**RHEUMATOID ARTHRITIS THERAPEUTICS: THE NEOTERIC APPROACHES**

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**Abstract**

Arthritis is a joint related disorder that leads to pain and stiffness, seized movement, swelling and increased sensitivity. World Health Organization defines chronic rheumatic conditions as “musculoskeletal conditions comprise over 150 diseases and syndromes, which are usually progressive and associated with pain.” Various types of arthritis such as Osteoarthritis, Rheumatoid Arthritis, Gout, Ankylosing Spondylitis etc. are common. Various statistical reports indicate that these musculoskeletal condition is prevalent than conditions like diabetes, AIDS, cancer and contributes to high morbidity and disability rate. The WHO is launching new chronic rheumatic conditions website soon. So, the current review is an insight into the various aspects of arthritis- first part of this article describes what is arthritis, its types and why it occurs; followed by conventional treatments available, their advantage and disadvantages. The non-conventional, newer therapies, like herbal molecules, various nanocarrier approaches, intra-articular drug delivery, and molecular modifications are emphasized in the next section. The review is strengthened with collection of clinical study reports, marketed study reports and patents.

**Keywords:** arthritis, nanoemulsions, microemulsions, intraarticular, cytokines

**Introduction**

Arthritis may informally be referred as disorder that affects the joints leading to stiffness and pain. It is a combination of two Latin and Greek words, “Arthron” means joint and “itis” meaning inflammation. World Health Organization defines chronic rheumatic conditions as “musculoskeletal conditions comprise over 150 diseases and syndromes, which are usually progressive and associated with pain. They can broadly be categorized as joint diseases, physical disability, spinal disorders, and conditions resulting from trauma.” (https://www.who.int/chp/topics/ rheumatic/en/).

These musculoskeletal condition is prevalent than conditions like diabetes, AIDS, cancer and contributes to high morbidity and disability rate. It leads to enhanced health and economic burden worldwide. As per WHO report, amongst chronic rheumatic conditions, prevalence of Rheumatic arthritis (RA) varies between 0.3% and 1%. It has also been reported that approximately 50% patients are not able to stick to full time job within 10 years of onset of disease.

Statistical analysis of RA condition indicates that it has affected about 24.5 million people as of 2015, worldwide, which accounts for 0.5 to 1% of health burden in developed countries. It has also been reported that this occurrence of this disorder is increasing at the rate of 5 and 50 per 100,000 people each year. The morbidity digits have also increased from 28,000 deaths in 1990 to 38,000 deaths in 2013. Indian statistics indicates 0.92% of adult population is affected by RA (Gupta et al., 2018). Life expectancy of Rheumatic Arthritis (RA) patient is shorter by 10 to 15 years, in general. It is associated with other medical complications, in addition to its own clinical disease symptoms. Among these, most common are cardiovascular diseases, which appear due to inflammation observed in RA. Other commonly reported complications include respiratory issues, anemia, dry mouth and salivary gland issues (Sjogren’s Syndrome), eye inflammation, extra-articular symptoms such as nodules on the hands, elbows, feet, eyes, lungs, and other organs (Handa et al., 2016).

In terms of economic burden, it has been reported that RA contributed to total medical costs and earnings losses of $304 billion (about 1 percent of the US. gross domestic product for 2013).

The escalation of rheumatological problems appears to be due to lack of knowledge about these conditions. In this review an attempt has been made to comprehensively describe- “what and why of RA, along with currently available approaches for the treatment of the disorder.

**1.1 What is Arthritis?**

Arthritis can affect people of any age group. The commonly affected age group is from 16 years onwards. The higher risk of arthritis is seen in the females in comparison to males (Syngle, 2006). The causative agents linked with the progress of arthritis comprise of various environmental and genetic factors that cause alteration in immunological events (Ahmed et al., 2005). Various causative factors for arthritis are insufficiency of the synovial fluid, cartilage impairment, autoimmune attack, infections. Some of the generally occurring types of arthritis are as follows (Patel et al., 2013):

- **Osteoarthritis (OA):** It is a disease that affects joints and includes the symptoms like lack of motion, swelling and weakness in legs and arms.

- **Rheumatoid Arthritis (RA):** An autoimmune disorder causing the immune system to damage its own tissues and cells. It mostly affects elbows, fingers, thumbs and knees.
1.2 Pathophysiology of arthritis

Osteoarthritis (OA) can be characterized by absence of movement, pain in joints, swelling and sensitivity. Synovitis and local inflammation as symptoms can be seen in OA patients. In OA, impairment of pro-inflammatory cytokines InterLeukin-1 and Tumor Necrosis Factor-α is seen in synovial fluid of OA that causes increase levels of prostaglandin, nitric oxide and leukotriene. These factors also cause the stimulation of the expression of mediators of inflammation and metalloproteinase. Another type is RA which is a chronic disease marked by stiffness, swelling, pain and further leading to loss of movements. Rheumatoid arthritis is a chronic, inflammatory auto-immune disorder causing pain and swelling. Rheumatoid arthritis pathogenesis has been also characterized by increase in level of pro-inflammatory TNF-α and cytokines IL-1. In RA, there is movement of leukocytes in the synovial tissue. The hyper proliferation of fibroblast produces various inflammation mediators (Ahmed et al., 2005).

General Symptoms of arthritis are reduction in aerobic fitness; pain in joints, difficulty in movement, swelling of joints, weight loss, fever, headache, sleep disturbance, low red blood cells (RBC).

1.3 Factors affecting appearance of arthritis

Due to multiple types of arthritis, the specific cause is unknown however a few common causes could be:

- **Age**: More the age, higher is the tendency of worn down of joints.
- **Gender**: Except gout, generally maximum types of arthritis are more random in women.
- **Genes**: In case of conditions like ankylosing spondylitis, rheumatoid arthritis and lupus are associated with specific genes.
- **Excess weight**: Excessive weight leads to arthritis in the knee which further leads to fast occurrence of arthritis in the body.
- **Injuries**: An injury may damage a joint leading to arthritis type of conditions.
- **Infection**: An infection caused by viruses, fungi or Bacteria can trigger the inflammation in joints.
- **Work**: Tough work on knees leading to knee bending and squats, can result in osteoarthritis.

2. CONVENTIONAL AND NON-CONVENTIONAL TREATMENT APPROACHES

Arthritis can be treated by conventional and non-conventional methods (Soeken et al., 2003).

- Conventional techniques include DMARD, NSAIDS, anti-malarial drugs, salts of gold and TNFα inhibitor.
- Non-conventional methods include herbal treatment. The most common herbs used are ginger, curcumin, resveratrol, guggulostereone, piperrine etc. The herbal treatment is now days highly used as a substitute method for the treatment of arthritis. This comes under the term complementary and alternative approach (CAM). Herbal treatment offers numerous advantages such as safety, less side effects and gives better results. Along with this, the chiropractic treatment is also widely used (Rao et al., 1999). Parenteral, topical, oral and nasal routes of administration are used for herbal formulations, but they have various side effects. Intra-articular administration for arthritis is a recent practice to treat the arthritis (Chen and Yang 2012). Table 1 enlists various classes of conventional drugs with their effects (Rahman et al., 2017).

Drawbacks of conventional cure of RA/OA

Rheumatoid arthritis in its own offers higher chances of infection and also the biologic therapies, such as DMARD’s (which controls immune system via number of different targets) lead to increased in this risk (Kahlellenberg and Fox, 2011; Mease et al., 2010). The infections mainly of soft tissue and pneumonia occur by using methotrexate and being amplified 2–4 times by co-administration with an anti-TNF treatment (Matos et al., 2010). A relative risk of infections is reported with DMARDs and other biologics (Radovits et al., 2010; Verstappen et al., 2003). The major threat for retrigger of tuberculosis (TB) is also seen in patients using anti-TNF medicines (Kelly and Saravanan, 2008). So, the test for exposure of TB and cure of dormant TB preceding to beginning of anti-TNF mediators is suggested. The safety measures need to be taken to avoid the risk of TB, though the particular threat of occurrence of TB by using these medications is not clearly understood. The blockers of TNF jointly upsurge the danger of fungal infections like histoplasmosis which is a matter of concern in a particular geographical area. Danger of using biological DMARDs, as well as virus Epstein-Barr, virus varicella-zoster and CMV are documented (Strand et al., 1999). Hepatitis B and C recurrence has conjointly arisen with biological DMARDs, therefore diagnosis is suggested prior to the medication and immunization also needed once proved (Strand et al., 1999; Curtis et al., 2007). In advanced multifocal leukoencephalopathy, the recurrence of infection by Jc virus, has been conjointly seen in rheumatoid arthritis patients cured with rituximab. (Bergholm et al., 2002) Since patients of rheumatoid arthritis is associated with danger of lymphoma after the occurrence of disease, the chances of
having cancer such as malignant neoplastic disease whereas taking immunological disorder medications remains a question till date. A recent associate analysis of a German RA registry didn’t realize an inflated risk of malignancy, either hematological or solid neoplasm, with the utilization of anti-TNF agents or anakinra. However, this enclosed solely four years of exposure data of patients (Strangfeld et al., 2010). Obstinate, a study done with French patients on anti-TNF treatment, showed a hyperbolic occurrence of cancer in case of patients taking infliximab or adalimumab (Hannonen et al., 1993). Different reaction diseases, like Sjögren’s syndrome, can as well uspurga the chance for evolving cancer, so creating it tougher to see the impact from immunological disorder medications (Siddiqui et al., 2004).

The toxicities related to drugs used in conventional treatment have been summarized in table 2 (Wadekar et al., 2015; Arya et al., 2011).

2.1 Non-conventional approaches for treatment of RA/OA

2.1.1 Non-conventional approach- Herbal Treatment approaches for Rheumatoid Arthritis

Herbal medicines have always been in interest to promote health since early times. Various traditional medicine systems include Indian medicine system (consisting of Ayurveda and Unani), Chinese medicinal system, and Amazonian ethno medicine. Ayurvedic system is categorized into 3 subcategories that are Pitta, Kapha and Vata based on their mental and physical composition, known as Prakriti. In India, ayurvedic medicines are generally given along with allopathic medicines by the doctors, having a scientific approach. This practice is mostly based on religious beliefs and is secretive. Herbal medicines can be used as antimicrobials, anti-inflammatory and antiviral in RA infections, wound healing and fever.

Current synthetic treatment of arthritis includes NSAIDs and DMARD’s but their use is limited due to various side effects and also these are very expensive. A class of drugs called biologics (antibodies and concerned receptors) reduces inflammation and damage of joints but these are also associated with risks. These risks can be life threatening infection or autoantibody production.

On the other hand, herbal drugs are affordable, socially acceptable and easy to prepare. It can be regarded as boon for the treatment of arthritis.

Herbs used in treatment of Arthritis

Some of the currently available herbs used for arthritis treatment are enlisted in table 3 (Chandrasekar and Chandrasekar, 2017).

- **Boswellia** - It’s another name is frankincense and comes under the class of complementary and alternative approach (CAM). It is used commonly due to its anti-inflammatory activity. It is supposed to work by inhibiting the mediators of inflammation (i.e. leukotrienes) that attacks healthy joints in RA.

- **C. Sinensis** (Green Tea) - Green tea is now days commonly preferred beverage. Many dieticians recommend green tea because it boosts the fat burning which may lead to reduce body fat in the long term and also have potential to treat arthritis. Green tea consists of constituents like polyphenols/catechins mainly epigallocatechin-3-gallate (EGCG) in high content. The effect was first seen in mice with collagen type II-induced arthritis (a poly arthritis animal model of anti-inflammatory activity) by administrating green tea polyphenols (GTP) in drinking water. (Ahmed et al., 2005; Siddiqui et al., 2004) Inhibition of inflammatory agents such as interferon –γ, TNF-α and COX2 was observed in mice fed with green tea and having arthritic joints.

- **U. tomentosa, U. guianensis** (Cat’s Claw) – Cat’s claw is also an anti-inflammatory herb which can be used for reducing swelling in arthritis. It also possesses immunomodulating and antioxidant activities. Conventionally, it is used to boost the immune system (Williams, 2001; Sandoval- Chacon et al., 1998).

- **T. Wilfordii Hook F- T. Wilfordii** is one of the oldest Chinese medicines and is found in Taiwan and Southern China. It’s commonly known as ‘Thunder God Vine’. Root part has the medicinal value which is used for the cure of several inflammatory and autoimmune diseases including RA. It is mainly applied to the skin in topical form (Tao and Lipsky, 2000). The commonest side effects of using this herb are hair loss, nausea, dryness, headaches and vomiting. (Qi and Kao, 2003)

- **Z. officinale** (Ginger) - Ginger is one of the most commonly used spices in the kitchen. It has a very strong flavor. The compound responsible for strong flavor also has anti-inflammatory action. It also possesses antioxidant and antiseptic properties. Ginger has been used for treating arthritis for thousand of years. Moreover, it is very useful in reducing swelling. In chinese medicine, ginger is used to elevate the blood circulation. The main constituents of ginger are gingerol, volatile oil, linoleic acid and has trace elements of phosphorus, potassium and magnesium. Studies have shown that extract of ginger is able to inhibit the production of TNF-α, COX-2 and PGE2. (Afzal et al., 2001; Thomson et al., 2002)

- **T. longa** (Turmeric) - It is also one of the most common spices found in the kitchen. It is used for its healing effect for any injury, skin infections, common cold, liver and urinary tract infections etc. The active constituent of turmeric is curcumin. Studies reported that turmeric slows down the progression of RA. It is one of the best herbs to reduce joint pain and is more effective when taken orally (Jacobs et al., 2001).

- **Linum Usitissimum** (Flax)- Flax is rich in Omega-3 (ALA) which helps to build a strong immune system and in reducing inflammation. Two table spoons of flax seeds or oil need to be included in diet.

- **Arctium Lappa or Arctium Minus** (Burdock Root) – It is comprised of fatty oils as active components which are responsible for its anti-inflammatory action. This herb is available in capsule dosage form.

- **Urtica Dioica** (Nettles)- Nettles are very good for health. It contains proteins, calcium, phosphorus, iron, magnesium, vitamin etc. This herb is used for all types of arthritis and gout. It can be given with NSAIDs to reduce the dose needed to be taken. It also helps to build the bones strong.
• Willow Bark- It is one of the oldest treatments for inflammation. It is used in OA related joint pain, mainly in knees, back, hips and neck. It should not be given to patients taking blood thinners or are allergic to aspirin (Ahmed et al., 2005).

• Guggulsterone - Guggul is a tree resin which has been widely used in ayurvedic medicine and is a common name for Commiphora species. Its constituents are gallic acid, guggulsterone [4, 17(20)-pregnadiene-3, 16-dione], flavanoids etc. This resin has very useful effects in the treatment of arthritis (Gupta, 2017; Shishodia and Aggarwal., 2004; Poonia et al., 2014). Guggulsterone inhibits MAP kinase and then inhibits NF-κB. It also inhibits inflammatory mediators like IFN-γ and nitric oxide (NO) etc. (Manjula et al., 2006).

• Resveratrol- It is a polyphenolic compound and has been found in various plants. It possesses antioxidant, antiinflammatory, antiviral activities etc. It acts by inhibiting NF-κB, COX-PGE2, TNF-α and IF-1β genes (Elmali et al., 2007; Manna et al., 2000).

2.1.2 Non-conventional approach: Nano-carriers in the treatment of RA/ OA

Due to various limitations like slow/less absorption, fast metabolism and severe side effects of biological therapies, it has become mandatory to look for other drug delivery approaches. One of the approaches is Nanotechnology. Nanoparticles are structures of sizes having range of 1 to 100 nm. Protection of the drug from degradation, avoidance of hepatic first pass metabolism, reduction in dosing frequency, increased efficacy and targeted delivery are some of the advantages of nano drug delivery systems. Nanoparticles are nontoxic, inert and non-immunogenic. Recent research explores the use of lipid nanoparticles in the treatment of arthritis. Various strategies like active and passive targeting with integration of anti-inflammatory drugs or herbs into the nano vesicles could increase the drug specificity to tissue and cells. (Chuang et al., 2018; Kapoor et al., 2014) Passive targeting associated with nanocarriers relies on the property of the delivery system. The passive targeting approach for cancer therapy rely on the enhanced permeability and retention (EPR) resulting in abnormal leaky vessels, that safeguards extravasations along with retaining the nanoparticles into the opening area of inflamed tissue (Yang et al., 2017). In this context, almost like abnormal vessels, cancer and inflammatory cell permeation at the affected sites are the outstanding features of RA. Therefore, the leaky vessels of RA are typically used as the target site for specific delivery of drug. Endothelial gaps are formed in RA. These gaps allow the plasma leakage inside the sites that are injured. Due to EPR effect, these nanoparticles can permeate through these gaps and exhibits slow sustained drug release. (Metselaar et al., 2004; Hofkens et al., 2011) Polyethylene glycol (PEG) is very useful for enhancing the efficacy of passive targeting along with lowering the uptake by reticuloendothelial system (RES) (Ganta et al., 2008).

Different types of nanocarriers used for the treatment of arthritis are (Sachan et al., 2013):

• Liposomes: Liposomes are spherical in shape consisting of phospholipids bilayers.

• Ethosomes: Lip vesicles containing ethanol in high content. These are composed of phospholipids.

• Transfersomes: These are composite bodies which penetrate through stratum corneum.

• Niosomes: Niosomes can be considered as an alternative for liposomes. It consists of non ionic surfactant.

• Solid lipid nanoparticles (SLNs): SLNs comprises of a solid lipid core matrix that solubilizes the lipophilic molecules.

• Nanostructured lipid carriers: The nanostructured lipid molecule transporters are prepared by accumulation of solid lipids along with liquid lipids inside the core.

Research Reports on Herbal Nanoformulations in the treatment of Rheumatoid Arthritis

Various active molecules in the treatment of arthritis are associated with certain limitations. Nanocarriers have been fabricated for enhanced therapeutic benefits with reduced toxic effects. For example, Thymoquinone (THQ), which is obtained from Nigella sativa oil (NSO) and it offers significant pharmacological anti-arthritis action. Polymeric nanoparticles of Thymoquinone were reported having entrapment efficiency (EE) of 97.5% and comparatively higher potency as compared to thymoquinone alone (Rahman et al., 2017; Singh et al., 2012). Triptolide exhibits anticancer, immunosuppressive and anti-fertility activity. But its use is associated with disadvantage like severe toxicity. The adverse effects were overcome by formulating transdermal microemulsions of triptolide which exhibited sustained, controlled and prolonged delivery. The triptolide-loaded microemulsions exhibited an increase in vitro penetration via mouse skin in comparison to an aqueous solution having 20% propylene glycol which contains 0.025% triptolide. No skin irritation was seen with microemulsion based gel of triptolide whereas aqueous solution of 20% propylene glycol containing 0.025% triptolide. No skin irritation was seen with microemulsion based gel of triptolide whereas aqueous solution of 20% propylene glycol containing 0.025% triptolide showed an increase in the skin irritation. Further, solid lipid nanoparticles of Triptolide (TP) showed appreciably reduced rat paw volume and exhibited shielding effect against hepatotoxicity (Chen et al., 2004). Triptolide (TP) microemulsion based hydrogel was found to be effective for rheumatoid arthritis with no substantial toxicity during the course of the study (Fan et al., 2013). Tetrandrine ethosomes were developed to increase the anti-artheritic activity of tetrandrine. Tetrandrine is a bisbenzylisoquinoline alkaloid which is taken from the roots of Stephania tetrandra S. Moore of the Menispermaceae family (Anderson et al., 1985). pH gradient loading method was used to make spherical shaped ethosomes. Ethosomal based topical delivery of tetrandrine showed higher skin permeation (Fan et al., 2013) and thereby higher absorption was observed as compared to liposomes. Tetrandrine nanospheres based hydrogel also showed increased absorption (Whitehouse et al., 1994; Xiaoyan et al., 2008). Curcumin is one of the basic ingredients found in the kitchen and also used in the treatment for various diseases. Curcumin is highly beneficial and extensively used in case of disorders causing inflammation but due to poor absorption, rapid systemic elimination and fast metabolism leads to reduction of its effectiveness as a therapeutic agent. Proniosomes of curcumin were formulated via ether injection method and further incorporated into gels. The developed gels were stable and showed enhanced skin permeation (Kumar and Rai, 2012). Proniosomal gels of curcumin were non-toxic, non-irritant and possess anti-artheritic and anti-inflammatory potential as compared to marketed formulations of...
indomethacin. Solid lipid nanoparticles of curcumin were developed for effective treatment of RA. The SLN showed characteristic down fall in rat paw volume (via down regulation of Immuno modulatory cascade and oxidative-inflammatary) (Arora et al., 2015) through complete Freund’s adjuvant (CFA)-induced arthritis in rats. Curcumin SLNs showed significant improvement in various symptoms of arthritis. The shielding action of curcumin and its SLNs was assessed in complete Freund’s adjavan (CFA)-induced arthritis in rats. Rats affected with arthritis showed a noticeable fall in paw withdrawal threshold in Randall-Selitto and von Frey hair test beside reduced reaction time in hot plate. Rats with arthritis also showed major joint hyperalgesia, joint rigidity and raised paw volume along with significant decrease in mobility score. C-SLN administration (10 and 30 mg/kg), was equated with free curcumin (10 and 30 mg/kg), it showed improved number of indications of arthritis in rats, advanced biochemical markers and protected radiological modifications in joints of rats having arthritis. The results showed that SLNs is a unique delivery method for delivering curcumin inside the inflamed joints and biopharmaceutical activity was also improved. Curcumin Nanoemulsion gel showed advanced skin penetration and skin retaining in comparison to solution of curcumin in oil (Nazi and Ahmad, 2015). Emulsification method was used to prepare curcumin (CR) nano emulsion (CR-NE) with oil (Labrafac PG/ glyceryl triacetate), surfactant: co-surfactant (S(wax)) (tween 80/ polyethylene glycol [PEG] 400) and water. The diagrammatic representation of pseudo-ternary phase was done and thermodynamic stability testing was executed. Through photon correlation spectroscopy and transmission electron spectroscopy characterization of droplet size and zeta potential for the preparation were assessed. Sinomenine is obtained from Sinomenium acutum, a very old Chinese therapeutic herb. It is an alkaloid that is being used for the cure which has been used for the treatment of RA. Sinomenine microemulsion based hydrogel showed increase in favorable action that caused suppression of paw inflammation via inhibiting PGE2, TNF-α and IL-1 (Zhang et al., 2007). Effectiveness was assessed for sinomenine microemulsion-based hydrogel (SMBH) on Freund’s complete adjuvant-induced arthritis (AA) in Wistar rats. Total glucosides of paenoy (TGP) is a dynamic constituent that is an extract of the roots of Paeonia lactiflora Pall. Total glucosides of paenoy (TGP) mechanisms were assessed for the preparation of adjuvant arthritis (AA). Total glucosides of paenoy (TGP) microemulsion highly affect the stability and bioavailability of the drug in gastrointestinal tract (GIT) leading to increase in absorption (Zhang et al., 2007). For the study rats were taken and adjuvant arthritis was induced and activities like IL-1 and Synovioocytes proliferation were revealed by 3-(4, 5-dimethylthiazal-2-yl) 2, 5-diphenyltetrazolium bromide (MTT) assay. Radioimmunoassay was used to evaluate TNF-α and PGE2. Through Western blot analysis phosphorylation of p38 kinase and expression of matrix metalloproteinases (MMPs), c-Junctor N-terminal kinase (JNK) and extracellular regulating kinase (ERK) were determined. Ultrastructure change of synoviocytes secondary inflammatory reaction and bone destruction was inhibited by TGP (25, 50 and 100 mg kg (-1), ig, days 14-21) in AA rats. The AA rats were administered with TGP (50 and 100 mg/kg, ig, days 14-21) where a significant decrease in the manufacture of IL-1, PGE2 and TNF-alpha by macrophase-like synoviocytes (MLS) was seen. The TGP (25 mg/kg) as well cause the fall of the production of PGE 2 by MLS in adjuvant arthritis suffering rats. Also, in adjuvant arthritis affected rats, the TGP (50 and 100 mg/kg, ig, days 14-21) could possibly inhibit the amplified phosphorylation of MAPKs, cell proliferation, and MMPs expression in fibroblast-like synoviocytes (FLS) enthused by supernatants of MLS. The results showed that TGP have an ability of offering anti-inflammatory properties by changing the pro-inflammatory mediator’s manufacture by MLS and phosphorylation of MAPks by FLS.

2.1.3 Non-conventional approach: Intra-Articular Drug Delivery Systems

Arthritis comprising of both Osteo and Rheumatoid arthritis remain one of the main challenge in medical analysis (Chen and Yang, 2012; Tuan et al., 2002). For each disorder, injury of animal tissue matrix and inflammation are vital symptoms. Though no bar treatment is thought, pharmaceutical approaches are there in the market to decrease or revise joint injury and inflammation. The administration of medication is achieved through intra-articularly, orally or parenterally as a result of the denaturation property of the various medications (like recombinant proteins) and therefore the restricted blood flow in animal tissue, parenteral or oral delivery of a drug to associate degree affecting joint suffers the issue of supply of highly bioactive drug concentration at the location of action with restricted general side-effects. Therefore, intra-articular administration is taken into account as a best method for the treatment of joint diseases or disorders.

2.1.4 Non-conventional approach: Drug Entrapment

To overpower the problems associated with giving direct injection the clinicians and researchers have prepared polymer entrapped drugs. Polymers have many advantages like providing good biocompatibility and adhesion on the articular cartilage. When the degradation of the polymer occurs then the encapsulated drug releases from polymer mixture for their desired functions. Due to which residence time and efficacy of drugs dramatically increases. Today, several natural or artificial polymers are being increasingly used for this purpose are poly (lactic-co-glycolic acid) (PLGA), albumin (Ratcliffe et al., 1987); Chitosan (Mattioli-Belmonte et al., 1999); Silk (Wang et al., 2007).

2.1.5 Non-conventional approach: Molecular Modification

Beside drug encapsulation, polymeric materials are highly used for molecularly modifying the raise in the molecular weight of compound, for example, PEGylation, as it has been seen for the TNF antagonist etanercept (Roberts and Harris 2002), by molecularly crosslinking, that has been seen in case of hyaluronan (Adams et al., 1995). Apparently, some materials have environmentally responsive properties. For example, an elastin-like polypeptide was change d to a “drug depot” to extend drug release (Allen et al., 1999). For example, an elastin-like polypeptide was changed to a “drug depot” to extend drug release (Allen et al., 2009).

3. CLINICAL STUDY REPORTS- COMPILED DATA

The research incorporating clinical investigation has been compiled in below section.
• Phaniendra et al. (2015) dealt with chemistry, formation and sources, and molecular targets of free radicals and it give a concise summary on the pathogenesis of various diseases conditions caused by ROS/RNS. The reactive oxygen species are able to damage proteins and DNA at cellular level. Free radicals add on to nearly hundreds of disorders in Homo sapiens including hypertension, atherosclerosis, ischemia, arthritis, central nervous system injury, gastritis, and cancer, reperfusion injury of many tissues, Parkinsonism, Alzheimer’s disease, AIDS and diabetes mellitus. A group of 40 patients were taken for this study and were divided into two subsections having 20 patients in each group. First sub section got conventional treatment with the combination of antioxidants like vitamin C, glutathione and thiols and other control group of twenty aged and sex-matched normal individuals. It was shown that the conventional group supplemented with antioxidants like vitamin C, thiols and glutathione had better results in treatment than control group.

• Woo and Hyun (2017) investigated the assessment of cardiovascular associated risk of herbal medicinal product i.e. SKI306K (Joins®) in treating osteoarthritis. The study included a total of 27253 patients who were over 20 years old. Single prescription of SKI306K, celecoxib or naproxen was given along with them for one year. The study revealed higher risk with celecoxib than naproxen. The herbal drug SKI306K did not have much risk as compared to naproxen.

• Soeken et al. (2003) investigated the herbal treatment amongst people having RA, for their safety and efficacy. There is an average sustenance for gamma linolenic acid (GLA), that is brought into being in many herbal therapies, aimed at lessening pain, tender joint count and rigidity. During clinical trials, herbal preparations given topically or orally for rheumatoid arthritis in which the patients were abruptly allocated to obtain one out of both herbal medication or control treatment, which is placebo or active therapy. The herbal preparation was comparatively safer for use.

• Chopra et al. (2000) evaluated RA-1 which is a standardised plant extract formulation that is said to be safe and effective in Indian Ayurveda. One hundred eighty-two RA patients participated in a 16 week randomized, double blind, placebo controlled, clinical drug trial in Pune, India. Many efficacy events were measured by (1) ACR 20% improvement response; (2) ACR core set 20% and 50% improvement. The active RA-1 group continued statistically larger at all assessment time points. In a trial having adequate power, rheumatoid arthritis-1 showed efficiency which was not considerably better to the robust placebo response, excluding the enhancement of joint swelling. Additionally, the outcome on RF and good safety profile led to an open label phase. (53)

• Alamanos and Drosos (2005) reported a study of rheumatoid arthritis throughout the previous decades, showing a huge dissimilarity of the diseases happening with various populations. The greater part of study was done in North American and Northern European regions that shows frequency of 0.5–1%, and a mean annual frequency of 0.02–0.05%. The frequency of the diseases seemed to be lesser in other regions of the world. Various studies from Japanese, North American and North European people show a decrease in the incidence as well as frequency of the diseases after 1960. Though, rheumatoid arthritis is known as multi factorial disease, resultant of the interactions of environmental as well as genetic factors that contribute for its occurrences and expressions.

• Cameron et al. (2009) studied about herbal medicinal products (HMPs) which work alongside the mediators of swelling utilized medication of RA. Various electronic databases (EMBASE, MEDLINE, AMED, CISCOM, Cochrane registers, CINAHL) were studied. Randomized controlled trials also included in the study which compares HMPs alongside active or inert controls in patients suffering from RA. Twenty studies examining 14 HMPs were added. Meta-analysis was constrained to data from earlier seven studies with oils from borage, blackcurrant and evening primrose consisting gamma linolenic acid (GLA). GLA dose equivalent or more than 1400 mg/day proved profitable for improvement in RA complaints however low dose (i.e. 500 mg/day) was unproductive. Three studies comparing product from Tripterygium wilfordii (thunder god vine) to placebos gave beneficial outcome. Severe adverse effects happened in one study. Left of the study having different HMPs was examined independently. In case of various HMPs used for the cure of rheumatoid arthritis, the indications for efficacy were inadequate for recommendation and usage. Mediations for HMPs comprising GLA or Tripterygium wilfordii extract appeared for producing beneficial use.

• Chopra et al. (2018) evaluated long duration efficiency of the ayurvedic drug RA-1(Artrex ™, 2 tablets twice daily) with combination of DMARD’s. A total of 165 patients were volunteered for 16 week randomized controlled study. 57 patients were given a fixed dose of prednisone. The rheumatologist add DMARD and steroids to patients showing improper responses; chloroquine and/or methotrexate were generally preferred. The research reported that RA-1 performed better results.

• Salihu et al. (2018) aims for documentation and validation of plant species having traditional medicinal value in North-West Nigeria used for treatment of arthritis. The study showed the use of herbal remedies for the treatment of arthritis. There is a requirement of a multidisciplinary method for retaining the valued data on herbal remedies used for validating and developing drugs in future.

• Bhalekar et al. (2017) Solid lipid nano-particles of piperine were formulated (SLN) for the cure of R.A. The results of ELISA showed the decrease in TNF-α in treated rat that may be the explanation for the DMARD action of piperine SLN.

• Kessler et al. (2018) evaluated the effectiveness of ayurvedic treatment in comparison with the conventional treatment in knee osteoarthritis. The ayurvedic treatment showed great results in reducing the symptoms of osteoarthritis.
• **Zhang et al. (2010)** assessed the effectiveness of blood cupping plus herbal medicine in the treatment of gouty arthritis. Larger patients were cured by this treatment and other showed improvement. This therapy showed good results in the treatment of gouty arthritis.

• **Aiyalu et al. (2016)** formulated and evaluated topical herbal gel for the management of arthritis in animal study. The gel consisted of *Cardiospermum halicacabum* and *Vitex negundo* leaf extracts to evaluate the effectiveness in arthritis induced rats. 12 preparations of gel were evaluated where 6 were made from carboxapol 934 and other six with carboxapol 940. The preparation with carboxapol 934 (F4) showed the better results from all. This study assessed the results of sinomenine on somatic cell activation to characterize its allergic effects and therefore the underlying mechanisms. The results indicated that sinomenine evoked inositol-1, 4, 5-trisphosphate (IP3) production and therefore the unharnessed of amine, lymphokine (IL)-6, and endoplasmic reticulum Ca\(^{2+}\) in P815 cells.

4. **MARKETED FORMULATIONS**

Various herbal marketed products along with the active ingredients and applications in rheumatoid arthritis are summarized in table 4.

5. **PATENT LITERATURE**

Summary of patents enclosing studies on various herbal combinations and homeopathic formulations in the treatment of arthritis have been summarized in table 5.

**Conflicts of Interest**

The authors declared no conflicts of interest.

**Acknowledgements**

The authors are thankful to Dr. Madhu Chitkara, Vice Chancellor, Chitkara University; Dr. Ashok Chitkara, Chancellor, Chitkara University; Dr. Sandeep Arora, Director, Chitkara College of Pharmacy for providing necessary facilities and support.

**Conclusion**

The conventional treatment for arthritis based on synthetic drugs has been associated with various side effects. Herbal compounds and various combinations has been a potential area of research to overcome the adverse effects associated with the conventional therapy. Incorporation of herbal compounds along with synthetic drugs provides a maintenance therapy of such kind of age related diseases (especially in elders) which lead to better patient compliance. Role of nanotechnology is also playing a role for formulating stable nanocarriers with better efficacy and lesser side effects.

Table 1: Various classes of conventional drugs for treatment of RA/OA

<table>
<thead>
<tr>
<th>S. No</th>
<th>Class</th>
<th>Drugs</th>
<th>Therapeutic outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Non-steroidal anti-inflammatory drugs (NSAIDs)</td>
<td>Ibuprofen, Aspirin, Naproxen, Celebrex</td>
<td>Reduced pain and inflammation</td>
</tr>
<tr>
<td>2</td>
<td>Biologics</td>
<td>Simponi®, Etanercept (Enbrel), Infliximab (Remicade)</td>
<td>Used with DMARDs, biologic response modifiers targeting the protein molecules involved in immune response.</td>
</tr>
<tr>
<td>3</td>
<td>Disease-modifying antirheumatic drugs (DMARDs)</td>
<td>Prednisone, Methotrexate (Treaxall) and Hydroxychloroquine (Plaquinil)</td>
<td>Used to treat RA, DMARDs reduce or halt the immune system from attacking the joints.</td>
</tr>
<tr>
<td>4</td>
<td>Corticosteroids</td>
<td>Methotrexate, Plaquinil</td>
<td>Reduce swelling and suppress the immune system.</td>
</tr>
<tr>
<td>5</td>
<td>Analgesics</td>
<td>Acetaminophen, Hydrocodone</td>
<td>Reduce pain but no effect on inflammation.</td>
</tr>
</tbody>
</table>

Table 2: Toxicities caused by Synthetic Drugs

<table>
<thead>
<tr>
<th>S.No</th>
<th>Drugs</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methotrexate (DMARD’s)</td>
<td>Hépatotoxicity, Stomatitis, alopecia, infrequent myelosuppression, life-threatening pulmonary toxicity.</td>
</tr>
<tr>
<td>2</td>
<td>Oral salts of gold</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>3</td>
<td>Injectable salts of gold</td>
<td>Myelosuppression, Stomatitis, Thrombocytopenia, rash</td>
</tr>
<tr>
<td>4</td>
<td>Cyclosporines</td>
<td>Impairment of renal system, high blood pressure, overgrowth of gingival</td>
</tr>
<tr>
<td>5</td>
<td>D-penicillamine</td>
<td>Stomatitis, Rash, Dyspepsia, Myelosuppression, Proteinuria</td>
</tr>
<tr>
<td>6</td>
<td>NSAIDs</td>
<td>Stomatitis, Indigestion, Hemorrhage, Uercration, Hepatic abnormalities, Renal abnormalities, Dermatologic abnormalities, Pulmonary neurological abnormalities, Displacement of protein bound drugs, Hematologic abnormalities, Possible systemic complications</td>
</tr>
</tbody>
</table>
Table 3: Various herbs and their botanical names, families, local name and parts of plants

<table>
<thead>
<tr>
<th>S. No</th>
<th>Plant name</th>
<th>Genus and local name</th>
<th>Useful portion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alpinia galangal Linn</td>
<td>Zingiberaceae, Arattai, Perarattai</td>
<td>Rhizomes</td>
</tr>
<tr>
<td>2</td>
<td>Anacyclus pyrethrum</td>
<td>Asteraceae, Akkirakkaram</td>
<td>Roots</td>
</tr>
<tr>
<td>3</td>
<td>Capparis deciduas</td>
<td>Capparaceae, Senkam, Sirakkali</td>
<td>Roots</td>
</tr>
<tr>
<td>4</td>
<td>Aquilaria agallocha</td>
<td>Thymeleaceae, Agalicundanam, Krsnaguru</td>
<td>Wood and Oil</td>
</tr>
<tr>
<td>5</td>
<td>Callicarpa macrophylla Vah</td>
<td>Verbenaceae, Nallai</td>
<td>Flowers and fruits</td>
</tr>
<tr>
<td>6</td>
<td>Aphanamixis polystachya wall</td>
<td>Meliaceae, Malampuluvan</td>
<td>Bark</td>
</tr>
<tr>
<td>7</td>
<td>Argemone Mexicana</td>
<td>Papaveraceae, Kutiyotti</td>
<td>Whole plant, Latex</td>
</tr>
<tr>
<td>8</td>
<td>Ficus benghalensis</td>
<td>Moraceae, Alamaram</td>
<td>Latex</td>
</tr>
<tr>
<td>9</td>
<td>Hygrophila auriculata</td>
<td>Acanthaceae, Nirmulli</td>
<td>Roots, Leaves and Seeds</td>
</tr>
<tr>
<td>10</td>
<td>Fritillaria roylei Hook</td>
<td>Orchidaceae, Kakoli</td>
<td>Bulbs</td>
</tr>
<tr>
<td>11</td>
<td>Heliotropium indicum Linn</td>
<td>Boraginaceae, Telkodukka</td>
<td>Whole plant</td>
</tr>
<tr>
<td>12</td>
<td>Holarrhena pubescens</td>
<td>Apocynaceae, Kutasappalai, Veppalai</td>
<td>Barks, Seeds and Leaves</td>
</tr>
<tr>
<td>13</td>
<td>Flacourtia jangomas</td>
<td>Flacourtiaceae, Vyyyankarai</td>
<td>Fruits</td>
</tr>
<tr>
<td>14</td>
<td>Gossypium herbaceum Linn</td>
<td>Malvaceae, Panju</td>
<td>Leaves</td>
</tr>
<tr>
<td>15</td>
<td>Justicia gendarussa Burn</td>
<td>Acanthaceae, Vataikkutti</td>
<td>Roots and Leaves</td>
</tr>
<tr>
<td>16</td>
<td>Mimosa pudica Linn</td>
<td>Mimosaceae, Tottalcurunki</td>
<td>Whole plant</td>
</tr>
<tr>
<td>17</td>
<td>Kaempferia galangal Linn</td>
<td>Zingiberaceae, kaccolam</td>
<td>Rhizomes and Leaves</td>
</tr>
<tr>
<td>18</td>
<td>Lantana camara Linn</td>
<td>Verbenaceae, Arismatic, Unnicceti</td>
<td>Fruits</td>
</tr>
<tr>
<td>19</td>
<td>Mangifera indica Linn</td>
<td>Anacardiaceae, Mamaram, Mankai</td>
<td>Roots and Barks</td>
</tr>
<tr>
<td>20</td>
<td>Lithium polyphylun D</td>
<td>Liliaceae, Ksirakakoli</td>
<td>Bulb</td>
</tr>
<tr>
<td>21</td>
<td>Naravelia zeylanica Linn</td>
<td>Ranunculaceae, Vatamkolli</td>
<td>Whole plant</td>
</tr>
<tr>
<td>22</td>
<td>Oroxyylum indicum Linn</td>
<td>Bignoniacae, Palaiyudaycci</td>
<td>Roots</td>
</tr>
<tr>
<td>23</td>
<td>Tribulus terrestris Linn</td>
<td>Zygophyllaceae, Nerinci</td>
<td>Whole Plant</td>
</tr>
<tr>
<td>24</td>
<td>Jasminum lanceolarium Roxb</td>
<td>Oleaceae, Makarandam</td>
<td>Leaves and Flowers</td>
</tr>
</tbody>
</table>

Table 4: Herbal Marketed Formulations for Arthritis Treatment

<table>
<thead>
<tr>
<th>Herbal Formulation</th>
<th>Active Ingredients</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG201/HIMALAYA</td>
<td>Angelica sinensis, cnidium officinale, cinnamomum, Aromaticum Nees</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Joint Care B</td>
<td>Alpinia galangal, vitex negundo, glycyorrhiza glabra, foeniculum</td>
<td>Anti-inflammatory, Joint flexibility and lubrication</td>
</tr>
<tr>
<td>Joint Aid Plus</td>
<td>Giloy, nirgundi, ginger, guggul, ashwagandha, shallaki</td>
<td>Anti-inflammatory, control rheumatoid arthritis disease</td>
</tr>
<tr>
<td>Curcumin Capsules</td>
<td>95%curcuminoid content and turmeric</td>
<td>Anti-inflammatory, Rejuvenating properties Useful in osteoarthritis</td>
</tr>
<tr>
<td>Coral Calcium Complex</td>
<td>Praval pishiti, akik pishiti, kamududa rasa, giloy satva</td>
<td>Reduce bone mass Reduce bone fragility, Anti-inflammatory</td>
</tr>
<tr>
<td>Bone support capsules</td>
<td>Asthishrinhkala, sudh laksha, sahijan, arjun, praval pishiti</td>
<td>Anti-inflammatory, Joint mobility Loss of synovial fluid</td>
</tr>
<tr>
<td>Boswellia curcumin</td>
<td>Active extract of turmeric</td>
<td>Anti-inflammatory Protect joints antirheumatoid arthritis</td>
</tr>
<tr>
<td>RumoGin 5 capsules</td>
<td>Curcumin, saunth,shallaki, maicha and pippali</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Aamvatantak churna</td>
<td>Ashwagndha, fenugreek(trigonella-foenum graceum), suranjan, tinospora, cordifolia, gorakshmudi, sonth</td>
<td>Anti-inflammatory, Remove all the toxins</td>
</tr>
</tbody>
</table>
Table 5: Patent literature on herbal compositions for arthritis

<table>
<thead>
<tr>
<th>Patent number</th>
<th>Title</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 7,074,435</td>
<td>Crude drug compositions for treating or preventing arthritic diseases and the preparation process</td>
<td>The present investigation is related to pharmaceutical composition essentially comprising a herbal extract of various crude drugs such as Choenomelis Fructus, Achyranthis Radix, Acanthopanax, Phlomidis Radix, Gentianae Radix additionally comprising herbal extract selected from group consisting of Angelicae Radix, Cnidii Rhizoma, Gastrodiae Rhizoma, Safflower, Cinnamomi Cortex, Joab's tear, Aurantii nobilis Pericarpium, Ledebouriellae Radix, Lonicerap japonica, Akebiea caulis, Caragana chamaglu, Licorice root. The above composition has been utilized for prevention and treatment of arthritic diseases as potent anti-inflammatory and anti-arthritic agents.</td>
<td>Cho et al., 2006</td>
</tr>
<tr>
<td>US10/478,048</td>
<td>Herbal drug composition for cartilage protection</td>
<td>The present study relates to a herbal drug composition for protection of cartilage and comprises a plant extract of Clematis Radix, Trichosanthis Radix, and Prunellae spica and also an optimal content of Rosmarinic acid such as reduce pain, inhibit the acute and chronic inflammation, and it induce enzyme activities and associated with degradation of joint tissues, also provide good cartilage protection activity effectively used as analgesic, blood circulation enhancer and arthritis therapeutic agent.</td>
<td>Han et al., 2004</td>
</tr>
<tr>
<td>US 10/456,193</td>
<td>Methods of making pharmaceutical formulations for the delivery of drugs having low aqueous solubility</td>
<td>The invention discloses the aqueous formulations of pharmaceutical agents, which have low aqueous solubility. Also the methods also produce a simple formulation as sterile products. The drug physically entrapped by matrix comprising a hydrophilic and hydrophobic block polymer, also the formulation is nanoparticle or sub nano range in size.</td>
<td>Unger et al., 2004</td>
</tr>
<tr>
<td>US6346519B1</td>
<td>Method and composition for treating arthritis</td>
<td>It describes the composition of herbal drug and methods which are used to treating arthritis, repairing of articular joint surfaces and also the relief of symptoms i.e., associated with arthritis. The nitric oxide synthesis inhibitor reduces the level of nitric oxide. Amino sugars are the building blocks of articular cartilage and also have anti-inflammatory actions.</td>
<td>Petrus, 2002</td>
</tr>
<tr>
<td>US6391346B1</td>
<td>Anti-inflammatory, sleep-promoting herbal composition and method of use</td>
<td>It describes an orally administered drug composition with the capability to reduce inflammation in animals, more preferably in humans, while promoting sleep for such animals which contain therapeutically effective amounts of a post-critical hydro alcoholic extracts of ginger, the supercritical extracts of hops, chamomile, ginger, valerian and Melissa possessing therapeutic effects. It is preferably orally administered on a daily basis for at least 4 weeks.</td>
<td>Newmark and Schulick, 2002</td>
</tr>
<tr>
<td>US5910308A</td>
<td>Herbal extract composition containing gynostemma pentaphyllum, crataegus pinnatifida and camellia sinensis</td>
<td>Current invention includes herbal extract composition based on extracts of Gynostemma pentaphyllum, Crataegus pinnatifida (leaves or berries), Camellia sinensis (green tea) etc. It describes the process for preparing herbal extracts based composition which comprises separately extraction of berries, leaf, and drying extraction eluates from the plants, and the herbal extracts powder in desired proportion to form the composition which has health promoting effects.</td>
<td>D'jang, 1999</td>
</tr>
<tr>
<td>US5908628A</td>
<td>Compositions with analgesic, antipyretic and anti-inflammatory properties</td>
<td>The present invention provides compositions comprising tacle, silkworm excrement, and ingredients of plants of species of the genera Stephania, Coix, Pinellia, Prunus. It treating various diseases, including osteoarthritis and rheumatoid arthritis.</td>
<td>Hou, 1999</td>
</tr>
<tr>
<td>US5683698A</td>
<td>Formulation for alleviating symptoms associated with arthritis</td>
<td>The invention describes a herbal formulation which reduces symptoms associated with rheumatoid arthritis, osteoarthritis and reactive arthritis. It reduces the production of pro-inflammatory cytokines.</td>
<td>Chavali and Forse, 1997</td>
</tr>
<tr>
<td>US7229648B2</td>
<td>Homeopathic formulations useful for treating pain and/or inflammation</td>
<td>The invention describes the method of making the homeopathic formulation by mixing the homeopathically formulated herbal active ingredients in a clear gel base. Various homeopathic formulations comprising tinctures and/or diluted extracts preferably subjected to potentization of at least 8 or 9 herbs selected from Bellis Perennis, Calendula Officinalis, Hamamelis Virginiana, Arnica Montana, Hypericum Perforatum, Aconitum Napellus, Ledom Palustre, Bryonia Alba and Ruta Graveolens; and second type consisting of, as active ingredients, tinctures and/or diluted extracts subjected to potentization of 5, 6 or 7 herbs selected from Bellis Perennis, Calendula Officinalis, Hamamelis Virginiana, Arnica Montana, Hypericum Perforatum, Aconitum Napellus, Ledom Palustre, Bryonia Alba and Ruta Graveolens.</td>
<td>Dreyer, 2007</td>
</tr>
</tbody>
</table>
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https://www.who.int/chp/topics/rheumatic/en/


Rheumatoid arthritis therapeutics: the neoteric approaches


Williams, J.E. (2001). Review of anti viral and immunomodulating properties of plants of the Peruvian rainforest with a particular emphasis on Una de Gato


