IJPSR (2013), Vol. 4, Issue 10 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 May, 2013; received in revised form, 17 July, 2013; accepted, 13 September, 2013; published 01 October, 2013

CURRENT STRATEGIES IN HERBAL DRUG DELIVERY FOR ARTHRITIS: AN OVERVIEW

Sunita Y. Ranade* and Ram S. Gaud

Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's Narsee Monjee Institute of Management Studies, Vile Parle (West), Mumbai – 400 056, Maharashtra, India

Keywords:

Arthritis, Herbal, Therapy, Novel drug delivery

Correspondence to Author:

Sunita Y. Ranade

Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's Narsee Monjee Institute of Management Studies, Vile Parle (West), Mumbai – 400 056, Maharashtra, India

E-mail: sunitaranade12@gmail.com

ABSTRACT: Arthritis is still a challenge for medical research. Pharmaceutical research has resulted in several new approaches for treatment/management of arthritis including drugs like the biologic disease modifying anti-rheumatic drugs (DMARDs). Several disadvantages like serious side effects, high costs and requirement of parenteral administration still invite more research in this area to provide a convenient, affordable therapy with lesser or no side effects. Traditionally used herbal medicines, due to their anti-inflammatory and immunomodulatory properties, have potential to be a therapy of choice for arthritis patients and are now extensively being studied. Although a number of these medicines are being used traditionally for their therapeutic activity, development of their novel drug delivery systems was not attractive to the scientists due to insufficient knowledge about their exact mechanism of action and difficulties in processing, standardising, extracting and identification of active constituents. Current research demonstrates that the effectiveness and bioavailability of herbal actives can be improved by understanding of exact mechanism of action and by formulating them into novel technologies like liposomes, phytosomes and transdermal drug delivery. The present review focuses on herbal medicines for arthritis along with various strategies adopted by scientists so as to improve the bioavailability, stability and to reduce the side effects of these medicines so as to provide consistently effective alternative medication for arthritis. The strategies include understanding mechanisms of their action, enhancing solubilities of poorly soluble actives and developing novel drug delivery systems of these herbal medicines.

INTRODUCTION: Arthritis is the condition in which inflammation of a joint occurs, usually accompanied by pain, swelling, and stiffness. It may be caused by infection, trauma, degenerative changes, metabolic disturbances, or other causes.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(10).3782-94

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.4(10).3782-94

Osteoarthritis (OA), rheumatoid arthritis (RA) or bacterial arthritis is usually the forms in which arthritis exists [1]. Arthritis is a health problem prevailing throughout the globe and the rate at which the number of people suffering from this condition worldwide is alarming.

OA is reported to affect approximately 13.9% of adults who are ≥25 years of age in the USA. Frequency of OA is reported to be higher in women, particularly after reaching 50 years of age. Women are reported to have greater risk for developing OA in the knee or hip [2].

RA is estimated to affect 1.5 million adults in USA. RA sufferers are typically younger than those who develop OA, with the incidence at its peak at 35 to 50 years of age. Women are reported to have higher incidence of RA [3]. It is estimated that the number of people with arthritis in the USA is expected to rise to 67 million by 2030 [4, 5]. In India, the prevalence of OA among elderly is nearly about 56.6% [6]. Prevalence of OA was reported to be in the range of 17% to 60.6% in India as shown by community survey data in rural and urban areas. RA has a prevalence of 0.75%, this would give a total of about seven million patients in India if projected to the whole population.

The prevalence of RA in India is higher than that reported from China, Indonesia, and Philippines [6]. Arthritis and related conditions have been found to be third largest contributors, behind cardiovascular disease and neurological disorders, to the direct expenditure on health in the western world and USA. [7].

The pathophysiology of OA and RA is distinct although the primary manifestations of both involve the joints. OA is characterized by progressive cartilage loss. Increased thickness of the subchondral plate, osteophytes and subchondral bone cysts are the characteristic features. Vascular invasion and further calcification of nearby articular cartilage may occur as the disease progresses, leading to decreased thickness of articular cartilage. Bone remodeling and enhanced cartilage deterioration takes place over time [8]. The inflammation is generally milder in severity than that observed in rheumatoid arthritis and typically involves the periarticular tissues.

Rheumatoid arthritis is a chronic, autoimmune syndrome. Autoimmune inflammation is a result of a response to self-antigens. Thus, a dysregulated immune system results in autoimmune diseases [9]. Synovial inflammation leading to cartilage and bone damage is characteristic of the disease. Persistent inflammation leads to progressive destruction of articular and periarticular structures which in turn, lead to deformity. Morning stiffness is a common problem for patients with rheumatoid arthritis [10, 11, 12]. Characteristic features of RA pathophysiology are increased angiogenesis, cellular hyperplasia, influx of inflammatory cells, changes in the expression of cell surface adhesion molecules and presence of many cytokines. Tumour necrosis factor (TNF) and interleukin-1 are in abundance in the joints. They are the stimulators of proliferation, metalloproteinase expression, adhesion molecule expression, and further secretion of other cytokines [13]. CD4 T cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils play major role in pathophysiology of rheumatoid arthritis. Presence of anti-cyclic citrullinated protein antibody (ACPA) and rheumatoid factor (RF) is highly specific for RA.

Autoantibodies (i.e. RFs) are produced by B cells. Abnormal production of numerous cytokines, chemokines and other inflammatory mediators is involved [12]. Formation of rheumatoid nodules is one of the most common extra-articular manifestations of RA. The outer zone of rheumatoid nodules is granulation tissue, palisading macrophages form the mid-zone, and a central zone is of necrotic material. Several pulmonary, ocular and neurologic manifestations are also observed [14].

Diverse options are available for treatment of arthritis in terms of their mechanisms of action and the mode of drug delivery; however, no single agent has been established to consistently offer a high level of tolerability and low incidence of adverse effects combined with a sustained level of efficacy in a broad patient population [15].

Management of osteoarthritis involves use of NSAIDS to control pain. Intra-articular corticosteroid injections, intra-articular injections of hyaluronic acid–like products, surgery for patients whose symptoms are not adequately controlled with medical therapy are other forms of therapy for osteoarthritis [16]. Management of rheumatoid arthritis aims to control the pain and swelling, delay the progression of disease and improve the quality of life. The current therapies for rheumatoid arthritis are as follows [17, 18]:

i. Non-steroidal anti-inflammatory drugs (NSAIDs)

ii. Glucocorticoids

iii. Non-biologic disease-modifying anti-rheumatic drugs (DMARDs) and

iv. Biologic DMARDs

There is increasing evidence that many current drug therapies attempt to suppress symptoms than addressing the underlying disease processes [19].

Non-steroidal anti-inflammatory Drugs (NSAIDs), the drugs with analgesic, antipyretic and anti-inflammatory effects due to their inhibitory action on cyclooxygenase (COX), can very effectively relieve pain and stiffness at RA onset. They are usually employed as bridge therapy until the slow-acting DMARDs become effective. However, long-term administration of NSAIDs may result in persistent adverse events, gastrointestinal (GI) complications, such as gastric ulceration, bleeding, dyspepsia and nausea being most significant. They also have the potential to be nephrotoxic which may result in nephrotic syndrome and interstitial nephritis. Cardiovascular adverse events like myocardial infarction and cardiac arrest have been observed with NSAIDs which are selective COX-2 inhibitors [20, 21].

Glucocorticoids (GCs), belonging to class of steroid hormones, have potent anti-inflammatory and immunosuppressive properties. Recent studies have established potential of with low-dosage long-term treatment with glucocorticoids in reducing the rate of erosion progression in RA [22]. Adverse effects of glucocorticoids occur in different organs and may be life threatening. The major complication of long-term GC therapy is gluococorticoid-induced osteoporosis. Side effects also include adrenal insufficiency, peptic ulcers, skin atrophy, infection and cataract [17].

Therapy with DMARDs is considered for all patients with rheumatoid arthritis. New, targeted biological therapies against proinflammatory cytokines have emerged as a result of increasing knowledge regarding the immunologic basis of RA and advances in biotechnology [23].

Newer drugs are designed with strict reference to pathophysiology of rheumatoid arthritis [24]. Risks associated with methotrexate, most commonly prescribed DMARD, are hepatotoxicity and cytopenia, as well as pneumonitis, particularly during the first year of treatment. In case of TNF inhibitors, infection by bacterial pathogens, atypical fungi and opportunistic pathogens is a major risk. Gastrointestinal perforation with tocilizumab, progressive multifocal leucoencephalopathy with rituximab and pulmonary infections with abatacept are some of the specific risks associated with biologic DMARDs [23, 25].

Appropriate management of arthritis can result in reduced pain and help to overcome functional limitations to a greater extent. Medication, physical or occupational therapy, patient education, weight loss, and surgery may be included in treatment and management of arthritis [26]. Though conventional treatment of rheumatoid arthritis is improving, treatment still remains unsatisfactory as remission is rare. Therefore, search remains on going for effective alternative and additional therapies for this disease. Complementary and alternative medicine (CAM) therapies are now being increasingly used. These therapies are a group of practices or products that are not currently used in the practice of conventional medicine [27]. Callahan LF, *et al* reported estimates of CAM use among adults with arthritis to be ranging from 59% to 90% [28].

The literature of Ayurveda describes various plants, to be used as whole, in part or as extracts for treating painful and inflammatory conditions like arthritis. Table 1 gives a list of some of the herbs reported for use in arthritis [29].

TABLE 1: SOME HERBS REPORTED FOR USE IN ARTHRITIS [29]

Name of the herb	Family
Alpinia galanga	Zingiberaceae
Aquilaria agallocha	Thymeleaceae
Argreiay nervosa	Convolvulaceae
Boswellia serrata	Burseraceae
Butea monosperma	Fabaceae
Callicarpa macrophylla	Verbenaceae
Capparis decidua	Capparaceae
Capsicum annuum	Solanaceae
Cardiospermum halicacabum	Sapindaceae
Carthamus tinctorus	Asteraceae
Ficus benghalensis	Moraceae
Gossypium herbaceum	Malvaceae
Hyocyamus niger	Solanaceae
Illicium verum	Magnoliaceae
Justicia gendarussa	Acanthaceae
Ocimum basilicum	Lamiaceae
Pandanus odoratissimus	Pandanaceae
Piper nigrum	Piperaceae
Ricinus communis	Euphoebiaceae

Rubia cordifolia	Rubiaceae
Sida Cordata	Malvaceae
Sida rhombifolia	Malvaceae
Tectona grandis	Verbenaceae
Trachyspermum roxburghianum	Apiaceae
Tribulus terrestris	Zygophyllaceae
Vitex negundo	Verbenaceae

A number of inexpensive herbal medicines have been reported in literature to be useful in rheumatoid arthritis due to their anti-inflammatory and immunosuppressive potential [30, 31]. The World Health Organization (WHO) recognizes Ayurveda as a complete system of natural medicine. It sponsored the first-ever study of a traditional medical system of complete, classical Ayurvedic treatment for rheumatoid arthritis (RA). The study was conducted in collaboration with the Indian Council for Medical Research (ICMR) and the *Ayurvedic* Trust, Coimbatore, Tamil Nadu, India, from 1977 to 1984 [32].

Herbal medicines have been recognized by physicians and patients for their lower incidences of side effects as compared to allopathic medicines. However, standardization and their quality assurance have been the major problem faced with herbal products. Herbal medicines were not considered for development of novel formulations for a long time as due to processing difficulties, such as standardization, extraction and identification of individual drug components in complex polyherbal systems and due to lack of scientific justification [33]. Batch-to-batch variations in efficacies of the herbal formulations which may result from natural and genetic alterations, seasonal changes, differences in soil and climatic conditions, and nutritional status of the medicinal plant have also been cause of concern as this may lead to issues regarding quality and purity of these formulations [34].

Therefore, there is a need to identify the active principles of these medicines as potential chemotherapeutic agents and monitor the safety of these active constituents [35]. There has been, thus, a need of scientific approach towards phytotherapeutics to deliver the components in a sustained manner so as to increase patient compliance and minimize the need for repeated administration.

A possible way to achieve this is designing novel drug delivery systems for herbal constituents. Novel drug delivery systems help to the reduce toxicity and increase the bioavailability thereby improving the therapeutic value of the active constituent.

Recently, pharmaceutical scientists have shifted their focus to designing a drug delivery system for herbal medicines using a scientific approach [36, 37].

Novel herbal formulations like polymeric nanoparticles, nanocapsules, liposomes, phyto-somes, nanoemulsions, microsphere, transfer-osomes, and ethosomes have been reported using plant extracts and active constituents. Enhancement of solubility, bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation are among the remarkable advantages that these novel formulations are reported to have over conventional formulations of plant actives and extracts [38].

This review focuses on some of herbs used traditionally for arthritis along with some of the strategies adopted by researchers to improve the efficacy of these herbs.

***Curcuma longa* (Zingiberaceae):** *Curcuma longa* (turmeric) has been used traditionally for its pain and wound-healing properties. Curcumin is a major curcuminoid found in turmeric to which the main biological effects of turmeric have been attributed to. Curcumin has been seen to have action on lymphocytes [39].

Curcumin is a polyphenolic phytochemical. It is a strong anti-inflammatory agent and an antioxidant [40]. Curcumin is reported to change the expression of various transcription factors, cell cycle proteins, and signal transducing kinases [41]. It is found to down regulate the secretion of a variety of proinflammatory cytokines and chemokines [42]. Studies in human or animal models have shown that curcumin ameliorates multiple sclerosis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease [43]. The systemic bioavailability of orally administered curcumin is relatively low [44].

Various studies have been reported for solubility improvement of curcumin and hence its bioavailability [45]. Several nanocarriers are now emerging as promising systems to overcome poor solubility and inconsistent bioavailability of curcumin [46]. A highly bioavailable form of curcumin is reported to be more effective in alleviating rheumatoid arthritis (RA) symptoms than the NSAID drug Voltaren [47]. A study by Kumar K *et al* reports floating microspheres of curcumin prepared with hydroxypropylmethyl cellulose, hydroxyethyl cellulose, polyvinyl pyrollidone (PVP K30) and Eudragit RS 100 in different ratios by emulsion solvent diffusion method. The study concluded that curcumin microspheres can be a promising drug delivery to obtain sustained release of curcumin [48]. Microparticles containing Curcumin with Eudragit S 100 have been reported for colon targeting by Madhavi M *et al* [49].

In another study, curcumin biodegradable microspheres were shown to be promising as prolonged release drug delivery system as compared to oral or subcutaneous route for better therapeutic management of inflammation [50]. The starch microspheres cross-linked by N, N'-methylene bisacrylamide were studied as carrier for curcumin by Zhu minpeng and Li suhong. According to the study, 80.53% of curcumin was released after 25 hours; sustained release of curcumin was observed [51].

Increased permeation through the skin was observed with transferosomes containing curcumin gel when compared with simple gel by Patel R. *et al* [52]. Cui J *et al* formulated self microemulsifying drug delivery system of curcumin using surfactant, co surfactant and ethyl oleate. Increased oral absorption of curcumin has been reported with this drug delivery system as compared to simple emulsion [53].

***Tripterygium wilfordii* (Celastraceae):** In Chinese medicine, extracts of *Tripterygium wilfordii* (Tw) are used to treat autoimmune and inflammatory conditions such as rheumatoid arthritis, systemic lupus erythmatosus, psoriatic arthritis and Behcet's disease [54]. Triptolide, a diterpenoid component isolated from Tw has been shown to have anti-inflammatory and immunosuppressive activities by its inhibitory effect on T-cells [55].

A trial compared Tw extract with sulfasalazine in 121 patients with active rheumatoid arthritis who continued oral prednisone and non-steroidal anti-inflammatory drugs but not disease modifying antirheumatic drugs. Among patients who continued treatment for 24 weeks, achievement of 20% improvement in American College of Rheumatology criteria was greater with TwHF than with sulfasalazine [56].

Immunosuppressive, cartilage protective and anti-inflammatory effects of *Tripterygium wilfordii* have been studied in literature. From these studies Tw has shown promise that it could serve as a source and template for novel antiarthritic and cartilage protective drugs. MMP inhibition may be an important mechanism for the observed beneficial effects of TWHF in patients with arthritis [57].

Liposomes of extracts of *Tripterygium wilfordii* have been reported to increase its stability and reduce side effects [58]. Celastrol, also known as tripterine, is derived from *Trypterygium wilfordii*. Celastrol exhibits potent anti-angiogenic and anti-inflammatory activities. Celastrol, potentiates TNF-induced apoptosis and suppresses invasion of tumor cells by inhibiting NF-kappaB-regulated gene products and TAK1-mediated NF-kappaB activation [59].

Despite the powerful beneficial bioactivity of celastrol, its clinical use has been limited mainly due to its poor water solubility. Therefore, improvement in its water solubility is necessary while still retaining its activities in order to develop new celastrol-based formulations. Nanoformulated poly(ethylene glycol)-block-poly(ε-caprolactone) (PEG-b-PCL) micelles have been reported to improve the water solubility of celastrol [60].

Surface-charged tripterine-loaded nanostructured lipid carriers (NLCs) were evaluated by Yan Chen et al. for the influence of the surface charge of NLCs on *in vitro* skin permeation and *in vivo* pharmacodynamics of tripterine. In the study, NLCs exhibited first order release of tripterine. Cationic NLCs were observed to increase the tripterine permeability coefficient 1.15- and 1.38-fold compared to that of neutral and anionic NLCs, respectively [61].

***Boswellia serrata* (Burseraceae):** The resin of *Boswellia* species (Salai guggul) has been used in medicines since ancient times. Gum-resin extracts of *Boswellia serrata* have been traditionally used in folk medicine for centuries to treat various inflammatory diseases like arthritis [62]. The resinous part of *Boswellia serrata* possesses monoterpenes, diterpenes, triterpenes, tetracyclic triterpenic acids and four major pentacyclic triterpenic acids i.e. β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid(KBA) and acetyl-11-keto-β-boswellic acid, responsible for inhibition of pro-inflammatory enzymes [63].

Studies have found that 3-O-acetyl-11-keto-beta-boswellic acid (AKBA) is the most biologically active component in the herb. It inhibits the action of 5-lipoxygenase, an enzyme in the biochemical cascade leading to inflammation [64]. Extracts from the gum resin of *Boswellia serrata* and some of its constituents including boswellic acids are also reported to affect the immune system in different ways. 11-keto-beta-boswellic acid and acetyl-11-keto-beta-boswellic acid have been observed to be active among the various boswellic acids (BA). However, other boswellic acids may also exhibit activity on the immune system [65].

Some of the branded formulations of Boswellia available for inflammatory and arthritic conditions are [66]: Boswellin®, a registered trademark by Sabinsa Corporation, is in the form of capsules or tablets containing boswellic acids ranging from 150-250 mgs/capsules or tabletsto be taken orally two to three times a day. Shallaki® contains 125 mg *Boswellia serrata* in each capsule and is manufactured by Himalayan Drug Company, Makali, Bangalore, as Licensed User of the Trade Mark owned by MMI Corporation. Rheumatic-X®, contains 20 mg 'Shallaki' besides a number of ingredients, manufactured by Sunrise Herbals, Varanasi (U.P., India), meant for rheumatoid, gouty, osteoarthritis and sciatic pain [66].

Pharmacokinetic studies of boswellic acid reveal its poor absorption through the intestine. Various studies to improve bioavailability of boswellic acids have been reported in literature [67]. Complexation of boswellic acid with phosphatidylcholine has been studied by Sharma et al. to enhance its bioavailability [68].

They prepared a complex of boswellic acid with phosphatidylcholine (PC). The complex was also converted into vesicles (phytosomes) and compared with other vesicular systems (liposomes and niosomes) by evaluating its anti-inflammatory effect. The complex showed better anti-inflammatory and hypolipidemic activity as compared to BA. Phytosomes, among all vesicular systems, were reported to show maximum anti-inflammatory activity. The study reports that enhanced bioavailability of the BA-PC complex may be due to the amphiphilic nature of the complex, which greatly enhanced the water and lipid solubility of the boswellic acid [68].

Husch J *et al* did a comparative murine of bioavailability study of Casperome™, a soy lecithin formulation of standardized *B. serrata* gum resin extract (BE), and its corresponding non-formulated extract. The study showed significantly higher plasma levels (up to 7-fold for KBA, and 3-fold for βBA quantified as area under the plasma concentration time curve, AUC_{last}) for weight equivalent and equimolar oral administration of Casperome™ compared to the non-formulated extract [69].

3-Acetyl-11-keto-beta-boswellic acid loaded-polymeric nanomicelles were developed and studied for topical anti-inflammatory and anti-arthritic activity by Goel A *et al* [70]. The study suggested that AKBA polymeric nanomicelle gel significantly enhanced skin permeability, and anti-inflammatory and anti-arthritic activity. In another study, transdermal films containing boswellic acid and curcumin were formulated for treatment of inflammation by Verma M *et al*. Combination of boswellic acid and curcumin was used to produce synergistic action. Transdermal films showed increased efficacy of the drugs [71].

Fartyal S *et al* studied of floating microspheres using boswellic (BA) as model drug for prolongation of the gastric retention time. Diffusion- controlled drug release from the microspheres was demonstrated in *in vitro* studies [72].

***Zingiber officinale* (Zingiberaceae):** *Zingiber officinale* (Ginger) has been known for its anti-inflammatory properties for centuries.

Ginger suppresses prostaglandin synthesis through inhibition of cyclooxygenase-1 and cyclo-oxygenase-2. Ginger has also been reported to suppress leukotriene biosynthesis by inhibiting 5-lipoxygenase [73].

Major focus of research related to anti-inflammatory effects of ginger has been on phenolic gingerols and related compounds. However literature reports that nongingerol components are also bioactive and can enhance the antiarthritic effects of gingerols [74]. Ginger oil has been demonstrated for its potent antiinflammatory and/or antirheumatic properties [75].

Baskar V *et al* demonstrated improved bio-availability ratio of anti-inflammatory compound from ginger from a nano transdermal delivery [76]. The ultra-flexible or ultra-deformable vesicle system was observed to be much more efficient in delivering a low/high molecular weight, hydrophobic/hydrophilic drugs deep into to the skin. In this study, transdermal mode of delivery showed substantial increase in the ratio of bioavailability of the gingerol in comparison to the other delivery methods.

WIPO Patent Application WO/2012/026829 titled 'Transdermal Patch' describes a transdermal patch containing one active ingredient, namely *Zingiber officinale* rhizome (commonly known as 'ginger'), for the treatment of an inflammatory condition such as in an arthritic condition. The invention aims to provide non-invasive treatment of the inflammatory condition, in the form of transdermal patch [77].

***Tanacetum parthenium* (Asteraceae):** *Tanacetum parthenium* (Feverfew), has been used as a folk remedy for rheumatoid arthritis and fever [78]. Sesquiterpene lactones are the important biologically active principles, parthenolide being the principal one. Greater than 30 sesquiterpene lactones have been identified in feverfew. In general, there are 5 different types of sesquiterpene lactones. These may be classified based on chemical ring structures. The eudesmanolides, germacranolides, and guaianolides are present in feverfew [79]. Parthenolide is a germacranolide. Parthenolide binds to and inhibits IκB kinase complex (IKK)β, it inhibits prostaglandin synthetase and reduces human neutrophil oxidative burst activity [80].

The crude feverfew extract and its purified parthenolide can modulate adhesion molecule expression in human synovial fibroblasts [81].

It is also reported that parthenolide depleted feverfew extract too has capacity to inhibit several pro-inflammatory enzymes including 5-lipoxygenase, phosphodiesterase-3 and phosphor-diesterase-4. It inhibits the release of proinflammatory mediators nitric oxide, prostaglandin (PG) E_2 and TNF- from macrophages and IFN- and IL-4 from human peripheral blood mononuclear cells [82].

Standardized spray-dried extract of feverfew was developed by Chaves SJ *et al* and enteric coated tablets of this extract were further designed and standardized. They evaluated the spray-dried extract of feverfew for its parthenolide, santin and total flavonoid content, parthenolide solubility, particle size, tapped density, hygroscopicity, angle of repose and moisture content. Enteric coated tablets containing the spray-dried extract were tested for their average weight, friability, hardness, and disintegration time. They observed that spray-dried extract exhibited consistent pharmaco-technical properties and direct compression technique could be used to produce tablets with required specifications [83].

***Camellia sinensis* (Theaceae):** The polyphenolic compounds from *Camellia sinensis* (green tea) are reported to possess anti-inflammatory properties [84]. Immunosuppressive effect of green tea has been shown in various experiments using animal models. Green tea has been reported to reduce autoimmune symptoms in the rat adjuvant arthritis, a model of human rheumatoid arthritis [85]. Epigallocatechin-3-gallate (EGCG), a component of green tea has been studied for its anti-inflammatory and immunomodulatory activities.

It has shown inhibitory effects on human monocyte-derived DCs (dendritic cells) and, consequently, on the T-cell-mediated immune responses [86]. Cartilage-preserving and chondro-protective action of EGCGs, its mechanisms and beneficial effects in arthritis have been reported through various studies [87]. Phytosomes of epigallocatechin 3-o-gallate from *Camellia sinensis* have been reported [88].

(−)-Epigallocatechin-3-gallate or (−)-EGCG loaded lipid nanocapsules (LNC) were prepared by Barras A. *et al* by applying the phase inversion process, and to enhance their apparent solubility and/or the stability. They observed that high encapsulation rates (95%) could be reached with simple chemical modification of (−)-EGCG. Thus, a stable colloidal suspensions of (−)-EGCG in water over 4 weeks was obtained. 100% degradation within 4 hours was observed with free (−)-EGCG solubilised in water. It was concluded that the drug-loaded LNC resolved initial problems of solubility and stability of (−)-EGCG [89].

***Commiphora mukul* (Burseraceae):** *Commiphora mukul* (Guggulipid) has been used in history of Ayurveda since a long time. The Commiphora tree, from which guggulipid is obtained is use in the treatment of bone fractures, arthritis, obesity, inflammation as mentioned in the classic Ayurvedic literature [90]. The beneficial effect of guggul in arthritis has been demonstrated in scientific studies [91].

Guggulsterone [4, 17(20)-pregnadiene-3, 16-dione] is the gum resin of the Commiphora tree. The sterol down regulates the expression of inflammatory gene products such as COX-2 and MMP-9 which are major players in the development of arthritis [92].

Patent EP 2088865 A2 (WO2008058156A2), 'Guggulphospholipid methods and compositions', describes methods for preparing synthetic Guggul-phospholipids, their fatty acid analogues and other bioactive molecules [93]. The invention mentions E-guggulsterone and Z- guggulsterone or mixture of E- and Z-guggulsterones. The patent relates to complexes such as liposomes, complexes, emulsions, vesicles, micelles, and mixed micelles, into which guggulphospholipids and other bioactive molecules can be incorporated, which can also include other active agents, such as hydrophobic or hydrophilic drugs.

A study by Verma S. *et al* reports preparation of 'guggulosomes' using guggulipid as a lipid drug carrier [94]. The guggulosomes were loaded with ibuprofen. Sustained release of the drug was observed. Also guggulusome prepared exhibited significant anti-inflammatory activity at 5 hours against carrageenan injection, suggesting that it may have a sustained and synergistic action [94].

***Glycyrrhiza glabra* (Fabaceae):** *Glycyrrhiza glabra* **(**Liquorice) is used for its immuno-modulatory, laxative, emmenagogue, contraceptive, galactagogue, anti-asthmatic, anti-viral properties in folk medicine [95]. Anti-microbial, anti-oxidant and anti-inflammatory properties are also demonstrated in literature [96]. The major metabolite of glycyrrhizin, present in liquorice root is glycyhrritinic acid. Liquorice extracts as well as glycyhrritinic acid have shown anti-inflammatory effects in various studies and may prove beneficial in conditions like rheumatoid arthritis [97, 98].

Glycyrrhizin has shown to possess absorption enhancing (bioavailability enhancing) activity [99,100].

Ammonium glycyrrhizinate was reported by Paolino D. et al. to be incorporated into ethosomes for dermal administration and used for treatment of inflammatory diseases of the skin. The ethosomal preparation showed increased bioavailability as a result of increased permeability of the drug [101].

Wang W. et al. prepared glycyrrhizinic acid nanoparticles by supercritical antisolvent process and explored the anti-inflammatory activity and mechanisms of in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages. They compared the activities of nanoparticles with those exhibited by unprocessed glycyhrrizinic acid particles. They found that glycyrrhizinic acid nanoparticle suspensions showed better anti-inflammatory activities than the unprocessed glycyrrhizinic acid [102].

***Plumbago zeylanica* (Plumbaginaceae):** The crude extracts of *P. zeylanica* have been used in china and other Asian countries as folk medicine for the treatment of cancer, rheumatoid arthritis and dysmenorrhea. Immunosuppressive properties of aqueous extract of *Plumbago zeylanica* were demonstrated in Balb/c mice [103]. Anti-arthritic potential has also been demonstrated [104].

Plumbagin is a natural bicyclic naphthoquinone derived from roots of *P. zeylanica*. The inhibitor has been known for its potent biological activities including anti-inflammatory, anti-tumor, and anti-bacterial activities [105]. Plumbagin was recrystallized by cold crystallisation technique using a variety of polar and non-polar solvents by Bothiraja C and plumbagin so obtained was

investigated for pharmaceutical properties. It was observed that size and shape of plumbagin varied with different solvents. Improvement in therapeutic efficacy of recrystallized plumbagin was demonstrated in i*n-vivo* anti-inflammatory study in Wistar rats. The researchers concluded that surface modification led to enhanced efficacy of plumbagin. This approach is capable of improving the bioavailability and clinical efficacy of other poorly water soluble phytomedicines [106].

***Vitis vinifera* (Vitaceae):** *Vitis vinifera* **(**Grape Seed) contains proanthocyanidins, resveratrol, with known antioxidant and anti-inflammatory properties, through the inhibitory effects of these on transcription factors like nuclear factor kappa B (NF-KB) or activator protein-1 (AP-1) [107]. The effect of resveratrol on the proliferation and apoptosis of synoviocytes in patients with rheumatoid arthritis (RA) in vitro was investigated by Tang LL *et al.* They concluded that resveratrol inhibits the proliferation of synoviocytes and induces cell apoptosis in rheumatoid arthritis in vitro [108]. Various studies have reported beneficial effects of reservatrol indicating its potential use as anti-arthritic [109, 110, 111].

Resveratrol has poor bioavailability, low water solubility, and is chemically unstable, has less favorable pharmacokinetic properties. To overcome these problems, Neves AR et al. developed solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) loaded with resveratrol by a modified hot homogenization technique and characterized them to evaluate the quality of the developed resveratrol-loaded nanoparticles [112].

Both SLNs and NLCs showed an average resveratrol entrapment efficiency of ~70%. Studies indicated good stability of these systems.

Also, resveratrol was found to mostly remain associated with the lipid nanoparticles after their incubation in digestive fluids in the *in vitro* simulation of gastrointestinal transit. The researchers concluded that SLNs and NLCs can be considered suitable carriers for oral administration of reservatrol, conferring protection to the incorporated resveratrol and allowing its controlled release after uptake [112].

Ansari KA *et al* studied complexation of reservatrol with cyclodextrin-based nanosponges (NS) to increase its solubility, stability and permeation. *Ex vivo* studies on these complexes indicated their potential to administer resveratrol NS complex as buccal delivery and topical application [113].

***Withania somnifera* (Solanaceae):** *Withania somnifera* (Ashwagandha) is an herb widely used in the traditional medical system of India for a variety of musculoskeletal conditions like arthritis, rheumatism [114]. The anti-inflammatory activity of the herb has been studied [115]. The effect of a *Withania somnifera* (WS) crude ethanol extract was studied on peripheral blood mononuclear cells of normal individuals and rheumatoid arthritis (RA) patients and synovial fluid mononuclear cells of RA patients *in vitro* by Singh D *et al* [116].

They found that the WS extract significantly suppressed lipopolysaccharide (LPS) induced production of proinflammatory cytokines TNF-alpha, IL-1beta and IL-12p40 in normal individuals and patients and in patients with rheumatoid arthritis. Their study demonstrated that the production of proinflammatory molecules was suppressed *in vitro* by WS crude ethanol extract. This activity was attributed partly through the inhibition of transcription factors NF-kappaB and AP-1 by the constituent withanolide. Goyal S *et al* have reviewed this herb so as to prepare novel topical gels containing this herb [117].

CONCLUSION: Herbal medicines are a promising alternative to conventional therapy for arthritis due to their lesser side effects and low cost. Formulation into new drug delivery technologies would further enhance the effectiveness of plant actives/extracts as a result of increased bio-availability and/or drug targeting.

Thorough studies are required to gain knowledge about the exact mechanism of action of these actives in order to make correct choice of drug delivery system to achieve maximum efficacy. Herbal medicines formulated into a novel drug delivery system thus can prove to be a therapy of choice for arthritis patients due to its safety, efficacy and affordability.

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How to cite this article:
Ranade SY and Gaud RS: Current strategies in Herbal Drug Delivery for Arthritis: An Overview. *Int J Pharm Sci Res* 2013: 4(10); 3782-3794. doi: 10.13040/IJPSR. 0975-8232.4(10).3782-94