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RESEARCH ARTICLE

POTENTIAL OF HERBAL PLANTS IN THE TREATMENT OF RHEUMATOID ARTHRITIS: A LITERATURE SURVEY

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ABSTRACT

This manuscript summarizes the various herbal plants used in the treatment of arthritis. Herbal medicines are popular within the vast majority of the world's population as remedies for diseases. The medicinal plants have great economic value all over the world. A very rich botanical wealth has been given to us by nature and a vast number of different types of plants grow in different parts of the world. There is significant evidence that plant extracts have the ability to grow into agents that can be used in disease prevention or treatment therapies. The manuscript focuses on the detailing of rheumatoid arthritis with their etiology and pathogenesis. It summarizes the herbal plants and their active constituent used in the management of rheumatoid arthritis and also summarizes the patent list related to the treatment of rheumatoid arthritis. In recent years the several medicinal plants are determined which shows the anti-arthritic function.

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INTRODUCTION

Rheumatoid arthritis has origins from the 19th century and a pedigree from the 20th century. Even though its name was adopted in the 1850s, the criteria for classification were developed just 50 years ago (1). It mostly affects the joints, but should be considered as a syndrome which includes extraarticular manifestations such as rheumatoid nodules, vasculitis or pulmonary involvement and systemic comorbidities. With an apparent reduction from north to south (in the northern hemisphere) and from urban to rural areas, rheumatoid arthritis has an incidence of 0·5% to 1%. There is a very high prevalence in certain Native American populations. The risk of rheumatoid arthritis is increased three to five times when family have positive history; in twins the concordance rates are get increased, suggesting genetic factors in pathogenesis (2). Genetic factors are responsible for 50% of the risk of developing rheumatoid arthritis; it mainly includes Human Leukocyte Antigen (HLA-DRB1). Rheumatoid arthritis affects 0·5-1·0% of adults in developed countries, with 5-50 per 100,000 new cases annually. In women and older adults, the condition is most typical. The prevalence in the adult Indian population of rheumatoid arthritis has been studied. As the first phase two qualified health workers performed a house-to-house survey of a rural population near Delhi. 44,551 adults represented the target population (over 16 years old).

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Using a questionnaire, the health workers identified potential cases of rheumatoid arthritis (RA).Then this cases further assessed by using the 1987 updated ARA criterion for the diagnosis of RA. A response rate of 89.5% was obtained and the health workers identified 3393 individuals as potential cases of RA. Of these, 299 met the updated ARA requirements for RA diagnosis, giving a prevalence of 0.75% (3).RA prevalence is 0.5-1% with a 3:1 ratio of a woman to a man. In women under 50 years, it is 4 to 5 times higher, but the ratio after 60 years becomes approximately 2 to 1 (4). Joint injury, impairment, reduced quality of life, cardiovascular and other comorbidities are caused by uncontrolled active rheumatoid arthritis (5).Symmetrical inflammatory polyarthritis, particularly of the hands and feet, is the most common RA presentation, although any synovial joint may be involved (6).
RA is a systemic autoimmune disorder characterized by symmetrical involvement of the peripheral joints, especially the small joints of the hands and wrists, feet, shoulders, elbows, knees and cervical spine (7).Compared with the healthy population, patients with RA show decreased quality of life in many domains, such as physical health, degree of freedom, climate and personal beliefs. Tiredness, stiffness, discomfort and reduced physical functioning affect quality of life in RA (8). Medical history, a physical examination and laboratory examinations are included in the medical diagnosis and evaluation of the patient. There is an elevated risk of the chronic health issues for children born to mothers with rheumatoid arthritis. The most common factor prompting patients to seek health treatment is the pain of arthritis. Diagnosis may be supported by characteristics such as

location, severity; level, nature and the course of pain. Some arthritis signs include stiffness, tiredness, reduced mobility, swollen joints and fatigue. The latter may be measured by means of inspection or direct joint palpation. An indicator of the amount of inflamed tissue is a count of the number of swollen joints (9). There are several different forms of arthritis that can be classified into two main groups: degenerative and inflammatory, which are broadly defined. The most prevalent form of degenerative arthritis is osteoarthritis (OA). A systemic disease with inflammation in many joints is present in inflammatory arthritis such as rheumatoid arthritis (RA) (10). Inflammatory arthritis involves particular types such as psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, juvenile idiopathic arthritis and reactive arthritis among others and is a type of rheumatic disorders involving synovial joint inflammation. Symptoms include joint pain, generalised exhaustion and stiffness, remissions and exacerbations (11).

Nowadays to control inflammation and to achieve remission, various groups of drugs with different modes of action are available. Glucocorticoids (GC) are commonly used in acute disease flares, either orally or as intraarticular injections, to relieve pain and swelling rapidly and to gain control of inflammation. Oral GC is for short-term use only and should be tapered to reduce side effects as soon as possible (up to 4 months).Disease Modifying Anti-Rheumatic Drugs (DMARD) to spare GC is required to regulate inflammation in the long run. There are a bunch of possibilities nowadays that can be obstacles or opportunities. Treatment of patients with RA is aimed at relieving pain and reducing inflammation, and the ultimate objective for all patients is to reach recovery or at least low disease activity. In this sense, 10 international guidelines have been collected by the European League Against Rheumatism (EULAR) on how to treat patients. In 2010, the treat-to-target (T2T) initiative was created by an international committee. The collaborative decision-making and frequent patient revaluation that targets recovery or at least low activity of the disease are essential to this initiative (12). The management of rheumatoid arthritis (RA) is guided by facts, and new EULAR guidelines for 2019 help to refine the effective position of various disease-modifying anti-rheumatic drugs (DMARDs) in treatment schedules. New drugs, primarily Janus Kinase inhibitors (JAKis), are currently in the development process, but particular therapeutic strategies seem to count more in terms of treatment responses than individual DMARDs, given the significant lack of head-to-head comparisons between specific biological (b) and targeted synthetic (its) DMARDs and the general perception of a similar efficacy profile across drugs. In this setting, where there is a scarcity of accurate biomarkers capable of predicting medication responses, treatment decisions are guided primarily by particular clinical or individual variables, given the recognised position of comorbidities, treatment-specific side effects, preferences of patients, and drug choice costs (13).

Etiology and Pathogenesis of Rheumatoid Arthritis and Role of Adaptive and Innate Immunity: The etiology and pathogenesis of rheumatoid arthritis are multifaceted and complex. Susceptibility and pathogenesis was aided by a combination of fixed (genes) and stochastic (random events and environment) influences. A description of mechanism of Rheumatoid arthritis are described in the in the figure 1.In individual innate immunity with underlying immune hyper-reactivity causes activation of fibroblast-like dendritic cells, synoviocytes and macrophages during the earliest stages, as demonstrated by the formation of auto antibodies. The genetic makeup of an individual including the existence of gene polymorphisms in genes that control immune responses and environmental exposure. Variety of sites including mucosal surfaces such as the joints or lungs the chronic inflammation leads to protein citrullination. A breakdown of tolerance may occur with the production of anti-citrullinated protein antibodies in a genetically susceptible organism. In order to present antigen and activate T cells, dendritic cells can move to the central lymphoid organs, which can activate B cells. These lymphocytes are able to migrate back to the synovium and strengthen the target organs adaptive immune responses. Furthermore, repeated activation of innate immunity can lead to chronic inflammation and possibly presentation of antigen in the synovium. Many cell types stimulate osteoclasts in the latter stages of the disease through the nuclear factor $_K$B (NF_KB)/receptor activator of NF_KB ligand (Receptor activator of nuclear factor kappa-B (RANK)/ Receptor activator of nuclear factor kappa-B ligand (RANKL)) method, but the greatest stimulation is possibly given by fibroblast-like synoviocytes and T cells. Autonomous fibroblast-like synoviocytes activation may also lead to this process (14).

Literature Review

Kaur *et al.* have been describes the herbal plant *Withania somnifera* Linn. which is also known as Ashwagandha for their anti-inflammatory and anti arthritic activity. The pharmacological function of the root is found due to the steroidal lactones and alkaloids. Withanine, pseudo-withanine, withanine, pseudo-tropine, tropine, somnine and somniferine are predominantly present among the alkaloids. Two acyl glucosides have been isolated from the roots, namely sitoindoside-8 and sitoindoside-7.The anti-arthritic effect in adjuvant-induced arthritic rats was demonstrated by oral administration of *Withenia somnifera* Linn. root powder (15). The use of Aloe vera in treatment of inflammation and arthritis was described by Balan *et al.* Painful inflammation of the joints is the main symptom of rheumatoid arthritis. Some clinical studies have been performed on Aloe vera and its use to relieve the pain of arthritis. Oral Aloe vera may be used in the treatment of chronic non-cancer pain especially caused by osteoarthritis (OA) pain. Topically, Aloe vera administration also reduces the inflammation. The anti-arthritis effect of aloe vera is caused by anthraquinone. The gel of the Aloe vera plant may also be applied directly to the swollen and painful joints. The gel, because of its anti-inflammatory effects, can offer relief from joint immobility and pain.It has recently been shown that aloe gel acts as an efficient gel base to prepare nimesulide emulgel for topical delivery in rheumatoid arthritis and other inflammatory conditions with a major anti-inflammatory effect (16). Kumar *et al.* have been investigated the *Boswellia Serrata* extract (BSE) for their anti-arthritis activity. BSEs consist of Boswellic acids such as acetyl-keto-beta-boswellic acid (KBA) and 11-KBA, which alters the levels of different cytokines and influence the cellular defence system.The resin portion contains β-boswellic acid, which has been have anti-inflammatory, anti-arthritic and antiatherosclerotic activity.By switching off pro inflammatory cytokines and mediators which start the process, *Boswellia serrata* extract has natural anti-inflammatory activities at sites where chronic inflammation is present.

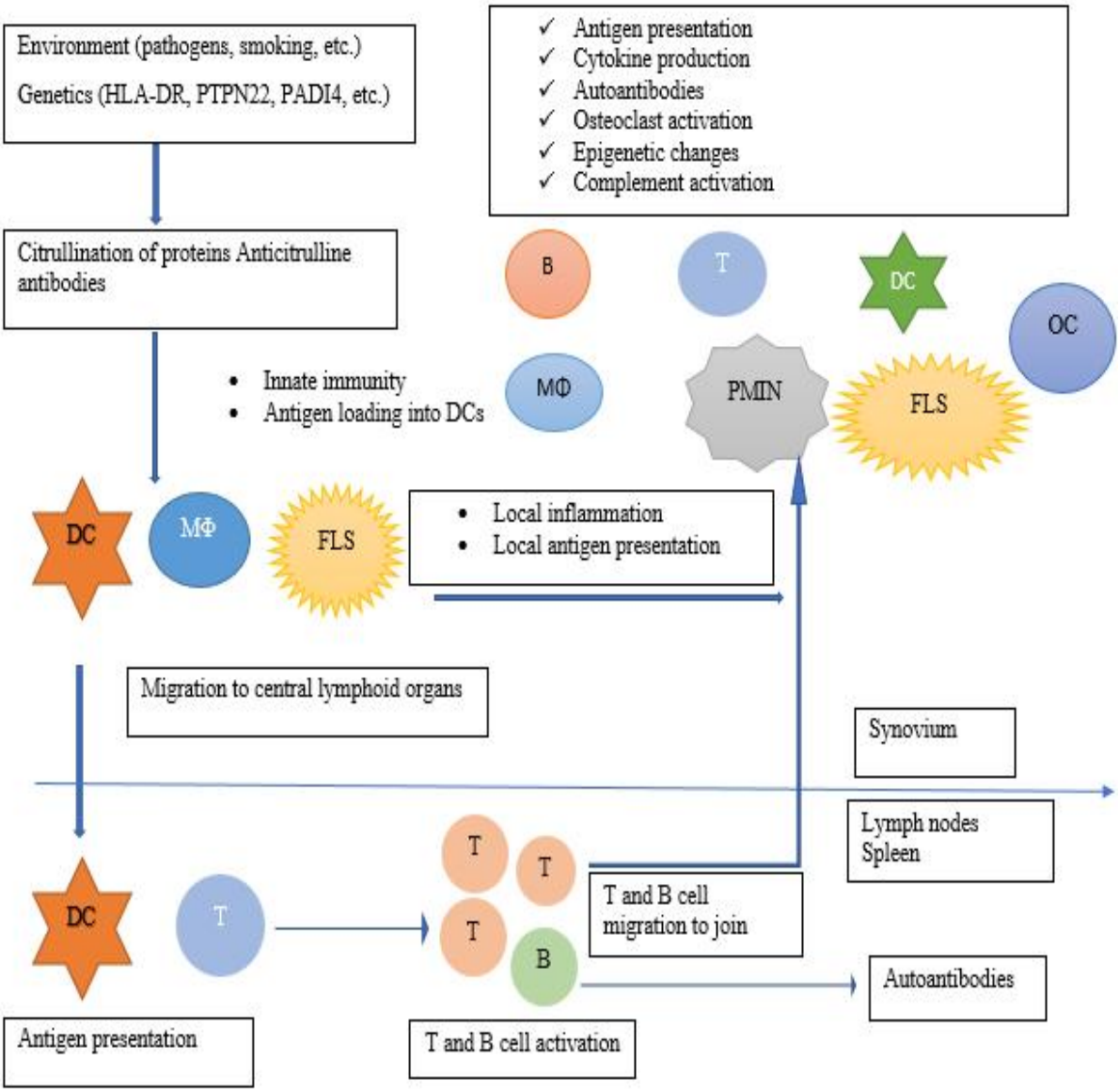

Figure 1. Schematic diagram of disease mechanism occurs in rheumatoid arthritis (14)

During the progression of arhritis these cytokines play a key role in chronic inflammation and tissue damage.Non-steroidal anti-inflammatory drugs may causethe breakdown of glycosaminoglycan synthesis which can accelerate the articular damage in arthritic conditions while the *Boswellia serrata* Linn.decreases the breakdown of synthesis of glycosaminoglycan (17). Bang *et al.* demonstrated the anti-inflammatory and anti-arthritic activity of piperine obtained from the black pepper (*Piper nigrum*). In vitro inhibitory activity against the enzymes responsible for leukotriene and prostaglandin biosynthesis, 5-lipoxygenase and COX-1, respectively, has been demonstrated by constituents of the piper species. These piperine effects tend to be beneficial for inflammatory disorders, such as rheumatoid arthritis, that are followed by intense pain (18). The anti-arthritic activity of Black cohosh or *Cimicifuga racemose* was demonstrated by Wobser *et al.* The isoflavone formononetin, caffeic, isoferulic, fukinolic acids and salicylic are included in a partial list of active compounds of Black cohosh. Fatty acids, sugars and tannins are also miscellaneous. Black cohosh decreases the development of inflammation due to arthritis (19). Castilhos *et al.* demonstrate the anti-arthritis activity of*Uncaria tomentosa*or Cat's Claw. It includes phytochemicals such as akuammigine, ajmalicin, campesterol, catechin, cinchonain, chlorogenic acid, corynoxein, corynantheine,epicatechin, daucosterol,harman, hirsutine, iso-pteropodin, lyaloside, loganic acid, mitraphylline, palmitoleic acid, oleanic acid, procyanidin, pteropodin, rutin, rhynchophylline, sitosterol, stigmasterol, speciophylline. Mainly the mitraphylline is reported for anti-inflammatory effects and it has been commonly used for the treatment of arthritis, rheumatism and other inflammatory diseases (20). Nahain *et al.* describes the *Zingiber officinale* or ginger for their rheumatoid arthritis effect. The most effective remedy for the treatment of arthritis pain is ginger extract. Sesquiterpenoids, with (-) zingiberene are the main constituents. The natural products responsible for anti-inflammatory function are sesquiterpene lactones (SLs). Other phytochemicals of ginger which have beneficial effect in rheumatoid arthritis and inflammation are diarylheptanoid, yakuchinone A, proanthocyanidin, 10-shogaol, 10-gingerol (21). The anti-arthritic activity of turmeric was determined by the Daily *et al.* Low-dose daily IP administration of purified curcuminoids (4 mg total curcuminoids/kg/d) inhibited joint inflammation in both acute and chronic phases of arthritis. Curcumin metabolites are found in high concentrations in the bloodstream after consumption. These curcumin metabolites may be responsible for the anti-inflammatory and antioxidant activities that reduce the symptoms of metabolic diseases

including osteoarthritis (22). Luk *et al.* describes the anti-arthritic activity of green tea.In Green Tea, the most important catechin is (-) epigallocatechin, which is a potent antioxidant. The decreased incidence and severity of collagen-induced arthritis was reflected in the marked inhibition of inflammatory mediators COX-2, IFNγ, and TNFα in the arthritic joints of green tea mice. Complete immunoglobulin (IgG) and collagen-specific type II IgG levels were found to be lower in the serum and arthritic joints of mice fed with green tea.Green tea has catechins (12-24% dry weight) as the main active ingredient, containing a significant number of phenolic hydroxyl groups (-OH). Epigallocatechin gallate (EGCG), epicatechin (EC), epigallocatechin (EGC) and epicatechin gallate (ECG) are among the four catechin monomers. It has been proposed that green tea and its main bioactive portion of the polyphenolic fraction of green tea, EGCG, are capable of protecting against cartilage loss and minimising OA progression over the past decade.Green tea catechins (GTCs) have recently shown the ability to re-establish skeletal muscle cell homeostasis and even mitigate muscle mass loss (23). Parihar *et al.* investigated the ethanolic extract of root bark of *Calotropis procera*which possess the anti-inflammatory activity. Mudarinin and asclepin are the principal active ingredients of *Calotropis procera*. The latex of this plant has potent antiinflammatory property in various animal models (24).

The antioxidants, anti-inflammatory and anti-rheumatic activity of *Ficus bengalensis*has been reported by Thite *et al.*Reported phytochemical studies have shown that *Ficus bengalensis* contains β-sitosterol, a-D-glucose, flavonoids, 5,7-dimethyl ether of leucopelargonidin, 3-0-β-D-galactosyl cellobioside, which is responsible for both immunomodulatory and anti-inflammatory pharmacological activities, suggests that *Ficus bengalensis* can induce possible anti-arthritic activity. The extract produced a noticeable inhibitory effect on edema, especially on secondary immunological arthritis and caused graded suppression of both levels of pain induced by formalin. There are several phytochemicals in the methanolic extract such as terpenoids, glycosides, alkaloids,flavonoids, steroids. The existence of flavonoids, saponin, tannins and steroids can be linked to their anti-rheumatic activity and to the modification of the autoimmune system (25). In the ayurvedic literature for the treatment of pain, inflammation and rheumatic disorders, the fruits of *Barringtonia racemosa* are recommended.Patil *et al.* describes the anti-arthritic activity of *Barringtonia racemosa Roxb.*It is used in rheumatoid arthritis and bartogenic acid is the active constituent responsible for this activity (BA). BA defends the haematological disturbances, primary and secondary arthritic lesions (26). *Cedrus deodara* wood has been used in Ayurvedic medical practise for the treatment of inflammation and rheumatoid arthritis since ancient times.Alkaloids, glycosides, flavonoids,phenolic compounds, proteins and saponins are the main constituents of *Cedrus deodara*. Shinde *et al.* was found its anti-arthritic activity which confirms its efficacy against arthritic disease in adjuvant induced arthritis in rats (27). Tinosporine, tinosporaside, tinosporide, cordifolide, heptacosanol, cordifol,clerodane furano diterpene, columbin, diterpenoid furanolactone and b-sitosterol are the major constituents of *Tinospora cordifolia*. Paval *et al.* describes the use of *Tinospora cordifolia* in rheumatoid arthritis therapy. At a dosage of 100 mg/kg it can shows the effective result against arthritis (28).

Polyphenols, triterpenoids,flavonoids, mangiferin, tannin, isomangiferin and gallic acid derivatives are the main constituents present in *mangifera indica*. Mangiferin is derived from mango from young leaves, bark and old leaves at high concentrations. Mangiferin demonstrates a powerful antioxidant effect. Garrido *et al.* describes that the *Mangifera indica* methanolic extract shows the anti-inflammatory behaviour in the arthritic parameter, such as paw edoema, arthritic index and rheumatoid factor (29). Mehta *et al.* describes the anti-arthritic activity of *Hemidesmus indicus*. Saponins, hemidesmine, tannins, hemidesmol, stearoptin, hemidesterol, pregnane glycosides, β-sitosterol, coumarin, indicusin, triterpenes, volatile oils, flavonoids and so on have been reported as their active constituents. Previous studies have shown that the hydroalcoholic root extract of *Hemidesmus indicus* inhibits the *in vitro* interaction between NF-κB & DNA.The outcome of the present study indicates the *Hemidesmus indicus* root hydroalcoholic extract shows the anti-arthritic effect. The sterols, terpens and phenolic compounds are the major phytoconstituent which plays the important role in this activity (30).

Ncytanthes arbortristis Linn. inhibits the acute inflammatory edema produced by different phlogistic agents carrageenan, histamine, formalin, 5-hydroxytryptamine and hyaluronidase which is reported by Saxena *et al.* Chronic and acute stages of arthritis induced with formaldehyde are greatly inhibited. *Nyctanthes arbortristis* Linn. was also found to suppress the immunological inflammation, viz. Freund's adjuvant arthritis (31). Amresh *et al.* have been found the antiarthritic activity of *Cissampelos pareira*from their roots.For relieving diarrhoea, pain and arthritis the ethanolic extract of the roots is useful. Ethanolic extract of the roots of *Cissampelos pareira* Linn. substantially protects against arthritis caused by complete Freund'sadjuvant in a dose-dependent manner (32). Rajendran *et al.* have been describes the role of *Premna serratifolia* Linn. wood in the treatment of arthritis. Wood of*Premna serratifolia* Linn. is stated to be useful in the treatment of arthritis in the indigenous system of medicine. The anti-arthritic behaviour observed due to the existence of phytoconstituents such as glycosides of irridiod, alkaloids, flavonoids and phenolic compound (33). The antiarthritic activity of *Vitex negundo* Linn. was investigated by Vijaya *et al.*Many polyphenolic compounds, glycosidic iridoids, terpenoids and alkaloids are primarily found in it which is responsible for the antiarthritic activity.In the study the petroleum ether extract of Vitex negundo Linn. was successfully used in the treatment of arthritis (34).

Ramani *et al.* have been demonstrated the antiarthritic activity of *Terminalia Chebula*. Terminalia Chebula is a component of Triphala which inhibits the collagenase and potenthyaluronidase which prevents the cartilage degradation. Studies have also shown both non-genotoxic and non-cytotoxic effects for both*in vitro* and *in vivo*. It containschebuline, chebulinic acid, tannic acid, resins, gallic acid, sinnosides, and anthraquinone phytochemical constituents.During study the acetone extract of *Terminalia Chebula* fruits shows the better antiarthritic activity (35). Talwar *et al.* have been determined the anti-inflammatory effect of *Terminalia paniculata*. It mainly consists flavanoids,alkaloids, saponin, triterpines, tannins. During study it was observed that aqueous extract of *Terminalia paniculata* showed significant anti-inflammatory activity for

Table 1. List of patents related with the treatment of rheumatoid arthritis

S. No.	Title	Patent Number	Description
1.	*Plectranthus amboinicus* fraction having anti-arthritis activity	KR101759751B1	Extraction of *Plectranthus amboinicus* which is rich in anti-arthritic activity and used in the treatment of arthritis was investigated (55).
2.	Plant extracts for the treatment of rheumatoid arthritis	US7531194B2	The use of extract of*Plectranthus Amboinicus*in the treatment of rheumatoid arthritis was described (56).
3.	Novel cannabis lines and extracts with anti-inflammatory potencies	US20200197463A1	It describes the new unique cannabis lines, extracts and methods for their use in anti-inflammatory, anti-arthritic therapies and modalities(57).
4.	Novel compositions for the treatment of inflammatory diseases	WO2020081513A	It relates to pharmaceutical compositions, pharmaceutical combinations and methods of treatment of inflammatory diseases (58).
5.	Treatment and Prevention of Bone and Joint Disorders	US20190261668A1	It describes about compositions and methods to treat and prevent the development and progression of osteoporosis and related disorders such as osteoarthritis and rhemstoid arthritis and for promoting overall bone and joint health (59).
6.	Pain Relief Formulation and Method of Treatment	US20200046790A1	It relates to a pain relief formulation, such as for reducing, alleviating or preventing pain such as for example pain associated with arthritis, rheumatism, infection, myalgia, muscle damage and neuralgia (60).
7.	Formulation of Curcumin with Enhanced Bioavailability of Curcumin and method of preparation and treatment thereof	US20190060253A1	It relates to oral supplementation of curcuminoid with essential oil of turmeric to enhance the bioavailability of curcumin for the prophylaxis , treatment, maintenance therapy and as add on therapy for disease conditions such as cancer, heart diseases, diabetes, rheumatoid arthritis, osteoarthritis, alzheimer's disease etc. (61).
8.	Therapeutic composition including plantain and aloe vera for treatment of arthritis and other afflictions	US6309675B1	It provides a therapeutic composition which combines the healing powers of plantain and Aloe vera for use in the treatment of arthritis and other afflictions, such as hematomas, skin rashes and infections (62).
9.	Physiologically-active composition based on collagen	CA2574907C	Collagen as an endogenous substance has been used for a long time in connection with the treatment of degenerative joint diseases and in particular predominantly for the treatment of arthroses and arthritic forms (63).
10.	Anti-arthritic and anti-paralytic herbal oil formulation and process for the preparation thereof	WO2018065836A1	Specifically, it concerns to anti-arthritic and anti-paralytic herbal topical oil formulation and process for the preparation (64).
11.	Plaster for treating gouty arthritis and preparation method thereof	CN111840485A	It relates to a plaster, for treating gouty arthritis and a preparation method (65).
12.	Traditional Chinese medicine for treating acute gouty arthritis and preparation method thereof	CN105617008A	It describes about a kind of Chinese medicine treating acute gouty arthritis (66).

acute and chronic inflammation (36). The antiarthritic activity of *Ammania baccifera* was investigated by Tripathy *et al.* It contains glycosides, sterols, saponin, alkaloids and triterpenoids. The alcoholic extract of *Ammania baccifera* shows the potent antiarthritic activity (37). Gupta *et al.* have been demonstrated the *Saraca asoca* Roxb. antiarthritic activity. Phytochemical research proves that the methanolic and ethanolic extracts of the plant contains the compounds such as carbohydrates, catechol, flavonoids, glycosides, hematoxylin, quercetin, leucocyanidin, steroids, proteins and tannins.The normal radiological images of the joint and histopathologic examination of the joint, stomach, liver and kidneyalso confirmed its major non-toxic, anti-inflammatory and anti-arthritic activity (38). The antiarthritic activity of *Justicia Gendarussa* was investigated by Paval *et al.* Phytochemical evaluations of the *Justicia Gendarussa*leaf extract showed the presence of the flavonoids apigenin and vitexin. Extract can also contain sitosterols, aromadendrin, reducing sugar, alkaloids and unidentified sterols.Vitexin can exert anti-inflammatory activityby inhibiting the 5-lipoxygenase pathway and COX-2 pathway which plays an important role in producing and maintaining the inflammation. Apigenin and vitexin isolated from the ethanolic extract showed the significant role in the treatment of rheumatoid arthritis (39). Yadav *et al.* describes the *Strychnos potatorum* Linn. antiarthritic activity. It contains diaboline and its acetate (major alkaloid), triterpenes sterols and mannogalactans responsible for its activity. In the study it was observed that *Strychnos potatorum* Linn. extract showed the potent antiarthritic activity (40). Kripa *et al.*have been describes the antiarthritic activity of *Leucas aspera* (Willd.).It contains triterpenoids, b-sitosterol, oleanolic acid, ursolic acid, glucoside, nicotine, sterols, diterpenes and phenolic compounds.Ethanolic extract of *Leucas aspera* showed the anti-rheumatoid arthritis effect in the study (41). The antiarthritic activity of *Premna corymbosa* was investigated by Karthikeyan *et al.* The presence of glycosides, alkaloids,flavanoids, triterpenoids and steroids was demonstrated by preliminary phytochemical leaf screening of *Premna corymbosa*. The ethanolic extract of *Leucas aspera* showed the anti-rheumatoid arthritis effect during the study (42). Narendhirakannan *et al.* have been evaluated the antiarthritic activity of *Cleome gynandra* Linn. It is used in the treatment of rheumatoid arthritis. It contains chemical ingredients such as tannins, triterpenes, anthroquinones, saponins, flavonoids, steroids, lectins, resins, glycosides, sugars phenolic compounds, alkaloids and all these compounds may be responsible for the anti-arthritic effects. *Cleome gynandra* Linn. ethanolic extract has anti-inflammatory activity against both acute and chronic inflammation. During study the *Cleome gynandra* Linn. ethanolic extract was showed a significant anti-arthritic activity (43).

Liu *et al.* have been investigated the antiarthritic activity of *Tripterygium wilfordii* Hook F. Triptolide is a major component of the extracts of *Tripterygium wilfordii*. Triptolide have been found to possess anti-inflammatory and immunosuppressive properties. *Tripterygium wilfordii* root extracts inhibit the macrophages, synovial fibroblasts, lymphocytes, chondrocytes, proinflammatory cytokines, proinflammatory mediators, adhesion molecules, and matrix metalloproteinases by macrophages. *Tripterygium wilfordii* root extract have been showed the significant antiarthritic activity (44). Hajja *et al.* have been described the anti-arthritic activity of *Glycyrrhiza glabra* (liquorice). In the conventional medical system, the rhizomes and roots of *Glycyrrhiza glabra*have been clinically used as anti-inflammatory for decades.In the liquorice root many valuable compounds such as glycyrrhizin and its aglycone, glycyrrhetinic acid are present. The components of liquorice flavonoids include flavonals, flavones, isoflavones, bihydroflavones, chalcones and bihydrochalcones. During the study it was observed that the methanolic extract of *Glycyrrhiza glabra*shows the potent anti-arthritic activity (45,46). The anti-arthritic activity of *Urtica* species were summarized by Abudoleh *et al.*The *Urtica pilulifera L.* contains some flavonoids, alkaloids and isolated compounds like isorhamnetin, kaempferol and quercetin, which have been shown to have anti-inflammatory activity. The most widely studied species is *Urtica dioica*, which has been provento have anti-arthritic activity and in another study petroleum ether seed extract of *Urtica pilulifera*have been proved to show anti-arthritic activity. During the study Abudoleh *et al.* have been determined the anti-arthritic activity of methanolic leaf extract of *Urtica pilulifera*and it was determined that the extract show the significant anti-arthritic activity (47).

Ghulam *et al.* have been demonstrated the anti-arthritic activity of methanolic extract of *Polygonum viviparum L.* without any analgesic, ulcerogenic and antipyretic activity. *Polygonum viviparum* rhizome methanolic extract was prepared and investigated for an acute and chronic inflammation the result showed significant anti-arthritic and anti-inflammatory activity, devoid of NSAID adverse effects (48). Several experimental pharmacological reports have been reported the anti-inflammatory ability of the bark of several cinnamon plants. The anti-inflammatory function of *Cinnamomum seiboldii* and *Cinnamomi cortex* a Japanese species has been attributed to a series of tannins. Vetal *et al.* have been reported the anti-inflammatory and anti-arthritic activity from bark of *Cinnamomum zeylanicum*. As an anti-arthritic agent, cinnamon barks ability for inflammation, pain and immune system makes it a successful candidate. Cinnamon bark polyphenol extract has been shown anti-inflammatory effects *in vitro* and therapeutic ability to prevent and cure of inflammatory diseases (49). Chandrudu *et al.* have been demonstrated the anti-arthritic property of *Hibiscus platinifolius* ethanolic extract. Carbohydrates, saponins, flavonoids, steroids, glycosides and alkaloids are the chemical constituents which are found in ethanolic extract of *Hibiscus platinifolius*. During the study it was observed that plant extract shows the potent anti-arthritic effect (50). In the treatment of rheumatism, the bark of *Alstonia scholaris* is traditionally used. Milky juice is mixed with oil and used for rheumatic irritation. The anti-arthritic activity of *Alstonia scholaris Linn.* leaves were determined by Arulmozhi *etal*. Echitamine, akaummicine, tubotaiwine, echitamidine, strictamine and picrinine are the major alkaloids found in *Alstonia scholaris*. Amino acids, phenol, sugars,tannins, saponins, cardiac glycosides, flavanoids, fixed oil, steroids and fats are also found in *Alstonia scholaris* flowers.The anti-arthritic activity was primarily accomplished by reducing the overall migration of leukocytes as well as monocytes and macrophages. It can be concluded from the study that *Alstonia scholaris*exhibits anti-arthritic behavior (51,52). Chitme *et al.* demonstrated the anti-arthritis activity of *Aristolochia Bracteata* extract. Alkaloids, hormones, triterpenoids, flavonoids, sugars, saponins, proteins and cardiac glycosides are the principal chemical components present in *Aristolochia Bracteata*. The extract of *Aristolochia Bracteata* shows the anti-inflammatory and anti-arthritic activity. By maintaining the synovial membrane and vascular permeability the*Aristolochia Bracteata*extract shows the anti-arthritic activity, thereby inhibiting the cytokines and infiltration of leukotriene (53). Root powder of *Boerhaavia diffusa Linn*. is used in the treatment of inflammatory diseases such as arthritis. Parmar *et al.* have been demonstrated the anti-arthritic activity of methanolic extract of *Boerhaavia diffusa Linn*.In the arthritic model, methanolic extract showed the best activity and its phytochemical analysis indicated the existence of flavonoids and phenolic compounds, so it may be possible that root extract anti-arthritic activity could be occurs due to the presence of flavonoids (54). The patent list related with the treatment of rheumatoid arthritis are summarized in table 1.

Conclusion

The manuscript discussed the various herbal plants used in the treatment of rheumatoid arthritis. Rheumatoid arthritis is the autoimmune disease which mainly affects the joints. The pathogenesis of the rheumatoid arthritis follows various mechanism so the treatment of disease become difficult. This manuscript focuses on the detailing of rheumatoid arthritis with their etiology and pathogenesis. It can also summarize the various herbal plants related literature surveys which were proves the efficacious effect of the herbal plants on the rheumatoid arthritis. Manuscript also summarizes the patent list related to the treatment of rheumatoid arthritis. In future the herbal plants can play an important role in the treatment of rheumatoid arthritis with great effectiveness.

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