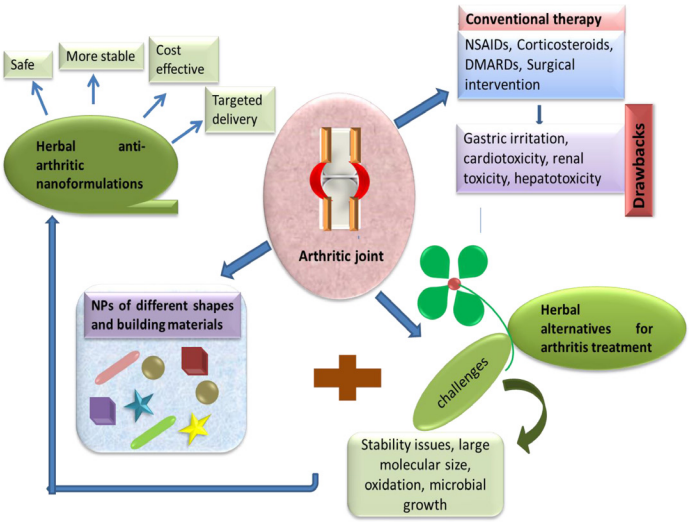

Figure 1: Anti-arthritic herbal nanoformulations.

medications for several diseases including that of arthritis. The established literatures on herbal drugs have included multiple plants, plant parts, plant extracts, and their isolated phyto-compounds for their ability to mitigate OA and RA. The following sections give in-detailed discussion on the potentials of plant and their preparations for the treatment of arthritis.

Role of plant and their preparations having potential anti-arthritic properties

The nature has endowed us with plenty of beneficial plants which we the humans have explored in numerous ways wherein the ancient people have precisely used either the whole plant or their parts in for treating many ailments and the researchers in modern world have extracted and isolated phytocompounds, from the plants. Therefore in this section the role of plants in the treatment of arthritis will be discussed by roughly categorising them according to their form which is crude extracts and isolated phytocompounds.

Plant crude extracts for the treatment of arthritis

Cleistopholis patens Benth

Cleistopholis patens B., belonging to the family *Annonaceae* is a tree having a height of 30m, abundantly found in Sierra Leone, Uganda and Zaire. The ethanol and aqueous extracts of the stem of this plant was found to produce anti-arthritic activity in chicken type II collagen in Complete Freund's Adjuvant (CFA) induced Wistar albino rats with no toxicity. The rat paw volume reduced for the arthritic rat groups treated with the plant extract which the authors have deduced to be due to the immunological protection provided by the plant extracts. It was also observed that upon treatment with these plant extracts, the rats started gaining weight which they lost due to arthritis induction, which indicated the ability of this Plant to reverse muscle degeneration.[22]

Clerodendrum serratum (L.) Moon

Clerodendrum serratum (L.) Moon, also known as Bharangi in Sanskrit and Blue glory in English belongs to the family Verbenaceae, is a deciduous shrub widely found in the Western Ghats of India. The aqueous standardized extract of the roots of this plant was found to possess anti-inflammatory potential when its membrane stabilizing activity was tested. The *in vivo* anti-arthritic activity study on CFA induced Wistar albino rats exhibited inhibition of COX-2 and TNF-α which have been deduced accordingly by observing the parameters like paw edema, arthritic index, and joint diameter. Plant extract showed improvement of arthritic condition in regard to body weight, arthritic score, paw edema, and joint diameter. The extract showed significant results for TNF-α and COX-2 ($p < 0.0001$).[23]

Moussonia deppeanna

Moussonia deppeanna is a Mexican medicinal plant, belonging to the family Gesneriaceae. It is also known as tlachichinole and is used for treatment of chronic inflammation-related diseases such as gastrointestinal diseases, kidney failure, and rheumatic pain. The ethanolic extract of this plant generates a moderate anti-edematous effect on CFA induced monoarthritic adult Balb/C male mice and showed positive effects on body weight gain of the experimental arthritic mice. It also exerted an immune-modulating effect on lymphocytes and leukocytes in peripheral blood and reduced follicular hyperplasia in the paw edema of arthritic mice, by providing protection from oxidative degradation of lipids and proteins, which results from lessening the endogenous antioxidant enzymatic response in both ganglionic and edema tissue.[24]

Withania somnifera

Withania somnifera Dunal, belonging to the family Solanaceae is also popularly known as Ashwagandha. The therapeutic properties of this plant have been attributed to the presence of phytosteroids Withanloids and Withaferin A.[25] The aqueous extract of the roots of Ashwagandha has been explored in this study to investigate its anti-arthritic potential on collagen induced arthritic rats. The oral administration of the aqueous root extract appreciably decreased the swelling and production of pro-inflammatory cytokines like TNF-α, IL-1β, IL-6, transcription factor NF-κB. Additionally, the reduction in the levels of transcription factor NF-κB, Metalloproteinase MMP-8 levels were observed after treatment, which were otherwise found to be elevated in arthritic rats. Similarly, with the treatment of this plant's root extract, the enzymatic activities of Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx), and Catalase (CAT), were restored to normal.[26]

Phellodendron amurense Ruprecht

Phellodendri cortex (PC), the dried trunk bark of *Phellodendron amurense* Ruprecht, belonging to the family Turaceae, was used traditionally as a powerful anti-inflammatory agent for and included in the prescription for treating inflammatory diseases. The methanolic extract of the dried roots of this plant have been found to improve arthritic symptoms through anti-inflammatory and immune-modulatory effects in collagen-induced arthritis in mice. And the oral administration of this extract have significantly decreased the arthritic score along with reducing the serum levels of anti-Col II IgG2a, TNF-α, PGE2, and IL-17 which otherwise were in elevated levels in arthritic mice. The extract also helped in inhibiting the expression of TNF-α and IL-17 in the arthritic joints by suppressing mRNA and proteins expression. The improvement in histopathology of joint architecture was also observed with the treatment of this extract.[27]

Vaccinium corymbosum L.

Also commonly known as blueberry is an edible fruit belonging to the genus Vaccinium and family Ericaceae. Blueberries are known to have multiple health benefits owing to their high phenolic contents, thus possessing antioxidant and anti-inflammatory properties.[28,29] Here, the ethanolic extract of blue berry fruits have been used to explore and establish its anti-arthritic potential using carrageenan-induced rat paw edema model and collagen-induced arthritis model in rats. The study findings suggested the positive anti-arthritic activity of the blueberry extract as it inhibited the paw edema formation in carrageenan-induced rat with reducing the clinical signs and symptoms of arthritis such as soft tissue swelling, osteophyte formation, bone resorption, etc. in collagen induced arthritic rats upon oral administration of blueberry extract.[30]

Saussurea lappa

Saussurea lappa is a plant widely distributed in the Himalayan region of India and China and have much traditional medicinal significance such as the roots and stalk of the plant has been mention in Unani system of medicine for the treatment of rheumatism. And the ethanolic extract of the plant has been found to possess antioxidant as well as anti-inflammatory properties.[31] In one study, the extract of this plant has been explored for their anti-arthritic potential in monosodium iodoacetate (MIA) OA mice model. When the arthritic induced mice were treated with *Saussurea lappa* extract, the levels of IL-6, IL-1β, and TNF-α decreased which were otherwise present at elevated levels in the mice serum. Furthermore, it was also observed that with treatment of this plant extract, the levels of Matrix metalloproteinase-13 (MMP-13) and Purinergic P2X7R significantly decreased along with reducing the expression of NF-κB p65 and IκBα which suggested the potential possessed by this plant in alleviating OA.[32]

Commiphora Extract Mixture

Commiphora extract mixture (HT083), the mixture of the extracts of *P. lactiflora* root and *C. myrrha* gum resin in 3:1 ratio,

were evaluated for their anti-arthritic effects on monosodium iodoacetate (MIA) induced OA models in male Sprague-Dawley rats. This treatment reversed the subchondral bone damage and cartilage erosion of the MIA-induced rats along with preventing the loss of weight-bearing in those rats. Additionally, the treatment with HT083 also depleted the serum concentration of IL-1 and also significantly countered the acetic acid-induced writhing response in mice. The *in vitro* anti-inflammatory study of this mixture performed on RAW264.7 cells revealed suppression of IL-1, IL-6, cyclo-oxygenase-2, and inducible nitric oxide synthase expression, thereby inhibiting nitric oxide production.[33]

Since it is not possible to list down the entire plants and their extract explored for the purpose of RA and OA management, some more plants reported in the literature purported to have anti-arthritic potential have been listed down in Table 1.

Table 1: Some plant extracts possessing anti-arthritic properties.

Sl. No.	Plants	Common Name	Family	Animal models	Dose (mg/kg)	References
1.	*Strychnos potatorum* L.	Clearing-nut tree	Loganiaceae	CFA -induced RA model in rats	200 mg/kg	[34]
2.	*Plumeria alba* L.	White champa	Apocynaceae	CFA -induced RA model in rats	100 and 200 mg/kg	[35]
3.	*Chenopodium album* L.	Bathua	Chenopodiac-eae	CFA- induced RA model in rats	200 mg/kg	[36]
4.	*Mesua ferrea* L.	Nagakeshar, Cobra's saffron	Clusiaceae	CFA-induced RA model in rats	300 and 500 mg/kg	[37]
5.	*Cissampelos pareira* L.	Hirsuta	Menispermac-eae	CFA-induced RA model in rats	100-400 mg/kg	[38]
6.	*Semecarpus anacardium* L.	Ballataka, Bhilwa	Anacardiacea-e	Adjuvant induced RA model in rats	150 mg/kg	[39]
7.	*Pterodon pubescens* B.	Sucupira	Fabaceae	Collagen-induced RA model in mice	5 and 50 mg/kg	[40]
8.	*Ajuga bracteosa*	Bugle	Labiatae	Turpentine oil-induced joint oedema in rats, Formaldehyde-induced arthritis in rat, CFA-induced arthritis in rats	5, 10, 20 mg/kg	[41]
9.	*Glycine tabacina* B.	Yan Dou	Leguminosae	Collagen-induced RA model in rats	1.11, 2.22 and 4.44 g/kg	[42]
10.	*Monotheca buxifolia*	-	Sapotaceae	CFA-induced RA model in rats	50, 100, and 150 mg/kg/day	[43]
11.	*Citrus limetta*	Sweet lemon	Rutaceae	Collagen-induced arthritis in rats.	30, 100, and 300 mg/kg	[44]
12.	*Citrus reticulata*	Mandarin	Rutaceae	CFA-induced RA model in rats	50mg/kg	[45]
13.	*Kaempferia parviflora*	Thai ginseng, krachai dum	Zingiberaceae	CFA-induced RA model in rats	150 and 300 mg/kg	[46]
14.	*Ephedra gerardiana*	Ma Huang, Gerard jointfi	Ephedraceae	CFA-induced RA model in rats	200 mg/kg	[47]
15.	*Tamarindus indica* L.	Tamarind	Fabaceae	CFA-induced RA model in rats	500 mg /kg	[48]

Isolated phytocompounds for the treatment of arthritis

Plant isolates or phytocompounds can be described as pure compounds with definite chemical structure and formula, derived from the extracts of plants and is also responsible for many biological activities. Most of the plant actives fall under a group of compounds such as glycosides, alkaloids, terpenoids, flavonoids, plant sterols.[15] These phytocompounds are discussed in the section below.

Alkaloids

Alkaloids belongs to a group of compounds derived from amino acids and can be sourced from many organisms such as fungi, bacteria, and plants. Sanguinarine is an alkaloid of benzylisoquinoline nature, isolated from plants like *Bocconia frutescens, Macleaya cordata*, *Argemone mexicana*, *Bocconia frutescens*, *Sanguinaria Canadensis,* and *Chelidonium majus*. This alkaloid has been approved by FDA and has the potential to inhibit formation of osteoclast so, is useful for inflammation. In a study by Ma *et al.* sanguinarine isolated from the roots of *Sanguinaria canadensis,* was studied on OA models where the findings suggested the suppression of NF-κB and JNK activation by this alkaloid. Furthermore, this alkaloid was also found to be successful in suppressing the expression of catabolic proteases in *in vitro, ex vivo,* and *in vivo* models along with suppressing metalloproteinase and disintegrin with thrombospondin motifs-5 in chondrocytes. The study results definitely act as evidence to the claim of successful alleviation of OA by this alkaloid.[49,50] Another such alkaloid is Piperine, is obtained from *Piper nigrum* L., also commonly known as black pepper belongs to the family Piperaceae is mentioned in the literature of Ayurveda and Chinese medicine for their medicinal properties.[51] A study by Bang *et al.* reported the anti-arthritic activity of piperine on collagen induced arthritis models of rats where the oral administration of piperine reduced paw volume and weight distribution ratio. It also reduced production of PGE2

and expression of IL6 and MMP13 along with suppressing the migration of activator protein-1.[52] A bis-benzyl isoquinoline alkaloid called tetrandrine, derived from *Stephania tetrandra* S. Moore was found to be effective in alleviating rheumatoid arthritis on adjuvant-induced arthritis murine model by inhibiting pannus formation, fibroblast overproliferation, and macrophage inflammatory response. It also decreased the IL-6 serum level significantly along with suppressing the infiltration and activation of neutrophils *in vivo*, which suggested the potency of the alkaloid in treating arthritis.[53] 3-Acetylaconitine is also an alkaloid, obtained from *Aconitum flavum* and *Aconitum pendulum*, belonging to the family Ranunculaceae. In a study by Tang *et al.* 3-Acetylaconitine isolated from the roots of *Aconitum flavum*, have found to induce anti-arthritic activity formaldehyde-induced rat model and carrageenan-induced edema in the adrenalectomized rat model. The authors have found reduction in swelling of the hind paw in the former arthritic model and reduction of edema in the later model.[15]

Flavonoids

Flavonoids are a group of compounds obtained from different parts of plants such as flowers, fruits, stems, bark, roots, and grains.[54] These compounds are polyphenolic in nature and around 6000 flavonoidal compounds have been reported having different biological activities with low toxicity.[55] Few such activities are antioxidant and anti-inflammatory activities by inhibiting the production of nitric oxide, pro-inflammatory cytokines, eicosanoids, and interfere with the NF-kB transcription factor.[56]

Baicalin and aglycone (baicalin-2) are two flavonoids found abundantly in *Scutellaria baicalensis* and *Oroxylum indicum* are found to be potential targets of rheumatoid arthritis as both of these possess antioxidant activity and anti-inflammatory activities since they are capable of reducing reactive oxygen species generation, NF-kB activity, and TNF-α generation.[57] Another natural flavanol is Kaempferol, sourced from several edible plants like broccoli, tea, beans, kale, spinach, etc. and is used traditionally to treat several inflammatory disorders. Cortes *et al.* studied the effect of kaempferol in RAW 264.7 cells where the decrease in COX-2 levels was observed along with inhibition of reactive oxygen species production via inhibition of TNF-α protein and iNOS expression.[58] And it was found to inhibit IL-4, NF-κB and C-reactive protein expression in liver cells.[59] Another report suggest the inhibition kaempferol produces anti-arthritic activity by inhibiting the proliferation of both IL-1-stimulated and unstimulated RASFs.[60] Gallic acid is another polyphenolic compound found naturally in green tea, grapes, oak bark, apple peels, and sumac. A study by Yoon *et al.* Investigated the apoptotic ability of gallic acid on fibroblast-like synoviocytes (FLS) and induced suppression of cytokines and chemokines, COX-2, and MMPs-9 from fibroblast-like synoviocytes from patients with rheumatoid arthritis. It was also found to regulate expression of protein related to apoptosis in addition to reducing pro-inflammatory genes expression in fibroblast-like synoviocytes from patients with rheumatoid arthritis. The authors thereby, came to the conclusion that gallic acid follows the anti-inflammatory and pro-apoptotic options for treatment of rheumatoid arthritis.[61]

Terpenoids

Terpenoids are extracted from various plant parts as secondary metabolites and approximately 24 terpenoids have been reported which proved to be effective in the management of inflammation and arthritis. These compounds are colourless in appearance and have a pleasant smell to them possessing high refractive index.[62,63] One such triterpene is nimbolide, obtained from neem (*Azadirachta indica*) flowers and leaves and possess a wide range of pharmacological activities. In a study by Cui *et al.*, the anti-arthritic activity of nimbolide on CFA-induced rat model was investigated where reduction in paw volume, arthritic score, edema formation, organ indices, was observed including gain in body weight of the animals. Moreover, the decrease in pro-inflammatory cytokines and normalising the increased level of NF-κB, COX-2, iNOS, IKKa, and P-IkBa, in treated rats also proved the anti-arthritic potential of this triterpene.[64] Eugenol is a terpenoid sourced from buds of clove (*Eugenia caryophyllata*), and constitutes majority of clove bud oil. Grespan *et al.* investigated its anti-arthritic activity on collagen type II – induced arthritis in DBA1/J mice model where the oral administration of eugenol significantly reduced cytokines and interferon level in the ankle joints of mice under study. Eugenol also inhibited mononuclear cell infiltration into the knee joints of arthritic mice.[65] Cannabidiol (CBD) are meroterpenoids, terpenophenolic compounds which are obtained from the plant *Cannabis sativa* L. (Cannabaceae). CBD is present as the main active constituent of this plant along with other constituents like amines, amides, phenolic compounds, phytosterols, terpenes, and carbohydrates.[66] CBD is known to produce anti-inflammatory response by inhibiting nitric oxide production by macrophages; inhibiting proliferative responses of T-lymphocytes. In a study by Malfait *et al.*, collagen-induced arthritis in DBA/1 mice model was chosen for demonstrating anti-arthritic activity where it was revealed that the oral administration of CBD manifested joint protection from severe damage. It also demonstrated reduction in collagen II-specific proliferation, TNF-α release and IFN-g production by synovial cells belonging to the knees of CBD-treated mice. Additionally, the *in vitro* anti-arthritic study revealed suppression of lymphocyte proliferation along with suppression of increased serum TNF level in arthritic mice. Based on these findings, the authors suggested the possession of anti-inflammatory and immunosuppressive activity of CBD, thereby inducing anti-arthritic activity.[67]

Since plethora of phytocompounds has been explored with the expectation of providing an alternate treatment option for

Table 2: List of plant-derived actives used for alleviating arthritis.

Sl. No.	Phytocompound	Plant source	*In vivo* arthritis model	Findings	Reference
1	Curcumin	*Curcuma longa* L.	Collagen-induced mouse model	Decreased production of BAFF, IFN and IL-6 in serum and suppressed IFN-induced BAFF expression and nuclear translocation after curcumin treatment	[68]
2	Brazilin	*Caesalpinia sappan* L.	Type-II collagen- induced mouse model	Significant reduction in inflammatory cytokines, acute inflammatory paw edema, and arthritis index score, improved bone mineral density	[69]
3	Chebulanin	*Terminalia chebula* retzius	Collagen-induced mouse model	Dose-dependent improvement in expression of IL-6, TNF-α, MMP-3,and COX-2 in joints and, ultimately, severity of arthritis	[70]
4	Ellagic acid	*Kirganelia reticulate*	Formaldehyde-induced rat paw edema model	Inhibition of cytokines and leukotriene infiltration, reduced paw edema volume, protected synovial membranes, and cartilage damage	[71]
5	Jatrorrhizine hydrochloride	*Berberis aristata* and *Coptis chinensis*	Collagen-induced rat model	Suppress TNF-α stimulated activation of NF-κB and mitogen-activated protein kinases (MAPKs), leading to suppression of proinflammatory mediators	[72]
6	Montanine	*Rhodophiala bifida*	Collagen-induced arthritis	Inhibition of lymphocyte proliferation and decreased FLS invasion	[73]
7	Bartogenic acid	*Barringtonia racemosa* Roxb.	CFA-induced arthritis in rats	Reduced serum markers, such as rheumatoid factor and C-reactive protein, protection against primary and secondary arthritis lesions	[74]
8	Ferulic acid	Rice and corn grains	CFA-induced arthritis in rats	Significant reduction in arthritic index, ESR levels, and the percentage of lymphocytes, reversal of rheumatoid factor and C-reactive protein to normal level	[75]
9	Resveratrol	Peanut, mulberry, cranberry, grape, and pistachio	CFA-induced arthritis in rats	Inhibits the mRNA expression of IL-1β and TNF-α, inhibits the enzymatic activity of COX-1 and COX-2.	[76]
10	Fangchinoline	*Stephania tetrandra S.* Moore	Collagen induced arthritis rat model	Reduces the levels of IFN-α, IL-6, NO, uric acid and ceruloplasmin, induces chondrocyte proliferation, thus reducing cartilage degeneration	[77]

continued...

Table 2: Cont'd.

Sl. No.	Phytocompound	Plant source	*In vivo* arthritis model	Findings	Reference
11	Liquiritin	*Glycyrrhiza uralensis*	Collagen induced arthritis rat model	Induces synovial membrane apoptosis, promotes DNA fragmentation, changes in the mitochondrial membrane, and decreases the Bcl-2/BAX rate, resulting in the reduction of inflammation	[78]
12	Oroxylin A	*Scutellariae baicalensis* Georgi	Collagen induced arthritis mouse model	Reduced serum levels of IL-1β, IL-6, TNF-α, and IL-17, increased number of regulatory T cells,	[79]
13	Berberine	*Cortex phellodendri, Mahonia bealei* and *Rhizoma coptidis.*	CFA-induced arthritis in rats	Decreasing IL-6 and IL-17 production and increasing the expression of IL-10 and TGF-β, it attenuates synovial hyperplasia and decreases the inflammatory infiltrate in the joint	[80]
14	Oxymatrine	*Sophora flavescens* Ait	Collagen-induced rat model	Regulate lymphocytes cellular response, decreasing the population of circulating Th17 lymphocytes and increasing the population of regulatory T lymphocytes	[81]
15	Asperosaponin VI	*Dipsacus asper*	Collagen-induced rat model	Inhibits osteoclast genesis by reducing the expression of genes and markers of signaling pathways that lead to osteoclast proliferation.	[82]

arthritis, it is an arduous task to cover all of them. Hence, some of them are listed in Table 2.

Nanocarrier based herbal formulations for arthritis

A major challenge in the treatment of arthritis using herbal drugs is their poor absorption, because most of the herbal drugs are unable to cross the lipid membranes, have large molecular sizes or are poorly absorbed, resulting in poor therapeutic effects and bioavailability. To achieve required therapeutic effects needed higher consumption of herbal drugs leading to unwanted toxicity.[83,84] Therefore, novel drug delivery systems is urgently needed to overcome above challenges. Nanotechnology is an attractive approach which breaks these barriers. Nanotechnology offers multiple benefits in treating human chronic diseases (like arthritis, cancer, diabetics, etc.) by site-specific and target oriented delivery of precise medicines. This advance nanotechnology is used to creation of very tiny particles, devices and systems which range from nano-scale. As nanoparticles (NPs) comprise materials designed at the atomic or molecular level, where active ingredient or drug either absorbed on the surface or entrapped within the nanoparticles core.[85-87] NPs can be categories into different types depending on their morphology, size and chemical properties. Some of them included polymeric nanoparticles (PNPs), metallic nanoparticles (MNPs), lipid-based nanoparticles (LBNPs).[88] Various NPs exhibit a wide range of physical and chemical properties that significantly affect their biomedical potential. Encapsulating the herbal drugs into NPs improve *in vivo* stability, minimize dosing frequency, extend their circulation time, allow for controlled and sustained release of drugs.[89] Basically, there are two approaches through which NPs deliver drugs; passive and active targeting approach. In passive targeting approach, where drugs specifically accumulating at the targeting sites through enhanced permeability and retention (EPR) effects, and avoid non-specific distribution. In active targeting approach, where nanoparticulate drug delivery systems further modified to improve therapeutic efficacy and minimize toxicity through the high affinity ligands to the receptors express under certain circumstances like disease condition.[90] Currently, various medicinal plants extracts or phytoconstituents based

Table 3: Some medicinal plant extract based nanoformulations.

I. Leaf Extracts based Nanoformulations:						
Medicinal plants	**Formulations**	**Methods of Preparation**	**Shapes**	**Sizes (nm)**	***In vivo* Anti-arthritis Effects**	**Refs.**
Ocimum Sanctum (Lamiaceae)	Nanostructured lipid carriers (NLCs)	Solvent evaporation method	Spherical	120	Significantly inhibits immune response and inflammatory mediator (PGE2), reducing vascular permeability	[91]
Cassia auriculata Linn. (Caesalpiniaceae)	CuO nanoparticles	Green synthesis	Spherical	23	-	[92]
Rabdosia rubescens (Labiatae)	CuO nanoparticles	Green synthesis	Spherical	30-90	Significantly reduced pro-inflammatory cytokines level and improved antioxidant enzymes status	[93]
Phoenix dactylifera (Arecaceae)	Silver nanoparticles	Green synthesis	Spherical	203	-	[94]
Cissus quadrangularis (Vitaceae)	CuO Nanoparticles	Green synthesis	Irregular	90	-	[95]
Mansoa alliacea (Bignoniaceae)	Gold nanoparticles	Green synthesis	Face centered cubic structure	30	*M. alliacea* extract based nanoformulation have shown almost same analgesic activity to the morphine	[96]
Tamarix articulata (Tamaricaceae)	Silver nanoparticles	Green synthesis	Spherical	25	-	[97]
Selaginella myosurus (Selaginellacea)	Silver nanoparticles	Green synthesis	Spherical	58.81	Inhibited edema rate as compared to control group that indicated drug having potential anti-inflammatory activity	[98]
Tectona grandis (Lamiaceae)	ZnO Nanoparticles	Green synthesis	Spherical	124.6	-	[99]
Manilkara zapota (Sapotaceae)	Gold nanoparticles	Green synthesis	Spherical	41.90	Decreases paw volume, joint diameter and pro-inflammatory cytokines.	[100]
II. Flowers Extracts based Nanoformulations						
Sambucus nigra L. (Adoxaceae)	PLGA and PCL- base nanoparticles	Emulsificatio-n/ solvent di-usion and solvent-displacement methods.	Spherical	471.3, 164.2	Inhibited oedema, decreases cytokines level such as TNF-α, IL-6.	[101]

continued...

Table 3: Cont'd.

Medicinal plants	Formulations	Methods of Preparation	Shapes	Sizes (nm)	*In vivo* Anti-arthritis Effects	Refs.
Nyctanthes arbor-tristis (Oleaceae)	ZnO nanoparticles	Green synthesis	Spherical	12-32	-	[102]
Woodfordia fruticose (Lythraceae)	Phytosomes	Solvent evaporation method	Spherical	213.1	-	[103]
Malva sylvestris (Malvaceae)	Silver nanoparticles	Green synthesis	Sphericaland hexagon-al	20-40	-	[104]
Datura inoxia (Solanaceae)	Silver nanoparticles	Green synthesis	Polygona-l	15-73	-	[105]
Lantana camara (Verbenaceae)	CuO nanoparticles	Green synthesis	Spherical	13-28	-	[106]
Abelmoschus esculentus (Malvaceae)	Silver nanoparticles	Green synthesis	Cubic	5.52-31.96	-	[107]
III. Fruits Extracts based Nanoformulations						
Phoenix dactylifera (Arecaceae)	Silver nanoparticles	Green synthesis	Face centered cubic structure	42	-	[108]
Piper nigrum (Piperaceae)	Silver nanoparticles	Green synthesis	Spherical	26	Significantly reduced paw edema, synovial hyperplasia, inflammatory infiltrates and cartilage/ bone erosion when compared to arthritis controls	[109]
Foeniculum vulgare Mill. (Apiaceae)	Selenium nanoparticles (SeNP)	Biological method	Spherical to irregular	47.14	SeNP prominently reduced paw volume, not adverse effects, and sign of bone erosion	[110]
Emblica Officinalis (Euphorbiace-ae)	Phytofabricate-d selenium nanoparticles	Biological method	Spherical	15-40	-	[111]
European black elderberry (Adoxaceae)	Silver nanoparticles	Green synthesis	Spherical	20-80	AgNPs significantly reduced paw edema volume and pro-inflammatory cytokines levels in carrageenan induced rats model	[112]
Prunus serrulata (Rosaceae)	Silver and gold nanoparticles	Green synthesis	Spherica, hexagonal	66, 65	-	[113]
Dillenia indica (Dilleniaceae)	Gold nanoparticles	Green synthesis	Cubic crystal	5-50	-	[114]
Hovenia dulcis (Rhamnacea-e)	Gold nanoparticles	Spherical, hexagonal	Spherical, hexagonal	15-20	-	[115]

continued...

Table 3: Cont'd.

Medicinal plants	Formulations	Methods of Preparation	Shapes	Sizes (nm)	*In vivo* Anti-arthritis Effects	Refs.
IV. Roots Extracts based Nano formulations						
Saussurea lappa (Compositae)	ZnO nanoparticles	Green synthesis	Hexagon-al	123.5	-	[116]
Curcuma longa Linn. (Zingiberacea-e)	Turmeric rhizome extract nanoparticles	Solvent displacement method	Spherical	159.6	-	[117]
Acorus calamus (Acoraceae)	Silver nanoparticles	Green synthesis	Spherical	20-35	-	[118]
Rhodiola rosea (Crassulaceae)	Silver nanoparticles	Green synthesis	Spherical	10	-	[119]
Marsilea quadrifolia Linn. (Marsileaceae)	Copper nanoparticles	Biogenic synthesis	Leaf like structure	25.20	-	[120]
Trillium govanianum Wall. (Trilliaceae)	Silver nanoparticles	Green synthesis	Cubic like structure	9.99	-	[121]

nanoparticulate carriers system has been developed for the treatment of arthritis as shown in Table 3 and 4.

Polymeric Nanoparticles (PNPs)

PNPs are colloidal drugs delivery system that works as a vectors or carriers for targeted delivery of drugs. Their sizes can range from 10 to 1000 nm and are comprised of either natural or synthetic polymers, where active constituents can be absorbed on the polymeric shell or encapsulated within the polymeric core.[143,144] Depending upon their internal structure, PNPs can be further classified into two types; nanocapsules (reservoir system), and nanospheres (matrix system). Nanocapsules are made of a liquid/ solid core (generally oily core) surrounded by a polymeric membrane, where active constituents can be dissolved in the nanocapsules core or absorbed onto their surface or both. Whereas, nanospheres are made of solid polymeric matrix, where the active constituents are either entrapped inside the matrix, or, absorbed onto surface, or both.[145,146] In contrast to other NPs, PNPs have given more importance because it can be easily prepared, have the ability to release drugs more slowly, possess higher stability and reduced frequency of administration.[89] Additionally, smart drug delivery system is achieved by surface modification of PNPs with different stimuli-responsive (i.e., pH, temperature, light, redox, and enzyme) materials. Some common advantages of this nanocarrier systems includes achieve targeted drugs delivery, controlled manner of drug release, reduced dosing frequency, improved bioavailability, protecting drugs from *in vivo* degradation, and reduced toxicity.[147,148] For arthritis, various plant extracts or phytoconstituents based PNPs have been reported in the literature (Table 3 and 4). However, they also have some drawbacks such as problems in scale-up process, difficulty in physical handling and lack of their toxicity assessments.[149,150]

Metallic Nanoparticles (MNPs)

In recent times, MNPs (at a size range between 1 to 100 nm) have gained increasing attention due to their high performance in many scientific fields, such as drug delivery, agriculture, and engineering.[151] However, MNPs offers significant advantages especially in the field of herbal drug delivery systems by improving therapeutic index of drug through site specificity, preventing multidrug resistance, providing synergistic action, reducing toxicity and their therapeutic dosing frequency.[152,153] Various herbal drugs based MNPs are given in Table 3 and 4.

There are three preparation technique widely employed for the synthesising of MNPS, such as physical, chemical and biological methods. However, lots of problem arise with physical and chemical methods of preparing MNPs, such as requirement of costly specialized equipment, consumes high amount of energy, occupies large space, times consuming, reagents required are highly reactive to environment and human.[154] Recently, biological methods are most commonly used for the synthesis of various MNPs due to their cost-effective, eco-friendly nature, and

Table 4: Some phytoconstituents based anti-arthritic nanoformulations.

Phyto-constituents	Formulations	Methods of Preparation	Shapes	Sizes (nm)	*In vivo* Anti-arthritis Effects	Refs.
Curcumin	Solid lipid nanoparticles (SLNs)	Emulsification method	Spherical	134.6	This formulation significantly reduced the joint inflammation, and improved mobility score, joint hyperalgesia and joint stiffness of CFA-injected rats model.	[122]
Rutin	Phytosomes	Solvent evaporation method	Rod	684-1628	Significantly reduced in paw volume of carrageenan induced rats model.	[123,124]
Quercetin	Nanoemulsion	Spontaneous emulsification Technique	Spherical	136.8	Significantly reduced in paw volume, arthritic index, stiffness score, and hematological parameters like RBC and Hb.	[125]
Berberine	Polymeric Micelles	Dialysis method	Spherical	153	Significantly reduced in paw volume, inhibited cytokines generation and bone destruction.	[126]
Piperine	Solid lipid nanoparticles	Melt emulsification method	Not available	128.80	Significantly reduced in paw volume, bone erosion and destruction.	[127]
Capsaicin	Transfersomes	Thin film hydration method	Spherical	94	This formulation significantly reduced in paw edema volume of carrageenan, formaldehyde and FCA induced rats model.	[128]
Eugenol	Polymeric nanoparticles	Ionic-gelation method	Spherical	30.8-37.95	Significantly reduced in edema volume, synovial hyperplasia, pannus formation, and erosion of cartilage/bone.	[129]
Apigenin	Solid lipid nanoparticles	HPLC method	Spherical	100.13-202.41	Significantly decreased in cytokines (TNF-α and IL-1β) level, and paw volume of arthritis induced rats.	[130]

continued...

Table 4: Cont'd.

Phyto-constituents	Formulations	Methods of Preparation	Shapes	Sizes (nm)	*In vivo* Anti-arthritis Effects	Refs.
Epigallocatechin-3-O-gallate	Nanoparticles	Ultrasonication	Spherical	186	Significantly reduced in paw volume and bone erosion of FCA induced rats.	[131]
Mangiferin	Nanoemulsions	Sonication method	Spherical	296	Significantly reduced oedema, oxidative stress, and infiltration of inflammatory cells.	[132]
Triptolide	Nanoparticles	Emulsion-Solvent Evaporation Method	Spherical	79	This Nanoformulations significantly reduced inflammation area, bone erosion and cartilage loss.	[133]
Naringenin	Nanocrystals	Planetary ball mill	Rod	282.5	Significantly reduced paw volume, arthritis scores, and inflammatory cells infiltration.	[134]
Caffeine	Gold nanoparticles	Green synthesis	Spherical	12-16	-	[135]
Fisetin	Polymer nanoparticles	Single emulsion evaporation method	Quite spherical	87.3-198.7	-	[136]
Silymarin	Polymer nanoparticles	Emulsification and solvent evaporation method	Spherical	180	-	[137]
Andrographolide	Silk fibroin nanoparticles	Emulsification method	Spherical	100-500	-	[138]
β-Sitosterol	Solid lipid nanoparticles	Double emulsion solvent displacement method	Spherical	67- 73.06	This formulation significantly reduction the cytokines and inflammatory mediators.	[139]
Nerolidol	Polymeric nanoparticles	Polymer interfacial deposition method	Spherical	219.5	Significantly inhibited neutrophil migration and controlled edema, neutrophil and lymphocyte infiltration.	[140]
Xylopic acid	Reconstituted high-density lipoprotein (rHDL) nanoparticles	Thin film dispersion method	Spherical	163	Significantly reduction the inflammatory cytokines level like TNF-α and NF-κB.	[141]
Withaferin-A	Liposomes	Thin film hydration method	Spherical	97.2	Significantly suppressed the ankle joint inflammation, edema and synovial macrophages.	[142]

rapid synthesis process, as compared to physical and chemical methods. Biological or so-called green methods in which the toxic chemicals are not used in the preparation techniques adopts bacteria, fungi, algae, and plants for synthesising NPs.[155,156] Among them, plant-mediated green synthesis has gained extensive popularity because of its being eco-friendly, accessibility, economical, execution-simplicity, and the possibility of large-scale production.[157] Different parts of the plants are used to synthesis of MNPs, such as leaves, flowers, roots, and seeds. Plant crude extract may contain several phytochemicals such as phenolic acid, flavonoids, alkaloids and terpenoids that are needed for the synthesis of MNPs via bio-reduction of metallic ions. Green synthesis of MNPs using plant extract involves three important parameters such as metal salt, reducing agent, and stabilizing or capping agent.[158] Currently, many researchers have employed green synthesis principle for synthesising various plants based MNPs, such as silver nanoparticles (AgNPs), gold nanoparticles (AuNPs), zinc oxide nanoparticles (ZnO NPs), and copper oxide nanoparticles (CuO NPs).[159-162]

Silver Nanoparticles (AgNPs)

In last few decades, AgNPs have gained extensive popularity in various fields such as biomedicine, catalysis, energy storage, and sensors, due to their unique physical, chemical and biological properties. Among these, AgNPs have been given special interest in biomedicine field due to their unique physio-chemical properties. AgNPs are also well known for their targeted therapy of various inflammatory diseases such as arthritis.[163,164] Many AgNPs are synthesized using different plant extracts or phytoconstituents having potential to enhance the therapeutic benefits. Moreover, they are also able to deliver the loaded contents inside the cells through improved cross-membrane transport along with releasing loaded contents in sustained and prolonged manner.[165,166]

Gold Nanoparticles (AuNPs)

The AuNPs are a novel option for treatments and diagnostics of various kinds of inflammatory diseases such as arthritis. However, its application has become limited due to their high incidents of side effects.[167] AuNPs cytotoxicity as well as cellular uptake depends on their particles size, shape, and surface functional properties. For example, cellular uptake increase by decreasing AuNPs particles size and decrease in cellular cytotoxicity was observed in case of CTAB (cetyltrimethylammonium-bromide) loaded cube and rod shaped particles as comparison to spherical and prismatic particles.[168,169] Green synthesis of AuNPs is one of the attractive alternative approaches which overcome the toxicity associated with other methods, especially in the chemical methods.[170]

Zinc Oxide Nanoparticles (ZnO NPs)

The ZnO NPs are given more importance in comparison to other metal and metal oxide nanoparticles, due to their excellent biomedical properties. Zinc is considered as one of the most important supplements to regulate various physiological processes such as metabolisms, enzyme regulation, maintaining cell redox balance, protein and DNA synthesis. ZnO NPs have a wide range of biological applications due to their easy preparation methods, biocompatibility, low cost, and they are also listed as "generally recognized as safe" (GRAS) by the U.S. FDA (21CFR182. 8991).[171,172] ZnO NPs are also well known for their antioxidant and free radical scavenging activities. Additional, they have potent ant-inflammatory activity that is highly beneficial for the treatment of various inflammatory diseases including arthritis.[173]

Copper Oxide Nanoparticles (CuO NPs)

Demand for CuO NPs is increasing in various fields due to their optical, catalytic, mechanical and electrical properties.[174] CuO NPs possess intrinsic antioxidant, anti-inflammatory, antibacterial, and anti-fungal properties. Among them, antioxidant and anti-inflammatory properties of CuO NPs are needed to design suitable drug delivery systems against various inflammatory diseases including arthritis.[175] A study reported that plant-mediated green synthesis of CuO NPs can scavenge free radicals, has improved stability, prevented agglomeration, and deformation of the NPs due to their antioxidant property of polyphenolic flavonoids compounds.[176] There are several factors such as method of preparation, solvents, surfactants, and temperature used in synthesizing CuO NPs, which are responsible for controlling the size and shape of the NPs.[174] Moreover, copper is a trace element that is required for normal physiological function including carbohydrate metabolisms, drug metabolisms, and antioxidant defence system.[177]

Lipid-Based Nanoparticles

Lipid-based nanocarriers are composed of various physiological lipids that are well known for their biocompatible, biodegradable, well tolerable, and nontoxic properties. From the last few decades, lipid-based nanocarriers such as liposomes, phytosomes, transferosomes, solid lipid nanoparticles (SLNs), and nano-structure lipid carriers (NLCs) have received great attention in anti-inflammatory drugs delivery.[178] A list of anti-inflammatory drugs used for arthritis is described in Table 3 and 4.

Liposomes

Liposomes are small artificial vesicular carrier systems that are usually composed of phospholipids, including glycero-phospholipids and sphingomyelins encapsulating hydrophobic, hydrophilic, and amphiphilic bioactive compounds with their self-assembling and cell-resembling behaviours.[179,180] Because of their unique properties, liposomes are able to alter the pharmacokinetic profile, enhance intracellular uptake, and

provide *in vitro* and *in vivo* stability of various anti-inflammatory drugs.[181] Multiple studies proved that curcumin has a potential therapeutic effect against progressive arthritis, which mainly inhibits the production and activity of inflammation-associated markers such as TNF-α, nuclear factor-κB (NF-κB), cyclooxygenase-2 (COX-2), mammalian target of rapamycin (mTOR), and interleukins. However, bioavailability of curcumin is low due to their poor solubility in water. Moreover, curcumin loaded liposomes improved bioavailability, and helped in preventing the first-pass metabolism.[182] A study also reported that triptolide-entrapped liposomes in a rat model of collagen-induced arthritis (CIA) showed slower release and a longer half-life in plasma as well as decreased toxicity when compared to free triptolide.[183] However, further modifications of liposomes are needed to overcome various drawbacks such as stability, reproducibility, entrapment efficiency, size distribution, and biological half-life.[184]

Phytosomes

The majority of the plant constituents, specifically phenolic compounds have limited therapeutic application owing to their poor lipid solubility, large molecular size, and their *in-vivo* degradation. However, phospholipids based drug delivery systems have been found promising for better and effective delivery of these water soluble phytoconstituents in the body.[185] This technique can be applied for both conventional and herbal doses forms, and are popularly known as phytosomes. The term "phyto" refers to the plant, while "some" refers to the cell-like. Phytosomes are usually prepared by reacting of one or two moles of standardized plant extract and phospholipids mainly phosphatidylcholine producing a lipid compatible molecular complex.[186] Phosphatidylcholine acts as a bifunctional compound and is comprised of a head (choline moiety) and tail (phosphatidyl moiety) parts. The choline head of the phosphatidylcholine build link between the bioactive compound and the phosphatidyl moiety while tail covers choline-bounded material.[187] Due to their unique properties, phosphatidylcholine are suitable for delivery of various anti-arthritis drugs from plant sources such as rutin, catechins and silymarin.[188-190]

Transferosomes

Transferosomes are the ultra-deformable or malleable vesicles, consisting of phospholipids and an edge activator where both hydrophilic and lipophilic drug can be encapsulated with the help of the self-assembling behaviour of phospholipids. Edge activators are used with the purpose of increasing the flexibility and ultra-deformability of the vesicles membranes.[191] The structure of transferosomes is almost similar to liposomes, but has better skin penetration properties.[192] A study showed that the designed transferosomes for the treatment of rheumatoid arthritis loaded with curcumin had the potential to deliver the drug into deeper layer of the skin tissues and produce anti-arthritic activity on CFA-induced rat model.[193] Another study reported the anti-arthritic activity of capsaicin-loaded transfersomes in CFA –induced arthritic rats where the reduction in paw volume, inhibition of pro-inflammatory mediators were observed.[128]

Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are colloidal drug delivery system composed of phospholipids, dispersed in water or in an aqueous surfactant solution. In last few decades, SLNs based drug delivery system have been given more attention due to their unique properties such as small size, large surface area, high drug loading, and their surface charge.[194] SLNs compared to other colloidal systems (such as liposomes and polymeric nanoparticles) have higher physicochemical stability, protects labile drug from degradation, and can be manufactured in large scale.[195] They can be used for the treatment of various inflammatory diseases including arthritis.[196] A study showed that hesperidin loaded solid lipid nanoparticle improves arthritic score and reduced joint inflammation in CFA-induced rat model. This indicated that hesperidin loaded solid lipid nanoparticle have the potential to improve anti-arthritic activity.[197]

Nanostructured lipid carriers (NLCs)

NLC, the second generation lipid nanoparticles was developed by the Müller group in 1999 and it improves the burst-release problem associated with SLNs. NLCs are nanosystems composed of a solid lipid matrix incorporated with oil or liquid lipid.[198] A study reported investigation of anti-arthritic potential of ursolic acid rich *Ocimum sanctum* L. leaf extract loaded nanostructured lipid carriers on adjuvant induced arthritis in rats by pharmacological and docking studies. The authors found that the formulation was successful in reducing the rat paw volume with decreased WBC count and enhanced RBC count. The formulation also reduced IL-1 and TNF-α level and findings of COX-1 and COX-2 study indicated the inhibitory effects of the formulation against these enzymes.[91] Another study reported the anti-arthritic activity of ginger extract loaded NLC on CFA-induced arthritis rat models, where the decrease in rat paw volume was observed and the microscopic observations suggested the ability of the treatment to mitigate arthritic lesions.[199]

Despite nanoformulations providing plenty of advantages, there are certain challenges that need addressing such as poor regulations for preparation and evaluation of nanomedicines, lack of standard toxicity and safety profile. These are the main reasons that despite abundant availability of literature on herbal anti-arthritic nanoformulations at preclinical stage, many studies fail to reach the clinical stage. This calls for reformation in regulatory guidelines on nanomedicines.

CONCLUSION

The damages caused by arthritic condition are unparalleled as it affects physical, psychological, and economical condition of the suffering individuals as well as their care-takers. And yet, there is no such therapeutic regiment that can permanently alleviate this condition and their peculiar and unclear etiology is one of the contributing factors to this. The conventional and present therapeutics and medications that are being provided to the patients associates with lot of adverse effects. Since remote ages, our ancestors have put their belief in plants and plant-based therapy for healing of many ailments, including arthritis. Many literatures dealing with herbal medicines listed many plants and their extracts possessing anti-arthritic potentials. Based on this, the researchers have investigated many plants, their extracts, and isolates tweaking the traditional methods with new age pharmaceuticals formulation techniques such as nanomedicine. Since, the crude plant products are prone to stability issues; they are being amalgamated with nano-medicinal technologies to achieve a better, safer, more stable, target-specific, novel drug delivery system, which leads to the development of anti-arthritic herbal formulations. In this review, we have tried to canvas the reported crude based anti-arthritic herbal drugs; phytocompound based herbal drugs having anti-arthritic potential, and most importantly their more better and improved nano counterparts. However, still there is a long way to pave to achieve such medicine that can completely alleviate arthritis, but the bright side is that there are scopes of achieving this with the developing formulation technologies and abundant flora provided by Mother Nature.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

OA: Osteoarthritis; **RA:** Rheumatoid arthritis; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **DMARDs:** Disease modifying anti-rheumatic drugs; **CFA:** Complete Freund's adjuvant; **COX-2:** cyclooxegenase-2; **TNF-α:** Tumor necrosis factor-α; **IL:** Interleukin; **NF-κB:** Nuclear factor-κB; **MMP:** Matrix metalloproteinase; **anti-colII IgG2a:** Anti-collagen II Immunoglobulin G2a; **PGE2:** Prostaglandin 2; **MIA:** Monosodium iodoacetate; **FDA:** Food and drug administration; **JNK:** C-Jun N-terminal kinase; **iNOS:** Indcible nitric oxde synthase; **RASFs:** Rheumatoid arthritis synovial fibroblasts; **FLS:** Fibroblast-like synoviocytes; **IKK:** IkB kinase; **CBD:** Cannabidiol; **BAFF:** B-cell activating factor; **IFN:** Interferons; **MAPKs:** Mitogen-activated protein kinases; **ESR:** Erythrocyte sedimentation rate; **NO:** Nitric oxide; **Bcl-2/BAX:** B-cell lymphoma protein 2-associated X; **Th17:** T helper 17 cells; **NPs:** Nanoparticles; **ZnONPs:** Zinc oxide nanoparticles; **Ag NPs:** Silver nanoparticles; **SeNPs:** Selenium nanoparticles; **RBC:** Red blood cells; **WBC:** White blood cells.

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