

**EVOLVING CONCEPTS AND TARGETING OF ARTHRITIS****Gyanesh Kumar Sahu<sup>1</sup>, Harish Sharma<sup>2</sup>, Chanchal Deep Kaur\*<sup>3</sup>**<sup>1</sup>Shri Rawatpura Sarkar Institute of Pharmacy, Kumhari, Durg, Chhattisgarh, India<sup>2</sup>Shri Shankaracharya Group of Institutions, Faculty of Pharmaceutical Sciences, Bhilai,  
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**ABSTRACT**

Arthritis pain affects millions of people worldwide yet we still have only a limited understanding of what makes our joints ache. This review examines the different types of arthritis domains that lead to the generation of painful sensation. When inflammation, joint nerves become sensitized to mechanical stimuli through the actions of neuropeptides, proteinase-activated receptors ion channel ligands and eicosanoids. Early diagnosis and effective treatment is considered to be important in the prevention of disability and joint damage in patients with arthritis. This review has led to the establishment of introducing different types of arthritis, an overview of implicated drugs and their

principle of targeting. There are various categories of medicines used for the treatment of arthritis with their own side effects. The targeting approach with novel delivery systems and use of phytoconstituents are the evolving areas of research for the treatment of various types of arthritis. The amalgamation of both the approaches could create new avenues of treatment therapy.

**KEY WORDS:** Rheumatoid Arthritis, Osteoarthritis, Fibromyalgia, Gout, Lupus.

**Summary**

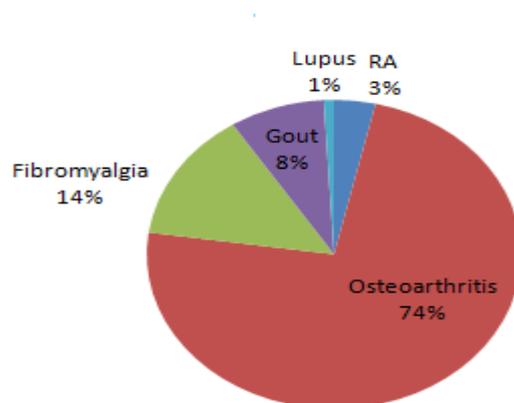
1. The review summarizes different types of arthritis, an overview of implicated drugs with their own side effects and their principle of targeting.
2. The targeting approach with novel delivery systems and use of phytoconstituents are the evolving areas of research for the treatment of various types of arthritis.

3. The amalgamation of both the approaches could create new avenues of treatment therapy.

## INTRODUCTION

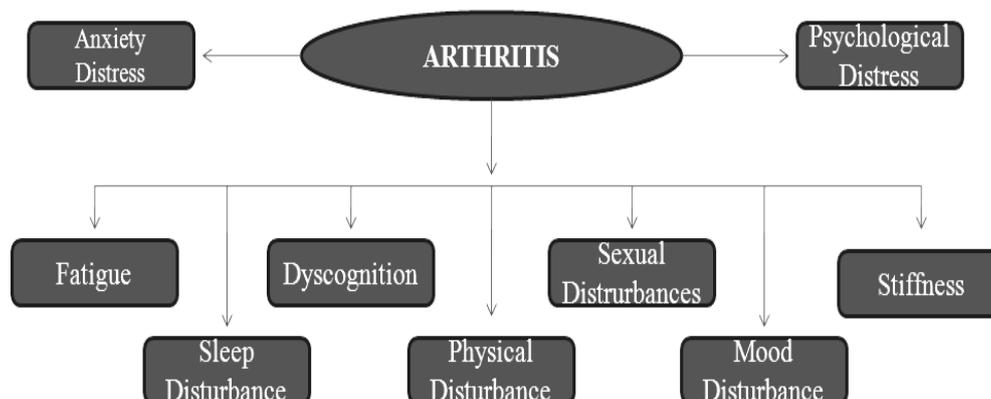
### Arthritis

Arthritis is not a single disease with a single cause. There are dozens of different types of arthritis, each with its own cause. It conditions are large contributors to illness, pain and disability in world wide. Accounting for more than 4% of the overall disease burden, measured in terms of disability-adjusted life years, they account for a significant proportion of healthy years of life lost.<sup>[1]</sup> Arthritis and musculoskeletal conditions also represent more than half of all chronic conditions globally (**Figure 1**) and are the most common cause of severe, long-term pain and physical disability (**Figure 2**).<sup>[2]</sup>



**Fig. 1: Different types of arthritis, affected in US adults.**

The figure depicts the various types of arthritis prevalent and their ratio of prevalence. The ratio shows that maximum affected cases are of osteoarthritis.



**Fig. 2: Arthritis domains.**

The figure shows important symptoms by which arthritis could be depicted

## THE FIVE MOST COMMON FORMS OF ARTHRITIS

There are various forms of arthritis with their own symptoms and impact. The **Table 1** depicts the occurrences of various types of arthritis

**Table 1: Different type of arthritis and their occurrences**

Sr. No.	Types of Arthritis	Occurrences
1.	Rheumatoid Arthritis	It occurs when the immune system turns against parts of the body it is designed to protect, causing pain, swelling, stiffness, and loss of mobility in the joints.
2.	Osteoarthritis	It occurs when cartilage, the tissue that cushions the ends of the bones within the joints, breaks down and wears away. In some cases, all of the cartilage may wear away, leaving bones that rub up against each other.
3.	Fibromyalgia	Fibromyalgia makes feel tired, causes muscle pain and "tender points." Tender points are places on the neck, shoulders, back, hips, arms or legs that hurt when touched.
4.	Gout	Gout occurs when there is a build-up of too much uric acid in the body causing hard, crystal- like deposits to go to the joint. Affected areas are very sore, red, warm, and swollen.
5.	Lupus	It occurs when the body's immune system attacks healthy cells and tissues by mistake. Lupus can damage joints, skin, blood vessels, lungs, kidneys, heart and brain.

### Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease that affects an estimated 1.3 million adults in the United States.<sup>[3]</sup> It primarily affects joints, causing joint pain, swelling, and stiffness, but can also affect other organs in the body. As the disease progresses and joint damage occurs, patients experience greater disability and decreasing quality of life. RA is associated with significant levels of morbidity and mortality and has a significant impact on total health care costs.<sup>[4,5]</sup>

### Impact of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, relapsing autoimmune disorder that is characterized by pain, synovial membrane inflammation and restricted joint movement due to tissue damages.<sup>[6]</sup> RA, bone deformations and disability of joint function occurred due to progressive erosion of articular cartilage in synovial joint via generation and infiltration of autoantibodies in it, leading to severe pain. Around 1% of the population of the world is suffering from RA.<sup>[7]</sup>

### **Osteoarthritis**

Osteoarthritis (OA), also called osteoarthroses or degenerative joint disease, is the most common type of arthritis. OA is a result of genetic, local mechanical stresses or systemic factors and is a chronic condition characterized by the breakdown and loss of the joint's cartilage, bony overgrowth and alterations in the ligaments, menisci and muscles around the joint. Cartilage is the part of the joint that cushions the ends of the bones and allows easy movement of joints. The breakdown of cartilage causes the bones to rub against each other. Symptoms of OA include joint pain, aching, stiffness and swelling resulting in decreased function and mobility.<sup>[8]</sup>

### **Impact of Osteoarthritis**

OA is highly prevalent and on the rise. Nearly 27 million adults have OA, a number expected to increase with longer life expectancies, the obesity epidemic. Half of all adults will develop symptomatic OA of the knee at some point in their livesii and that risk increases with obesity to two of every three obese adults.<sup>[8]</sup> OA typically affects only certain joints, such as the hips, hands, knees, low back and neck. After age 50, women are more often affected by OA than men.<sup>[9]</sup>

### **Fibromyalgia**

Fibromyalgia is a common health problem that causes widespread pain and tenderness (sensitive to touch). The pain and tenderness tend to come and go, and move about the body. Fibromyalgia is a common, multidimensional disorder with complex symptomatology and relatively poor treatment outcomes.<sup>[10, 11]</sup> Fibromyalgia is characterized by widespread pain for longer than 3 months and bilateral sites of amplified tenderness.<sup>[10]</sup> In most patients, fibromyalgia is associated with fatigue, sleep dysfunction, stiffness, depression, anxiety, cognitive disturbance, or exercise intolerance,<sup>[11-13]</sup> and is reported to be more common in women and individuals with other rheumatic conditions.<sup>[14]</sup> The prevalence of fibromyalgia is estimated to be 2% in the USA<sup>[15,16]</sup> and Canada.<sup>[17]</sup> The etiology and pathophysiology of fibromyalgia remain unclear. Current hypotheses center on atypical sensory processing in the central nervous system and dysfunction of skeletal muscle nociception and the hypothalamic–pituitary–adrenal axis.<sup>[18-21]</sup>

### **Impact of Fibromyalgia**

FM has either a gradual or a post-traumatic onset. The pain is described as a persistent, diffuse, deep, aching, throbbing, sensation in muscles and is most often continuous.

Clinical symptoms associated with FM are affective dysfunction, cognitive deficits, short-term memory loss, headache, nonrestorative sleep, and daytime tiredness resembling physical fatigue. A number of clinical conditions occur more frequently in FM than in the general population (comorbidities): depression, anxiety, irritable, bowel syndrome (IBS), fatigue, sleep disturbances, dysmenorrhea, interstitial cystitis, other rheumatic conditions, and temporomandibular joint disorder.<sup>[22,23]</sup>

### **Gout**

Gout is a type of inflammatory arthritis that is triggered by the crystallization of uric acid within the joints and is often associated with hyperuricemia. Acute gout is typically intermittent, constituting one of the most painful conditions experienced by humans. Chronic tophaceous gout usually develops after years of acute intermittent gout, although tophi occasionally can be part of the initial presentation. In addition to the morbidity that is attributable to gout itself, the disease is associated with such conditions as the insulin resistance syndrome, hypertension, nephropathy, and disorders associated with increased cell turnover.<sup>[24, 25]</sup>

### **Impact of Gout**

The prevalence increased with increasing age and reached 9% in men and 6% in women older than 80 years of age. Dietary and lifestyle trends and the increasing prevalence of obesity and the metabolic syndrome may explain the increasing incidence of gout.<sup>[26]</sup>

### **Lupus**

Lupus (systemic lupus erythematosus) is a chronic, remitting and relapsing autoimmune disorder characterized by unpredictable disease flares and remissions. In lupus, the body's immune system, which normally functions to protect against foreign invaders, becomes hyperactive, forming antibodies that attack normal tissues and organs, including the skin, joints, kidneys, brain, heart, lungs, and blood. Lupus is characterized by periods of illness, called flares, and periods of wellness, or remission.<sup>[27-30]</sup>

### **Impact of Lupus**

Many SLE symptoms and related functional impairments are difficult or impossible to measure through laboratory or physician assessments.<sup>[31-34]</sup> The development of SLE is a complex immune process that is brought about by dysregulation of B- and T-lymphocytes, the production of auto-antibodies, and the formation of immune complexes.<sup>[35]</sup> SLE

predominantly affects adults, usually women of childbearing age (20 to 40 years), at a female to male ratio of 9:1 to 15:1. Approximately 8% to 15% of SLE cases occur in children. Older adults diagnosed with SLE, such as postmenopausal women, usually have a milder form. Genetic and racial factors are also associated with an increased risk of developing SLE.<sup>[36-39]</sup> Common location, sign and symptoms of different types of arthritis have been discussed in

**Table 2: Common location, sign and symptoms of different types of arthritis**

Sr. No.	Types of Arthritis	Common location	Sign and symptoms
1.	Rheumatoid Arthritis	The wrist joints and the finger joints closest to the hand. It can also affect other parts of the body aside from the joints.	Pain, Swelling, Stiffness, Loss of joint movement
2.	Osteoarthritis	Occurs in the hands (at the ends of the fingers and thumbs), knees, and hips.	Stiffness, Swelling, Crunching feeling
3.	Fibromyalgia	Tender points are often on the neck, shoulders, back, hips, arms or legs that hurt when touched.	Muscle pain, fatigue, trouble sleeping, morning stiffness, headaches
4.	Gout	Most common in big toe, insteps, ankles, heels, knees, wrists, fingers, and elbows.	Pain, swelling, redness, heat, stiffness
5.	Lupus	Attacks healthy cells and tissues damaging parts of the body such as the joints, skin, kidneys, heart, lungs, blood vessels and brain.	Pain, swelling, muscle pain, fatigue, facial rash

### MEDICINES FOR RHEUMATOID ARTHRITIS

Medicines are used for the treatment of Rheumatoid Arthritis as they reduce joint swelling and relieve pain. Most people need to keep taking RA medicines for life. The important two categories of RA medicines used are, Disease-Modifying Antirheumatic Drugs (DMARDs) (pronounced DEE-mar-ds) and steroids (pronounced STAIR-oyds).

#### Disease-Modifying Antirheumatic Drugs (DMARDs)

The drugs that work best for RA are called DMARDs, common DMARDs used in RA are shown in **Table 3**. These medicines don't just relieve pain. They slow or stop the changes in the joints. DMARDs come in two groups. Some are pills. The others are given by shot or IV. Both suppress the immune system. That means they slow down the body's attack on itself.<sup>[40]</sup>

**Table 3: Common Disease-Modifying Antirheumatic Drugs ( DMARDs) used in RA**

Sr. No.	Class	Generic Name	Brand Name
1.	DMARDs (pills)	Hydroxychloroquine	Plaquenil®
2.	DMARDs (pills)	Leflunomide	Arava®
3.	DMARDs (pills)	Methotrexate	Rheumatrex®
4.	DMARDs (IV)	Infliximab	Remicade®
5.	DMARDs (IV)	Rituximab	Rituxan®

### Steroids

Steroids help with joint pain and swelling, but it is not known if they can slow down the disease. It has potent immunosuppressant and anti-inflammatory activity and can be inducted almost at any stage in RA along with first or second line drugs. Prednisone is the name of a steroid often used for RA.<sup>[41]</sup>

### TREATMENT FOR OSTEOARTHRITIS

Osteoarthritis is thought to affect more than 10 to 12% of the population.<sup>[42, 43]</sup> With the increasing number of elderly, the prevalence and impact of OA is expected to increase over the next decades. Pain relief and improvement of functional disability is the primary goal of treatment, which often needs to be continued for long periods of time.<sup>[44, 45]</sup> Most patients with symptoms of OA are treated by primary care physicians. Nonpharmacological interventions, such as patient education, exercise, or occupational therapy, are the mainstay of treatment, but oral medication is often an important element of therapy.<sup>46</sup> In primary care, nonsteroidal antiinflammatory drugs (NSAID) are prescribed in 35 to 78% of patients with OA.<sup>[47-50]</sup>

### TREATMENT FOR FIBROMYALGIA

The management of fibromyalgia patients involves a complex interplay between pharmacological management of pain and associated symptoms and the use of non-pharmacological modalities. As the elimination of all FMS symptoms (i.e. a cure) is not currently possible; the philosophy of management is symptom palliation and functional restoration. Unfortunately there is as yet no cure for fibromyalgia. In addition, although many drugs are used to help treat the symptoms, none have been found to be especially helpful. The standard analgesics used in Fibromyalgia are depicted in **Table 4**. The presentation of fibromyalgia symptomatology is highly variable and each patient must have an individualized evaluation before deciding on an initial treatment plan.<sup>[51]</sup>

**Table 4: Standard Analgesics used in Fibromyalgia**

Sr. No.	Generic Name	Property	Side Effect
1.	Paracetamol	Weak analgesic	Rare
2.	NSAIDs (Ibuprofen, diclofenac, naproxen, celecoxib)	Reducing inflammation	stomach pains and indigestion, long term use has also been shown to increase the risk of kidney failure
3.	Morphine, Oxycodone, Fentanyl and Buprenorphine	Strong opiates	drowsiness, constipation and sickness
4.	Tramadol	Intermediate Strength opiate	drowsiness, constipation and sickness
5.	Codeine and dihydrocodeine	Weak opiates	drowsiness, constipation and sickness

### TREATMENT FOR GOUT

Gout is challenging in the setting of chronic kidney disease (CKD). Common gout treatments have been associated with severe adverse events in patients with renal dysfunction.<sup>[52-56]</sup>

#### Acute Gout

Acute gout manifests as sudden onset of severe inflammation in a small joint due to precipitation of urate crystals in the joint space. The joint becomes red, swollen and extremely painful: requires immediate treatment. The **Table 5** shows some of the category of drugs used in the treatment of acute gout.<sup>[57]</sup>

**Table 5: Drugs used in Acute gout**

Sr. No.	Categories	Drugs	Side effect
1.	NSAIDs	Indomethacin, naproxen, piroxicam, diclofenac, etoricoxib	edema, hyperkalemia, hypernatremia, hypertension
2.	Alkaloid	Clochicine	Gastrointestinal upset, neutropenia
3.	Corticosteroids	Prednisolone	high blood glucose levels, immunosuppression, weight gain, facial swelling, depression, mania, psychosis, or other psychiatric symptoms

#### Chronic Gout

When pain and stiffness persist in joints between attacks, gout has become chronic. Other cardinal features are hyperuricaemia, tophi and urate stones in the kidney; some common drugs which is used in chronic gout are shown in **Table 6**.<sup>[58]</sup>

**Table 6: Drugs used in Chronic gout**

Sr. No.	Categories	Drugs	Side effect
1.	Uricosuric	Probenecid	Peptic ulcer, rashes
2.	Uricosuric	Sulfinpyrazone	Gastric irritation, rashes, blood dyscrasias.
3.	Uric acid synthesis inhibitor	Allopurinol	Hypersensitivity reaction consisting of rashes, fever, malaise and muscle pain

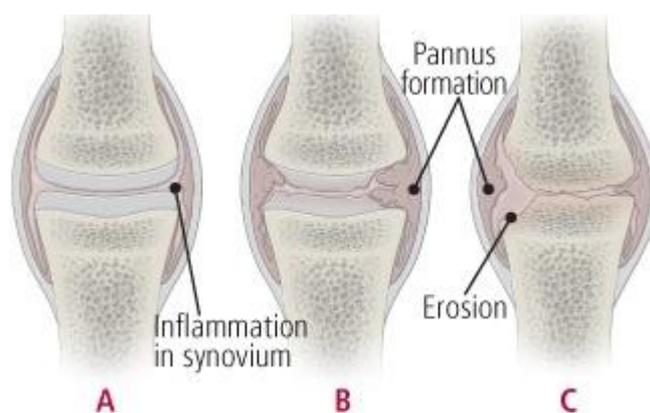
### TREATMENT FOR LUPUS

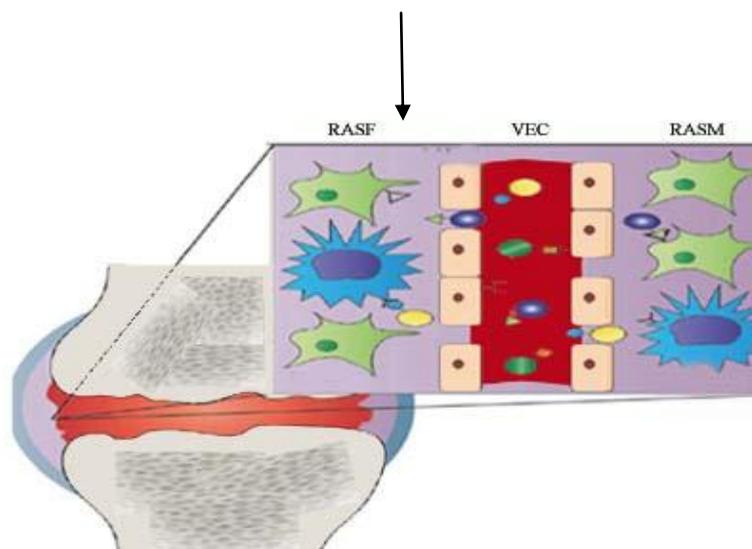
Treatment of systemic lupus erythematosus (SLE) is guided by the individual patient's manifestations. Fever, rash, musculoskeletal manifestations, and serositis generally respond to treatment with hydroxychloroquine, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids in low to moderate doses, as necessary, for acute flares. Medications such as methotrexate may be useful in chronic lupus arthritis, and azathioprine and mycophenolate have been widely used in lupus of moderate severity.<sup>[59]</sup>

### PRINCIPLES OF TARGETING DRUG DELIVERY

#### Passive targeting

In cancer treatment, drug carrier systems with a large hydrodynamic radius to prevent renal filtration and increase circulation time can passively target diseased tissue as a result of leaky vasculature and inadequate lymphatic drainage, an effect known as "enhanced permeation and retention" (EPR).<sup>[60-62]</sup> Although inflammatory tissue, as found with rheumatoid arthritis, does not display abnormal lymphatic drainage,<sup>[63]</sup> long-circulating delivery systems have been shown to selectively accumulate within the inflamed synovial tissue, i.e. the pannus.<sup>[64-67]</sup> The pannus possesses an increased vascular permeability similar to that of solid tumors and consequently, the vasculature can be exploited for passive targeting in an analogous manner (shown in **Figure 3**).<sup>[68]</sup>





**Fig. 3: A,B,C. Drug delivery strategies in the treatment of rheumatoid arthritis.**

Passive targeting can be achieved by creating carriers that can only pass through leaky vasculature, while active targeting can be facilitated by a ligand that is specific for receptors of rheumatoid arthritis synovial fibroblasts (RASFs), rheumatoid arthritis synovial macrophages (RASMs), or activated vascular endothelial cells (VECs).

### Active targeting

In addition to the potential for passive targeting, the two primary cell types found within the pannus tissue, rheumatoid arthritis synovial fibroblasts (RASFs) and rheumatoid arthritis synovial macrophages (RASMs) selectively express surface receptors, such as CD44,<sup>[69,70]</sup> folate receptor  $\beta$ ,<sup>[71,72]</sup> and integrin  $\alpha_v\beta_3$ <sup>[73]</sup> that are candidates for active targeting. Angiogenic vascular endothelial cells (VECs) are also present as a result of neovascularization, and the E-selectin adhesion molecule has been identified as another viable target for drug delivery.<sup>[74]</sup>

### Carrier systems

In general, drug delivery systems can be divided into two categories: polymer-drug conjugates and nanoparticulate carrier systems. “Nanoparticles” in this sense include liposomes and micelles, as well as traditional metallic and polymeric nanoparticles. As drug delivery systems have become increasingly advanced, the distinction between these two categories has become less clear.<sup>[74]</sup>

## HERBAL DRUG THERAPY FOR ARTHRITIS

The various types of adverse effects observed in the use of different categories of medicines have promoted the use of phytoconstituents in the treatment therapy of arthritis. The polyphenols and flavonoids from antioxidant category of drugs are also gaining importance as they are radical scavengers and suppress proliferation and inflammation along with the reduction in oxidative stress. <sup>[75,76]</sup> Gama linoleic acid, capsaicin have been used in the topical medications <sup>[77]</sup>.

## CONCLUSION

Managing people's foot and leg problems that are associated with arthritis often will involve the podiatrist working closely with other members of the multi-disciplinary team. As such the arthritis will try to ensure that problems are addressed in a timely and reflecting the needs, appropriate manner and wishes of the individual who has arthritis. There are several treatment options to choose from for arthritis, which include a range of medications and physical therapy. The patient's willingness to participate in their own treatment and self-care plays a big role in controlling arthritis. The targeting approach with novel delivery systems and use of phytoconstituents are the evolving areas of research for the treatment of various types of arthritis. The amalgamation of both the approaches could create new avenues of treatment therapy.

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