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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.

- **Gout:** It occurs due to increase in level of uric acid in body, leading to pain in joints.
- **Ankylosing Spondylitis (AS):** In this disease, spine is the most commonly affected area, associated with the symptoms of stiffness and pain.
- **Lupus arthritis:** It is also autoimmune disease and causes tissue damage and illness.
- **Juvenile arthritis (JA):** It mainly affects children aged 16 yr or younger. It causes inflammation of synovium.
- **Psoriatic arthritis (PA):** It is a chronic disease which leads to swelling of joints and skin. The signs of PA are conjunctivitis, pitting of nail, morning stiffness and pain in lower back.
- **Fibromyalgia:** It mainly affects females than males. Its indicators are morning stiffness, pain, disturbance in sleep and fatigue.
- **Septic arthritis:** It occurs due to infection of synovium and synovial fluid. Its symptoms are anorexia, nausea, fatigue etc.

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 TNF α inhibitor.
- Non-conventional methods include herbal treatment. The most common herbs used are ginger, curcumin, resveratrol, guggulosterone, piperine 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 (Kahlengberg 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 conjointly 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 leukoencephalpathy, 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). Obstinately, 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 Sjogren's syndrome, can as well upsurge 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 immuno-modulating 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. (Qiu 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 anti-oxidant 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 Usitaissimum*** (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** ***Arcticum 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).
- **Guggulosterone -** 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, guggulosterone [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). Guggulosterone inhibits MAP kinase and then inhibits NF-kB. 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 possess antioxidant, antiarthritis, antiviral activities etc. It acts by inhibiting NF-kB, 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:** Lipid 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-arthritic 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 anti-cancer, 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 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-arthritic 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 tetrandine 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-arthritic 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 oxide–inflammatory) (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 adjuvant (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 arthiritis. 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 (Naz 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_{mix}) (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 paeony (TGP) is an dynamic constituent that is an extract of the roots of Paeonia lactiflora Pall. Total glucosides of paeony (TGP) mechanisms were assessed for the management of adjuvant arthritis (AA). Total glucosides of paeony (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 Synoviocytes proliferation were revealed by 3-(4, 5-2dimethylthiazal-2yl) 2, 5-diphenyltetrazoliumbromide (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-Junction 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 macrophage-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 changed to a thermosensitive gel after injection to a joint, due to the alteration of temperature; such materials will intra-articularly develop 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 diseased 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 received by them once 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 rigidness. 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 efficiency 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 arthiritis-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 contributes 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 arthirtitis, 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 carbapol 934 and other six with carbapol 940. The preparation with carbapol 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.

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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

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

Table 2: Toxicities caused by Synthetic Drugs

S.No	Drugs	Toxicity
1	Methotrexate (DMARD's)	Hepatotoxicity, Stomatitis, alopecia, infrequent myelosuppression, life-threatening pulmonary toxicity.
2	Oral salts of gold	Diarrhoea
3	Injectable salts of gold	Myelosuppression, Stomatitis, Thrombocytopenia, rash
4	Cyclosporines	Impairment of renal system, high blood pressure, overgrowth of gingival
5	D-penicillamine	Stomatitis, Rash, Dyspepsia, Myelosuppression, Proteinuria
6	NSAIDs	Stomatitis, Indigestion, Hemorrhage, Ulceration, Hepatic abnormalities, Renal abnormalities, Dermatologic abnormalities, Pulmonary neurological abnormalities, Displacement of protein bound drugs, Hematologic abnormalities, Possible systemic complications

Table 3: Various herbs and their botanical names, families, local name and parts of plants

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

Table 4: Herbal Marketed Formulations for Arthritis Treatment

Herbal Formulation	Active Ingredients	Uses
PG201/ HIMALAYA	Angelica sinensis, cnidium officinale, cinnamomum, Aromaticum Nees	Anti-inflammatory
Joint Care B	Alpinia galangal, vitex negundo, glycyrrhiza glabra, foeniciulum	Anti-inflammatory Joint flexibility and lubrication
Joint Aid Plus	Giloy, nirgundi, ginger, guggul, ashwgandha, shallaki	Anti-inflammatory, control rheumatoid arthritis disease
Curcumin Capsules	95%curcuminoid content and turmeric	Anti-inflammatory Rejuvenating properties Useful in osteoarthritis
Coral Calcium Complex	Praval pishti, akik pishti, kamdudha rasa, giloy satva	Reduce bone mass Reduce bone fragility , Anti-inflammatory
Bone support capsules	Asthishrinkhala, sudh laksha, sahijan, arjun , praval pishti	Anti-inflammatory Joint mobility Loss of synovial fluid
Boswellia curcumin	Active extract of turmeric	Anti-inflammatory Protect joints antirheumatoid arthritis
RumoGin 5 capsules	Curcumin, saunth,shallaki, maicha and pippali	Anti-inflammatory
Aamvatantak churna	Ashwgandha, fenugreek(trigonella- foenum graceum), suranjan, tinospora, cordifolia, gorakhmundi, sonth	Anti-inflammatory Remove all the toxins

Table 5: Patent literature on herbal compositions for arthritis

Patent number	Title	Description	References
US 7,074,435	Crude drug compositions for treating or preventing arthritic diseases and the preparation process	The present investigation is related to pharmaceutical composition essentially comprising a herbal extracts of various crude drugs such as Chaenomelis 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, Job's tear, Aurantii nobilis Pericapium, Ledebouriellae Radix, Lonicera japonica, Akebiae caulis, Caragana chamlagu, Licorice root. The above composition has been utilized for prevention and treatment of arthritic diseases as potent anti-inflammatory and anti-arthritic agents.	Cho *et al*., 2006
US10/478,048	Herbal drug composition for cartilage protection	The present study relates to a herbal drug composition for protection of cartilage and comprising a plant extracts 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.	Han *et al*., 2004
US 10/456,193	Methods of making pharmaceutical formulations for the delivery of drugs having low aqueous solubility	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.	Unger *et al*., 2004
US6346519B1	Method and composition for treating arthritis	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	Petrus, 2002
US6391346B1	Anti-inflammatory, sleep-promoting herbal composition and method of use	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 possesssing therapeutic effects. It is preferably orally administered on a daily basis for at least 4 weeks.	Newmark and Schulick, 2002
US5910308A	Herbal extract composition containing gynostemma pentaphyllum, crataegus pinnatifida and camellia sinensis	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.	D'jang, 1999
US5908628A	Compositions with analgesic, antipyretic and anti-inflammatory properties	The present invention provides compositions comprising talc, silkworm excrement, and ingredients of plants of species of the genera Stephania, Coix, Pinellia, Prunus. It treating various diseases, including osteoarthritis and rheumatoid arthritis.	Hou, 1999
US5683698A	Formulation for alleviating symptoms associated with arthritis	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.	Chavali and Forse, 1997
US7229648B2	Homeopathic formulations useful for treating pain and/or inflammation	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, Ledum Palustre, Bryonia Albaand 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, Ledum Palustre, Bryonia Alba and Ruta Graveolens.	Dreyer, 2007

References

Adams, M.E.; Atkinson, M.H.; Lussier, A.J.; Schulz, J.I.; Siminovitch, K.A.; Wade, J.P. and Zummer, M. (1995). The role of visco-supplementation with hylan GF 20 (Synvisc®) in the treatment of osteoarthritis of the knee: a Canadian multicenter trial comparing hylan GF 20 alone, hylan GF 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthritis and cartilage, 3(4): 213-225.

Afzal, M.; Al-Hadidi, D.; Menon, M.; Pesek, J. and Dhami, M.S. (2001). Ginger: an ethnomedical, chemical and pharmacological review. Drug Metabolism and Drug Interactions, 18(3-4):159-90.

Ahmed, S.; Anuntiyo, J.; Malemud, C.J. and Haqqi, T.M. (2005). Biological basis for the use of botanicals in osteoarthritis and rheumatoid arthritis: a review. Evidence-Based Complementary and Alternative Medicine, 2(3): 301-308.

Aiyalu, R.; Govindarjan, A. and Ramasamy, A. (2016). Formulation and evaluation of topical herbal gel for the treatment of arthritis in animal model. Brazilian Journal of Pharmaceutical Sciences, 52(3): 493-507.

Alamanos, Y. and Drosos, A.A. (2005). Epidemiology of adult rheumatoid arthritis. Autoimmunity Reviews, 4(3): 130-136.

Allen, K.D.; Adams Jr, S.B. and Setton, L.A. (2009). Evaluating intra-articular drug delivery for the treatment of osteoarthritis in a rat model. Tissue Engineering Part B: Reviews, 16(1): 81-92.

Anderson, K.O.; Bradley, L.A.; Young, L.D.; McDaniel, L.K. and Wise, C.M. (1985). Rheumatoid arthritis: review of psychological factors related to etiology, effects, and treatment. Psychological bulletin, 98(2): 358.

Arora, R.; Kuhad, A.; Kaur, I.P. and Chopra, K. (2015). Curcumin loaded solid lipid nanoparticles ameliorate adjuvant-induced arthritis in rats. European Journal of Pain, 19(7): 940-952.

Arya, V. Gupta, V.K. and Kaur, R. (2011). A review on plants having anti-arthritic potential. International Journal of Pharmaceutical Sciences Review and Research, 7(2): 131-136.

Bergholm, R.; Leirisalo-Repo, M.; Vehkavaara, S.; Ma¨kimattila, S.; Taskinen, M.R. and Yki-Ja¨rvinen, H. (2002). Impaired responsiveness to NO in newly diagnosed patients with rheumatoid arthritis. Arteriosclerosis, Thrombosis, and Vascular Biology, 22(10): 1637-1641.

Bhalekar, M.R.; Madgulkar, A.R.; Desale, P.S. and Marium, G. (2017). Formulation of piperine solid lipid nanoparticles (SLN) for treatment of rheumatoid arthritis. Drug Development and Industrial Pharmacy, 43(6): 1003-1010.

Cameron, M.; Gagnier, J.J.; Little, C.V.; Parsons, T.J.; Blümle, A. and Chrubasik, S. (2009). Evidence of effectiveness of herbal medicinal products in the treatment of arthritis. Phytotherapy Research, 23(11): 1497-1515.

Chandrasekar, R. and Chandrasekar, S. (2017). Natural herbal treatment for rheumatoid arthritis-A review. International Journal of Pharmaceutical Sciences and Research, 8(2): 368.

Chavali, S.R. and Forse, R.A. (1997). Formulation for alleviating symptoms associated with arthritis. U.S. Patent No. 5,683,698. Washington, DC: U.S. Patent and Trademark Office.

Chen, H.; Chang, X.; Weng, T.; Zhao, X.; Gao, Z.; Yang, Y.; Xu, H. and Yang, X. (2004). A study of microemulsion systems for transdermal delivery of triptolide. Journal of Controlled Release, 98(3): 427-436.

Chen, Q.A.; Gibney, E.; Fitch, J.M.; Linsenmayer, C.; Schmid, T.M. and Linsenmayer, T.F. (1990). Long-range movement and fibril association of type X collagen within embryonic cartilage matrix. Proceedings of the National Academy of Sciences, 87(20): 8046-8050.

Chen, Y. and Yang, K. (2012). Intra-articular drug delivery systems for arthritis treatment. Rheumatology, 2: e106.

Cho, B.W.; Jin, M.; Jung, H.J.; Shin, S.S.; Kim, S.; Jeon, H.; Oh, J.H.; Eo, H.K. and Kim, B. (2006). Crude drug compositions for treating or preventing arthritic diseases and the preparation process. U.S. Patent No. 7,074,435. Washington, DC: U.S. Patent and Trademark Office.

Chopra, A.; Saluja, M.; Kianifard, T.; Chitre, D. and Venugopalan, A. (2018). Long term effectiveness of RA-1 as a monotherapy and in combination with disease modifying anti-rheumatic drugs in the treatment of rheumatoid arthritis. Journal of Ayurveda and Integrative Medicine, 9(3): 201-208.

Chopra, A.; Lavin, P.; Patwardhan, B. and Chitre, D. (2000). Randomized double blind trial of an ayurvedic plant derived formulation for treatment of rheumatoid arthritis. The Journal of Rheumatology, 27(6): 1365-1372.

Chuang, S.Y.; Lin, C.H.; Huang, T.H. and Fang, J.Y (2018). Lipid-based nanoparticles as a potential delivery approach in the treatment of rheumatoid arthritis. Nanomaterials, 8(1): 42.

Curtis, J.R.; Patkar, N.; Xie, A.; Martin, C.; Allison, J.J.; Saag, M.; Shatin, D. and Saag, K.G. (2007). Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor α antagonists. Arthritis and Rheumatism, 56(4): 1125-1133.

D'jang, A.H. (1999). Herbal extract composition containing gynostemma pentaphyllum, crataegus pinnatifida and camellia sinensis. U.S. Patent No. 5,910,308. Washington, DC: U.S. Patent and Trademark Office.

Dreyer, L.R. (2007). Homeopathic formulations useful for treating pain and/or inflammation. U.S. Patent No. 7,229,648. Washington, DC: U.S. Patent and Trademark Office.

Elmali, N.; Baysal, O.; Harma, A.; Esenkaya, I. and Mizrak, B. (2007). Effects of resveratrol in inflammatory arthritis. Inflammation, 30(1-2): 1-6.

Fan, C.; Li, X.; Zhou, Y.; Zhao, Y.; Ma, S.; Li, W.; Liu, Y. and Li, G. (2013). Enhanced topical delivery of

tetrandrine by ethosomes for treatment of arthritis. BioMed Research International, Article ID 161943.

Ganta, S.; Devalapally, H.; Shahiwala, A. and Amiji, M. (2008). A review of stimuli-responsive nanocarriers for drug and gene delivery. Journal of Controlled Release, 126(3): 187-204.

Gupta, B.M. and Ahmed, K.M. (2018). Pancreatitis Research in India: A Scientometric Assessment of Publications during 2007-16. EC Gastroenterology and Digestive System, 5: 37-47.

Gupta, M. (2017). Natural products in treatment of rheumatoid arthritis. International Journal of Green Pharmacy, 11(03): S356.

Han, C.K.; Kwak, W.J.; Joung, K.; Yoo, H.; Kum, D.; Cho, Y.B.; Ryu, K.; Rhee, H.; Kim, T.; Jung, I. and Lee, S. (2004). Herbal drug composition for cartilage protection. U.S. Patent Application No. 10/478,048.

Handa, R.; Rao, U.R.K.; Lewis, J.F.; Rambhad, G.; Shiff, S. and Ghia, C.J. (2016). Literature review of rheumatoid arthritis in India. International Journal of Rheumatic Diseases, 19(5): 440-451.

Hannonen, P.; Möttönen, T.; Hakola, M. and Oka, M. (1993). Sulfasalazine in early rheumatoid arthritis. A 48-week double-blind, prospective, placebo-controlled study. Arthritis and Rheumatism: Official Journal of the American College of Rheumatology, 36(11): 1501-1509.

Hofkens, W.; Storm, G.; Van Den Berg, W.B. and Van Lent, P.L. (2011). Liposomal targeting of glucocorticoids to the inflamed synovium inhibits cartilage matrix destruction during murine antigen-induced arthritis. International Journal of Pharmaceutics, 416(2): 486-492.

Hou, L. (1999). Compositions with analgesic, antipyretic and anti-inflammatory properties. U.S. Patent No. 5,908,628. Washington, DC: U.S. Patent and Trademark Office.

https://www.who.int/chp/topics/rheumatic/en/

Jacobs, J.W.G.; Rasker, J.J. and Bijlsma, J.W.J (2001). Alternative medicine in rheumatology: Threat or challenge? Clinical and Experimental Rheumatology, 19(2): 117-120.

Kahlenberg, J.M. and Fox, D.A. (2011). Advances in the medical treatment of rheumatoid arthritis. Hand clinics, 27(1): 11-20.

Kapoor, B.; Singh, S.K.; Gulati, M.; Gupta, R. and Vaidya, Y. (2014). Application of liposomes in treatment of rheumatoid arthritis: quo vadis. The scientific world Journal, Article ID 978351.

Kelly, C. and Saravanan, V. (2008). Treatment strategies for a rheumatoid arthritis patient with interstitial lung disease. Expert Opinion on Pharmacotherapy, 9(18): 3221-3230.

Kessler, C.S.; Dhiman, K.S.; Kumar, A.; Ostermann, T.; Gupta, S.; Morandi, A.; Mittwede, M.; Stapelfeldt, E.; Spoo, M.; Icke, K. and Michalsen, A. (2018). Effectiveness of an Ayurveda treatment approach in knee osteoarthritis–a randomized controlled trial. Osteoarthritis and Cartilage, 26(5): 620-630.

Kumar, K. and Rai, A.K. (2012). Proniosomal formulation of curcumin having anti-inflammatory and anti-arthritic activity in different experimental animal models. Die Pharmazie-An International Journal of Pharmaceutical Sciences, 67(10): 852-857.

Manjula, N.; Gayathri, B.; Vinaykumar, K.S.; Shankernarayanan, N.P.; Vishwakarma, R.A. and Balakrishnan, A. (2006). Inhibition of MAP kinases by crude extract and pure compound isolated from Commiphora mukul leads to down regulation of TNF-α, IL-1β and IL-2. International Immunopharmacology, 6(2): 122-132.

Manna, S.K.; Mukhopadhyay, A. and Aggarwal, B.B. (2000). Resveratrol suppresses TNF-induced activation of nuclear transcription factors NF-κB, activator protein-1, and apoptosis: potential role of reactive oxygen intermediates and lipid peroxidation. The Journal of Immunology, 164(12): 6509-6519.

Matos, M.A.; Tannuri, U. and Guarniero, R. (2010). The effect of zoledronate during bone healing. Journal of Orthopaedics and Traumatology, 11(1): 7-12.

Mattioli-Belmonte, M.; Gigante, A.; Muzzarelli, R.A.A.; Politano, R.; De Benedittis, A.; Specchia, N.; Buffa, A.; Biagini, G. and Greco, F. (1999). N, N-dicarboxymethyl chitosan as delivery agent for bone morphogenetic protein in the repair of articular cartilage. Medical and Biological Engineering and Computing, 37(1): 130-134.

Mease, P.J.; Cohen, S.; Gaylis, N.B.; Chubick, A.; Kaell, A.T.; Greenwald, M.; Agarwal, S.; Yin, M. and Kelman, A. (2010). Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: results from the SUNRISE trial. The Journal of Rheumatology, 37(5): 917-927.

Metselaar, J.M.; Van den Berg, W.B.; Holthuysen, A.E.M.; Wauben, M.H.M.; Storm, G. and Van Lent, P.L.E.M. (2004). Liposomal targeting of glucocorticoids to synovial lining cells strongly increases therapeutic benefit in collagen type II arthritis. Annals of the Rheumatic Diseases, 63(4): 348-353.

Naz, Z. and Ahmad, F.J. (2015). Curcumin-loaded colloidal carrier system: formulation optimization, mechanistic insight, ex vivo and in vivo evaluation. International Journal of Nanomedicine, 10: 4293.

Newmark, T. and Schulick, P. (2002). Newmark T, Schulick P, inventors; New Chapter Inc, assignee. Anti-inflammatory, sleep-promoting herbal composition and method of use. U.S. Patent No. 6,391,346. Washington, DC: U.S. Patent and Trademark Office.

Patel, D.; Kaur, G.; Sawant, M.G. and Deshmukh, P. (2013). Herbal Medicine– A natural cure to arthritis. Indian Journal of Natural Products and Resources, 4(1): 27-35.

Petrus, E.J. (2002). Method and composition for treating arthritis U.S. Patent No. 6,346,519. Washington, DC: U.S. Patent and Trademark Office.

Phaniendra, A.; Jestadi, D.B. and Periyasamy, L. (2015). Free radicals: properties, sources, targets, and their implication in various diseases. Indian Journal of Clinical Biochemistry, 30(1): 11-26.

Poonia, P.; Mittal, S.K.; Gupta, V.K. and Singh, J. (2014). Sweety. Gum guggul: An Ayurvedic boom. Int J Pharmacogn Phytochem Res, 6: 347-54.

Qiu, D. and Kao, P.N. (2003). Immunosuppressive and anti-inflammatory mechanisms of triptolide, the principal active diterpenoid from the Chinese medicinal herb *Tripterygium wilfordii* Hook. f. Drugs in R and D, 4(1): 1-18.

Radovits, B.J.; Fransen, J.; Al-Shamma, S.; Eijsbouts, A.M.; Van Riel, P.L.C.M. and Laan, R.F.J.M. (2010). Excess mortality emerges after 10 years in an inception cohort of early rheumatoid arthritis. Arthritis Care and Research, 62(3): 362-370.

Rahman, M.; Beg, S.; Verma, A.; Al-Abbasi, F.A.; Anwar, F.; Saini, S.; Akhter, S. and Kumar, V. (2017). Phytoconstituents as pharmacotherapeutics in rheumatoid arthritis: challenges and scope of nano/submicromedicine in its effective delivery. Journal of Pharmacy and Pharmacology, 69(1): 1-14.

Rao, J.K.; Mihaliak, K.; Kroenke, K.; Bradley, J.; Tierney, W.M. and Weinberger, M. (1999). Use of complementary therapies for arthritis among patients of rheumatologists. Annals of Internal Medicine, 131: 409-416.

Ratcliffe, J.H.; Hunneyball, I.M.; Wilson, C.G.; Smith, A. and Davis, S.S. (1987). Albumin microspheres for intra-articular drug delivery: Investigation of their retention in normal and arthritic knee joints of rabbits. Journal of Pharmacy and Pharmacology, 39(4): 290-295.

RobertsMJ, B. H. J., and Harris, J. M (2002). Chemistry for peptide and protein PEGlation. Advanced Drug Delivery Reviews, 54(4): 459-476.

Sachan, R.; Parashar, T.; Soniya, S.V.; Singh, G.; Tyagi, S.; Patel, C. and Gupta, A. (2013). Drug carrier transfersomes: a novel tool for transdermal drug delivery system. International Journal of Research and Development in Pharmacy and Life Sciences, 2(2): 309-316.

Salihu, T.; Olukunle, J.O.; Adenubi, O.T.; Mbaoji, C. and Zarma, M.H. (2018). Ethnomedicinal plant species commonly used to manage arthritis in North-West Nigeria. South African Journal of Botany, 118: 33-43.

Sandoval-Chacon, M.; Thompson, J.H.; Zhang, X.J.; Liu, X.; Mannick, E.E.; Sadowska-Krowicka, H.; Charbonnet, R.M.; Clark, D.A. and Miller, M.J.S. (1998). Anti-inflammatory actions of cat's claw: the role of NF-kB. Alimentary Pharmacology and Therapeutics, 12(12): 1279-1290.

Shishodia, S. and Aggarwal, B.B. (2004). Guggulsterone inhibits NF-κB and IκBα kinase activation, suppresses expression of anti-apoptotic gene products, and enhances apoptosis. Journal of Biological Chemistry, 279(45): 47148-47158.

Siddiqui, I.A.; Afaq, F.; Adhami, V.M.; Ahmad, N. and Mukhtar, H. (2004). Antioxidants of the beverage tea in promotion of human health. Antioxidants and Redox Signaling, 6(3):571-582.

Singh, A.; Ahmad, I.; Akhter, S.; Zaki Ahmad, M.; Iqbal, Z. and J Ahmad, F. (2012). Thymoquinone: major molecular targets, prominent pharmacological actions and drug delivery concerns. Current Bioactive Compounds, 8(4): 334-344.

Soeken, K.L.; Miller, S.A. and Ernst, E. (2003). Herbal medicines for the treatment of rheumatoid arthritis: a systematic review. Rheumatology, 42(5): 652-659.

Strand, V.; Cohen, S.; Schiff, M.; Weaver, A.; Fleischmann, R.; Cannon, G.; Fox, R.; Moreland, L.; Olsen, N.; Furst, D. and Caldwell, J. (1999). Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Archives of Internal Medicine, 159(21): 2542-2550.

Strangfeld, A.; Hierse, F.; Rau, R.; Burmester, G.R.; Krummel-Lorenz, B.; Demary, W.; Listing, J. and Zink, A. (2010). Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Research and Therapy, 12(1): R5.

Syngle, A. (2006). Arthritis and its treatment. In Prevention and treatment of age-related diseases (pp. 105-132). Springer, Dordrecht.

Tao, X. and Lipsky, P.E (2000). The Chinese anti-inflammatory and immunosuppressive herbal remedy Tripterygium wilfordii Hook F. Rheumatic Disease Clinics of North America, 26(1): 29-50.

Thomson, M.; Al-Qattan, K.K.; Al-Sawan, S.M.; Alnaqeeb, M.A.; Khan, I. and Ali, M. (2002). The use of ginger (Zingiber officinale Rosc.) as a potential anti-inflammatory and antithrombotic agent. Prostaglandins, Leukotrienes and Essential Fatty Acids, 67(6): 475-478.

Tuan, R.S.; Boland, G. and Tuli, R. (2002). Adult mesenchymal stem cells and cell-based tissue engineering. Arthritis Res Ther, 5(1): 32.

Unger, E.; Ramaswami, V.; Zutshi, R.; LaBell, R. and Pigman, E. (2004). Methods of making pharmaceutical formulations for the delivery of drugs having low aqueous solubility U.S. Patent Application No. 10/456,193.

Verstappen, S.M.; Jacobs, J.W.; Bijlsma, J.W.; Heurkens, A.H.; van Booma-Frankfort, C.; Borg, E.J.T.; Hofman, D.M. and van der Veen, M.J. (2003). Five year followup of rheumatoid arthritis patients after early treatment with disease-modifying antirheumatic drugs versus treatment according to the pyramid approach in the first year. Arthritis and Rheumatism: Official Journal of the American College of Rheumatology, 48(7): 1797-1807.

Wadekar, J.B.; Sawant, R.L. and Patel, U.B. (2015). Rheumatoid arthritis and herbal drugs: A review. Journal of Phytopharmacology, 4: 311-8.

Wang, X.; Wenk, E.; Matsumoto, A.; Meinel, L.; Li, C. and Kaplan, D.L. (2007). Silk microspheres for encapsulation and controlled release. Journal of Controlled Release, 117(3): 360-370.

Whitehouse, M.W.; Fairlie, D.P. and Thong, Y.H. (1994). Anti-inflammatory activity of the isoquinoline alkaloid, tetrandrine, against established adjuvant arthritis in rats. Agents and Actions, 42(3-4): 123-127.

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

and Sangre de Grado. Alternative Medicine Review, 6(6): 567-580.

Woo, Y. and Hyun, M.K. (2017). Evaluation of cardiovascular risk associated with SKI306X use in patients with osteoarthritis and rheumatoid arthritis. Journal of Ethnopharmacology, 207: 42-46.

Xiaoyan, A.; Jun, Y.; Min, W.; Haiyue, Z.; Li, C.; Kangde, Y. and Fanglian, Y. (2008). Preparation of chitosan–gelatin scaffold containing tetrandrine-loaded nano-aggregates and its controlled release behavior. International Journal of Pharmaceutics, 350(1-2): 257-264.

Yang, M.; Feng, X.; Ding, J.; Chang, F. and Chen, X. (2017). Nanotherapeutics relieve rheumatoid arthritis. Journal of Controlled Release, 252: 108-124.

Zhang, S.J.; Liu, J.P. and He, K.Q. (2010). Treatment of acute gouty arthritis by blood-letting cupping plus herbal medicine. Journal of traditional Chinese medicine= Chung i tsa chih ying wen pan, 30(1): 18-20.

Zhang, X.Z.; Zhu, H.D.; Meng, S.F. and Pan, X.G. (2007). Preparation of sinomenine microemulsion and its transdermal absorption. Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi= China journal of Chinese materia medica, 32(19).

Zheng, Y.Q. and Wei, W. (2005). Total glucosides of paeony suppresses adjuvant arthritis in rats and intervenes cytokine-signaling between different types of synoviocytes. International Immunopharmacology, 5(10): 1560-1573.