

# Perspective of Plant Medicine in Therapy of Rheumatoid Arthritis

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## Gautam *et al.*: Plant Medicine in Therapy of Rheumatoid Arthritis

**Rheumatoid Arthritis is a systemic autoimmune disease characterized by chronic, inflammatory condition. The adverse effects of long-term use of presently available anti-arthritic or non-steroidal anti-inflammatory drugs are gastrointestinal symptoms, cardiovascular complications, renal impairment, myelosuppression etc. and this requires continuous monitoring and eventually increasing the cost of treatment. Thus complementary and alternative medicines may fulfill the demand for patients suffering from this disease. Moreover, herbal therapy has been safe and effective enough to treat rheumatoid arthritis. With these backgrounds, the present review includes different 37 plants reported for anti-arthritic or anti-inflammatory effect. Also enlisted 37 bioactive principals reported for anti-arthritic effect with their source, mechanism of action and commercial herbal products available in the market for treatment of rheumatoid arthritis. The compiled information regarding plants and their role in the treatment of rheumatoid arthritis will help to justify the use of plant-derived medicine in the therapy of rheumatoid arthritis in future.**

**Key words: Rheumatoid arthritis, anti-arthritic plants, herbal products, mechanism of action, medicinal plants, bioactive compounds**

Out of 7 billion people in the world, World Health Organization (WHO) states that 0.3-1 % of the population is suffering from Rheumatoid arthritis (RA)<sup>[1]</sup> and 20 % of total population of India is afflicted by this disease<sup>[2]</sup>. Arthritis is a very common disorder that affected 50 million Americans in the year 2007-2009. According to the data provided by the National Health Interview Survey in 2007, 11.2 million, or nearly one in four aged adults with arthritis (24 %), also had heart disease. As per a cross-sectional study, in India 45 % rheumatic diseases patients have co-morbidities such as hypertension, hypothyroidism and diabetes mellitus. Hence, timely diagnosis of associated co-morbid conditions is very much necessary for efficient management of rheumatic diseases<sup>[3]</sup>. The most common morbidity among adults with arthritis was heart disease. Among people with arthritis, 19 % (9.0 million) also had chronic respiratory conditions and 16 % (7.3 million) also had diabetes. Of the four conditions studied, stroke was the least common condition and affected 3.2 million people with

arthritis<sup>[4]</sup>. As per WHO, in developed countries at least 50 % RA patients are not capable of doing their full-time job probably due to the disability arises within 10 year of onset of disease<sup>[5]</sup>. In India, 0.92 % adults are suffering from RA. However, timely detection and aggressive treatment can prevent permanent disability, but that is not materialized in several cases. In India, around 20-40 new cases per 100 thousand population reporting every year and females are more susceptible for the disease. It was also reported that RA disease in females remains silent during pregnancy and onset of disease is observed after child delivery. Cigarette smoking, coffee and oral contraceptive pills reported as risk factor for developing of RA<sup>[6]</sup>.

RA is a systemic autoimmune disease characterized by

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chronic, inflammatory condition. The people suffering from RA are symptomized with pain, swelling, stiffness, destruction of cartilage and bone<sup>[1]</sup>. The four main symptoms of RA if present for 6 or more which confirms its diagnosis and this includes: morning stiffness in and around joints that lasts for one hour before maximal improvement is noted, swelling (arthritis) of soft tissue around three or more joints, swelling of proximal interphalangeal, metacarpophalangeal or wrist joint, symmetric arthritis<sup>[7]</sup>. Although the exact etiology is unknown but release of free radicals as a by-product of cellular metabolism may induce the generation of interleukins (IL) and Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) from T-cells. These intermediates in response produces growth factors, cytokines and adhesive molecules on immune cells which causes inflammation and destruction of tissues<sup>[8]</sup>. Due to RA, the pathological changes observed are hyperplasia of synovial membrane, infiltration of inflammatory cells. These changes results in articular destruction and cartilage erosion<sup>[9]</sup>. This disease can be treated by either eliminating symptoms or slowing down its progression, which may lead to improvement of the quality of life<sup>[10]</sup>.

Keeping the goal of treatment in mind, presently used drugs can vary which includes: over the counter drugs (acetaminophen, ibuprofen); Disease modifying anti-rheumatic drugs (methotrexate (MTX), penicillamine); Nonsteroidal anti-inflammatory drugs (NSAIDs) (diclofenac, ketoprofen) and biological agents (TNF- $\alpha$  blockers, rituxan). Though these therapeutic agents reduce infection and joint destruction, numerous side effects appear on prolonged use. The long-term use of these drugs leads to GI symptoms (ulcer, indigestion, and stomatitis), cardiovascular complications, hematologic toxicity, diarrhea, immune reactions, renal impairment, myelosuppression etc. This requires continuous monitoring which increases the cost of the treatment<sup>[2,7,11]</sup>.

The promising role as an anti-arthritic agent has been shown by many plants that are being used traditionally by various tribal and rural cultures worldwide. Herbal therapy has been safe and effective enough to treat RA and many are under scientific observation<sup>[12]</sup>.

Several mechanisms of action of plants to treat RA have been revealed with no observable side effects as compared to conventional therapy. The plants containing polyphenols exhibit their anti-rheumatic property by inhibiting inflammation either by modulating mitogen-activated protein kinases (MAPK) signaling pathway or by inhibiting Nuclear factor Kappa-Beta (NF- $\kappa$ B)

pathway and Activator protein-1 (AP-1) transcription factors. They also inhibit the production of inflammatory cytokines and chemokine which further suppress the activity of Cyclooxygenase (COX) and inhibition of the inducible nitric oxide synthase (iNOs) further decreases the production of free radicals such as reactive oxygen and nitrogen species<sup>[13,14]</sup>. Excessive production of nitric oxide (NO) which is a short-lived free radical produced from L-arginine is responsible for producing various inflammation and carcinogens at the site of inflammation which is inhibited by ethanolic extract of *Alpinia officinarum* rhizomes<sup>[15]</sup>. Flavonoids present in some plants like *Clausena anisata*, *Kigelia africana*, *Melianthus comosus* can inhibit the bio-synthesis of prostaglandins (PGs) which are the end products of immunologic responses in RA<sup>[16]</sup>. Flavonoids possess activity that inhibits inflammation and development of the induced granuloma. Quercetin like flavonoids blocks both COX and Lipoxygenase (LOX) pathways. Rutin and quercetin also possess anti-oxidant activity which suppresses the macrophage phagocytosis in RA<sup>[17]</sup>. Immune-suppressive effect is also exhibited by some plants like *Tripterygium wilfordii* which potentially inhibits the expression of pro-inflammatory cytokines, lymphocytes and synovial fibroblasts by inducing apoptosis in lymphocytes and synovial fibroblast and inhibition of proliferation<sup>[18]</sup>. Immunomodulatory effect exhibited by some plants like Amla and Shankpushpi causes reduction in the induction of NO synthase and these plants suppress lymphocyte proliferation in response to adjuvant induced arthritis (AIA). They inhibit T-cell activation indicated by decreased lymphocyte proliferation. It proves that these plants have immunosuppressive effect mediated by T-cells<sup>[19]</sup>. Also, *Camellia sinensis* (green tea) inhibits TNF- $\alpha$ , Interferon- $\gamma$ , NF- $\kappa$ B, iNOS and COX by its active component Epigallocatechin-3-gallate. NO production is inhibited by Gingerol (*Zingiber officinalis*) and inhibits COX and LOX pathways thus inhibiting Prostaglandin-E2 (PGE2) synthesis. Hence, the various active constituents present in the plants aims at inhibiting pro-inflammatory cytokines which causes inflammation in the joints and cartilage destruction which are the distinguishing characteristics of RA<sup>[20]</sup>.

Therefore, we have reviewed and summed most of the herbal plants with their possible mechanism that helps treat RA with no long-term side effects as compared to conventional approach and thus improving RA patient's state of diseased condition. The important plants exerting an anti-arthritic activity are listed below with

their respective roles as a therapy for RA.

## PLANTS USED IN THE THERAPY OF RA:

### *Adhatoda vasica* Nees:

*Adhatoda vasica* Nees belonging to the family Acanthaceae is an official drug in pharmacopoeia, India 1994. Pyrroloquinazoline alkaloid present in this plant possesses an anti-inflammatory property which was exhibited against adjuvant-induced experimental arthritis mice. Treatment with *Adhatoda vasica* extract (AVE) at different dose of (50, 100 & 200) mg/kg significantly inhibited the progression of arthritis. Its administration reduced pro-inflammatory cytokines in serum and synovial tissues. It is observed that Toll like receptor (TLR-2) expression is suppressed in collagen induced arthritis in mice with the AVE administration. TLR-2 (component of innate immune system) is expressed on the macrophages and dendritic cell surfaces that is responsible for B and T-lymphocyte response generation under pathogenic incursion<sup>[21]</sup>.

### *Ajuga bracteosa* Wall ex Benth:

*Ajuga bracteosa* belongs to the family Labiatae. Traditionally the plant is used for treatment of rheumatism, gout, palsy, diuretic, and also used as tonic, stimulant, astringent etc. in the Ayurveda and traditional healthcare systems of India. Phytochemically *A. bracteosa* has ajugarin I, lupulin A, withaferin A, reptoside and 6-deoxyharpagide<sup>[22]</sup>. 70 % ethanolic extract of *A. bracteosa* was evaluated for anti-arthritis activity against turpentine oil, formaldehyde (acute non immunological models) and complete Freund's adjuvant (CFA) induced (Chronic immunological) arthritics in albino rats. In the experiment turpentine oil and formaldehyde induced acute non immunological inflammation that was significantly checked by *A. bracteosa* in a dose dependent manner. The CFA also induced chronic immunological arthritis characterized by marked oedema in hind paw that persisted for weeks (primary reaction). The primary reaction followed by oedema in contra-lateral and front paws along with appearance of arthritic nodules in ear and tail i.e. delayed systemic response (secondary reaction). The X ray pictures of CFA induced arthritic rats also showed significant reduction in inflammation by *A. bracteosa* extract that was comparable to standard aspirin treated rats<sup>[23]</sup>.

### *Aconitum carmechaeli* Debeaux:

*Aconitum carmechaeli* Debx is an indispensable medicinal plant having anti-inflammatory, anti-rheumatic and neurological indications<sup>[24]</sup>. Chemical analysis has revealed that tuberous roots of *Aconitum* contain the alkaloids: benzoylmecasonine, aconitine, hyaconitine, heteratisine, heterophyllisine, heterophylline, heterophyllidine, atidine, isotisine, hetidine, hetsinone and benzoylheteratisine, and the plant contains: heteratisine, heterophyllisine, atidine, isotisine, hetidine, hetsinone and benzoylheteratisine<sup>[25]</sup>. The mother and lateral root of *A. carmichaelii* Debx, called as "Chuanwu" (CW) and "Fuzi" in Chinese respectively, CW has an anti-arthritic effect in CFA induced arthritis rats<sup>[26]</sup> and methanol extracts of crude *Aconitum* roots have anti-inflammatory effects in inhibiting acid-induced vascular permeability and carrageen-induced hind paw edema in mice. The anti-arthritic properties may be due to immune-depression and down-regulation of inflammatory cytokines, which may be a potential candidate for the treatment of RA<sup>[27]</sup>. Aconibal<sup>®</sup> and MTX showed the potential beneficial effects in RA management<sup>[28]</sup>.

### *Angelica sinensis*:

*Angelica sinensis* belongs to family Apiaceae. In China, *A. sinensis* has been used for the treatment of gynecological diseases, constipation, fever and hemorrhoids. The plant has also been used as a hematinic for nourishing blood, regulating menstruation, and relaxing bowels<sup>[29,30]</sup>. Over 70 compounds have been identified from *A. sinensis*, including essential oils such as ligustilide, butylphthalide and senkyunolide A, phthalide dimers, organic acids and their esters such as ferulic acid, polyacetylenes, vitamins and amino acids. Z-ligustilide (water insoluble and heat stable), among which Z-butylidenephthalide and ferulic acid are thought to be the most biologically active components<sup>[31-33]</sup>. Ethyl acetate fraction from *A. sinensis* (Essential Amino Acids) inhibited IL-1 $\beta$  induced RA synovial fibroblasts; matrix metalloproteinases (MMPs1&2), COX-2, and PGE2 production<sup>[34]</sup>. The combined action of sodium ferulate and polysaccharidic fraction of *A. sinensis* would prevent cartilage destruction in osteoarthritis and favor cartilage repair<sup>[35]</sup>. Calycosin is known to be one of the components of *Angelica sinensis*, which has been indicated to have an important role in the treatment of RA<sup>[36]</sup>.

### *Alpina officinarum*:

It is known as lesser galangal and belongs to the family Zingiberaceae. It is an annual plant cultivated in

Southern Asia. The rhizomes which are called galangal have been used as an anti-inflammatory, analgesic, stomachic and carminative since ages in traditional medicine. Its anti-inflammatory effect contributes in treating RA and osteo-arthritis. The rhizomes are dried underground and extracted using ethanol. Use of 80 % of ethanolic extract in CFA- induced chronic arthritis; Carrageenan induced paw edema in Sprague- Dawley rats showed anti-inflammatory activity. However, the effect was exerted in a dose dependent manner. Long term arthritis has been the purported cause of mental disturbances which may be due to the abnormal expression of a C-p55, Fos proto-oncogene (c-Fos) antigen in the limbic system. It is known from literature that memory plays role in adaptation to pain. 200 mg/kg and 500 mg/kg of the extracted when given orally for 23 d led to the reduction of the expression of c-Fos protein antigen in the hippocampus region of the brain of CFA injected rats. Thus it is evident that the extract not only inhibits inflammatory mediators but it can also assist the psychiatric condition by recovering c-Fos expression in the hippocampus region in RA condition<sup>[15]</sup>.

#### ***Barleria prionitis:***

The extract at a dose of 250 mg/kg showed most potent and significant ( $p \leq 0.05-0.01$ ) paw edema inhibition which is supported by the results of body weight, biochemical parameters, motor incoordination and nociceptive threshold in CFA induced arthritis model<sup>[6]</sup>. The aqueous plant extract showed anti-inflammatory activity by inhibiting PGs synthesis<sup>[37]</sup>.

#### ***Bryonia alba:***

*Bryonia alba*. L is a well-known herb for the treatment and cure of many ailments in central Europe<sup>[38]</sup>. *B. alba* in the form of a homeopathic formulation does exhibits promising results at various instance such as the xanthine oxidase and xanthine dehydrogenase activity<sup>[39]</sup>.

#### ***Barringtonia racemosa Roxb.:***

It is a tree in the family Lecythidaceae found in coastal swamp forest of South Africa, India, Srilanka, Thailand. In the ayurvedic literature, its fruits are used for treatment of pain, inflammation and rheumatic conditions. Out of various constituents present in the plant, the Bartogenic acid (BA) isolated from the fruit has been shown to be effective when its evaluation was done in the CFA-induced arthritis in rats. This plant is also useful

in as an anti-tumor, anti-nociceptive, antifungal etc. the extract obtained by cold maceration revealed that ethyl acetate fractions had potent anti-inflammatory activity. This extract was further fractionated on silica gel chromatography column whereby BA was isolated and its confirmation was done by chromatography and spectral data. Different dose of BA<sup>[2,5,10]</sup> mg/kg/d by mouth (p.o.) can protect the rat from arthritic lesions (primary and secondary). The secondary lesion is reduced due to potent suppression of cell mediated immunity in arthritic rat by BA. However, anti-inflammatory effect is more than immune-suppressive effect as shown by reduced arthritic score. Reduced body weight during inflammation due to insufficient absorption of nutrients from intestine is ameliorated by the standard drug Diclofenac sodium and BA both. Also, white blood cell (WBC) count raised by IL-1 $\beta$ -mediator in arthritic patients is normalized by BA. All these positive results to improve arthritic condition, manage pain and inflamed condition supports the use of *B. racemosa* and has led to its validation in ethno-medicinal use<sup>[40]</sup>.

#### ***Crinum asiaticum:***

*Crinum asiaticum* L. belongs to the Amaryllidaceae family group of plants. Antinociceptive, anti-inflammatory, and hepatoprotective effects of lycorine (a constituent of *C. asiaticum*) has been reported<sup>[41]</sup>. Anti-inflammatory effect of *C. asiaticum* by the inhibition of iNOS and the release of PGE2, IL-6, and IL-8 has also been recorded<sup>[42]</sup>. The bulb of *C. asiaticum* is also useful in inflamed joints and sprains. Roasted bulb is used as rubefacient in rheumatism<sup>[43]</sup>. *C. asiaticum* leaf extract has potential anti-inflammatory effect to be recorded as plant-derived complementary medicine<sup>[44]</sup>. *C. asiaticum* Linn plant is used in Malaysia as a rheumatic remedy and to relieve local pain<sup>[45]</sup>.

#### ***Curcuma longa:***

Turmeric and its curcumin-enriched extracts have been used for treating arthritis<sup>[46]</sup>. The curcumin metabolites may be responsible for the anti-inflammatory and antioxidant activities that reduce the symptoms of metabolic diseases including osteoarthritis<sup>[47,48]</sup>. The oral supplementation of curcumin at the dose of 110 mg/ml/kg/d has a potential to delay and improve joint abnormality and injury in Sprague-Dawley rats with collagen-induced arthritis CIA<sup>[49]</sup>. Curcumin also inhibited formaldehyde induced arthritis in rats at a dose of 40 mg/kg<sup>[50]</sup>. Curcumin given at 1200 mg daily was effective in improving joint swelling, morning

stiffness, and walking time<sup>[51]</sup>. Turmeric has shown to alleviate the pain of inflammation in diseases such as RA and psoriasis, overall promoting the immune system response of acute inflammation for its therapeutic abilities and alleviating chronic inflammation<sup>[52]</sup>. Cell culture studies, animal experiments and clinical trials indicate that curcumin may be potential as a therapeutic agent in diseases such as inflammatory bowel disease, pancreatitis, arthritis, and chronic anterior uveitis<sup>[53]</sup>. Turmeric extract containing curcuminoids prevents experimental RA<sup>[54]</sup>.

#### ***Coriandrum sativum*:**

*Coriandrum sativum* has been widely used in traditional medicine for treatment of RA and diabetes. Coriander seed possesses anti-arthritis activity, anti-inflammatory activity, antioxidant activity and hypolipidemic activity<sup>[55]</sup>. The anti-arthritis activity of coriander may be attributed to the modulation of pro-inflammatory cytokines in the synovium<sup>[56]</sup>. Cineole (one of the compounds of essential oil of coriander) and linoleic acid present in coriander possess anti-arthritis properties<sup>[57]</sup>. A reduction in primarily macrophage-derived pro-inflammatory cytokines, viz., IL-6 and IL-1  $\beta$ , and the cytokine receptor TNF-R1 observed in the *C. sativum* hydro alcoholic extract treated group<sup>[58]</sup>.

#### ***Clerodendrum serratum*:**

*Clerodendrum serratum* have potent anti-rheumatic and antipyretic properties. The ethanolic root extract of *C. serratum* showed significant anti-inflammatory activity in carrageenan induced paw oedema in rats, and also in the cotton pellet model in experimental mice, rats and rabbits at concentrations of 50, 100 and 200 mg/kg<sup>[59]</sup>. The crude extracts of the aerial parts and roots of the plant *C. serratum* L. possess potential anti-rheumatic activity by supporting the folkloric use of the plant to treat various inflammatory conditions<sup>[60]</sup>. Root potion is used for chronic joints disease<sup>[61]</sup>. In carrageenan induced paw edema test *C. serratum* has shown significant suppression of edema<sup>[62]</sup>.

#### ***Costus speciosus*:**

*Costus speciosus* belongs to the family Zingiberaceae which is an erect plant of about 2.7 m tall with tuberous root and sub-woody stem. It has many uses such as antioxidant, anti-cancer, anti-inflammatory, hepatoprotective, adaptogenic etc. In one of the *in vitro* studies, the effect of costunolide on the production of pro-inflammatory mediators was targeted and the mechanism was stimulated with lipo-polysaccharides

(LPS) in a murine BV-2 cell culture. It was found that the level of inflammatory mediators such as TNF- $\alpha$ , IL, IL-1, NOS and COX-2 in activated microglia was attenuated by costunolide through inhibition of NF- $\kappa$ B and MAPkinase pathways. It proves that rheumatism due to inflammation can be treated by *C. speciosus*<sup>[63]</sup>. CFA induced arthritis model is the best available experimental model of RA. When this model was used against the methanolic extract of *C. speciosus*, the extract exhibited a significant anti-arthritic activity in a dose dependent manner where the progression of the RA was inhibited. The extract can successfully suppress the swelling of paws of rats in both acute and chronic phase of inflammation<sup>[64]</sup>.

#### ***Cedrus deodara* (Roxb.) Loud.:**

*Cedrus deodara* (Roxb.) Loud. belongs to the family Pinaceae and it is found in the Western Himalayas in Eastern Afganistan, Northern-Central India, South Western Tibet and Western Nepal. The oil and gum of *Cedrus deodara* have medicinal value in treating inflammation, dyspepsia, itching, elephantiasis, insomnia, hiccough, fever, bronchitis and piles. Especially leaves can be used to treat inflammation. The bitter wood has wide application in treating fever, rheumatism, piles, palsy, epilepsy, skin disease and urinary disorder. A review on *Cedrus deodara* revealed that the volatile oil extract of wood of this plant showed significant inhibition of carrageenan induced rat paw edema where the dose of 50 and 100 mg/kg body weight was given. It was also seen that the extract (50mg/kg and 100mg/kg body weight) showed significant inhibition of exudative- proliferative and chronic phase of inflammation<sup>[65]</sup>. The volatile oil extracted by steam distillation was used against AIA in rats. The secondary lesions developed in the ears, forelimbs and tails were scored<sup>[66]</sup>.

#### ***Callicarpa macropophylla*:**

The leaves root and flower of *Callicarpa macropophylla* has an anti-inflammatory property. Its leaves also have analgesic and anti-pyretic effect. It belongs to the family Verbenaceae. When *in vitro* anti-arthritis activity was assessed, it was observed that the protein (albumin) denaturation was inhibited significantly at different doses (50  $\mu$ g/ml, 100  $\mu$ g/ml, 200  $\mu$ g/ml, 400  $\mu$ g/ml and 800  $\mu$ g/ml showed 59.47 %, 64.10 %, 88.64 %, 98.21 %, and 130.52 % protection respectively). The standard drug used was Diclofenac sodium. Inhibition of albumin denaturation by *C. macropophylla* was assessed because denaturation of the tissue protein

takes place in arthritic diseases and is a cause of inflammation. It is reported that auto-antigen produced in certain arthritic diseases may be due to denaturation of proteins *in vivo*. Therefore, this plant can prevent protein denaturation and has significance in anti-inflammatory drug development<sup>[67]</sup>. The *in vivo* test was also done using carrageenan as a phlogistic agent where the anti-inflammatory activity was evaluated by carrageenan paw edema method. It was found that the ethanolic and aqueous extracts of *C. macrphylla* contained carbohydrate, steroids, flavonoids and tannins. One or more of these phyto-constituents may inhibit the histamine, serotonin, PGs synthesis which plays the major role in inflammation<sup>[3]</sup>.

#### ***Citrullus colocynthis:***

*Citrullus colocynthis* Schrad belongs to the family Cucurbitaceae. Fresh immature fruits and seeds can be taken for extraction where water can be used for the maceration. To obtain the alkaloid, dried plant part is macerated in ammonium hydroxide (5 ml), ethanol (10 ml), and di-ethyl ether (30 ml). Then the mixture is separated by ether (150 ml) and chloroform (50 ml) and then treated with sulphuric acid. The base (precipitate) can be separated by adding ammonium hydroxide and the supernatant by adding chloroform following filtration. The LD<sub>50</sub> is calculated to be 1 and 4 mg/kg. Both phase of inflammation induced by carrageenan paw edema in rats was reduced which showed dose-dependent anti-inflammatory activity. The mechanism of the extract is that the production of the pro-inflammatory cytokines like IL-6 and IL-1 $\beta$  and COX-2 expression is decreased while it increases the anti-inflammatory cytokine IL-4 in carrageenan-injected paw edema. Hence the use of *C. colocynthis* is justified in treating RA<sup>[68]</sup>. One of the literature mentioned that the glycoside quercetin present in the fruit extract provided immunological protection henceforth the swelling in the paws caused by development of arthritis in rats was reduced<sup>[69]</sup>.

#### ***Cinnamomum zeylanicum:***

*C. zeylanicum* belongs to a family Lauraceae. Its bark has medicinal values such as anti-inflammatory, analgesic, rheumatism and anti-pyretic effect as reported in many traditional literatures. Immune-modulatory effect is also possessed by cinnamon. The active constituent that exert the activity are gallic acid and polyphenols. When the *C. zeylanicum* bark (CPP) was administered orally with a dose of 50, 100, 200 mg/kg/d for 9 d after 12<sup>th</sup> d of induction by adjuvant induced arthritic rats, there was significant dose-dependent improvement in

the weight of rats. Also, serum TNF- $\alpha$  concentration got significantly decreased in CPP treated rats (200mg/kg/d). It can be said that CPP inhibits the PGs synthesis and its release because CCP showed its effectiveness only in the 3<sup>rd</sup> h of its administration and it is known that carrageenan induced edema in rats is attributed by the release of histamine/serotonin followed by PGs. Hence, it can be concluded that *C. zeylanicum* does have anti-arthritic activity<sup>[70]</sup>.

#### ***Celastrus paniculatus willd:***

It is one of the reputed plants in Ayurveda belonging to the family Celastraceae. The woody tree is India innate species and is distributed across Malaysia, China and Australia. Methanolic extract of flowers of *C. paniculatus* possess anti-inflammatory property along with analgesic activity. The herbal oil extracted from the seed by cold-pressed expression technique is used for treating rheumatism and gout as mentioned in the indigenous medicine system. The plant extract at a dose of 300 mg/kg exerts inhibitory effect on carrageenan induce paw edema in rats<sup>[71,72]</sup>.

#### ***Euphorbia tirucalli:***

The plant is known for its medicinal value, such as antibacterial, antifungal, antiviral, anti-parasitic, anti-arthritic, anti-diabetic, antioxidant<sup>[73]</sup>. The plant is reported to be used traditionally in inflammatory disorders such as rheumatism and gout, to relieve pain in rheumatism and toothache, in nervine diseases, dropsy and deafness, and as a purgative<sup>[74]</sup>. Triterpenoids from *E. tirucalli* may be used as a potent natural anti-inflammatory therapeutic agent for the treatment of arthritis like disorders<sup>[75]</sup>. The bio-polymeric fraction showed dose dependent anti-arthritic activity and also showed *in vivo* immune-modulatory capacity being a major component in inhibiting arthritis<sup>[76]</sup>.

#### ***Lavandula stoechas L.:***

*Lavandula stoechas* L. belongs to family Lamiaceae. Phytochemical screening of extract of *L. stoechas* show presence of tannins, catechic tannins, flavonoids, sterols, coumarins, quinones, leucoanthocyanins and mucilages compounds. Anti-inflammatory activities and sub-acute toxicity of hydro-ethanolic and polyphenols (flavonoid, tannin and mucilage) extracts from aerial part (branches, flowers and leaves) of *L. stoechas* was studied. The anti-inflammatory activity was evaluated by Carrageenan-Induced Rat Paw Edema method. The hydro-ethanolic extract of *L. stoechas* (5 and 10 %) inhibited the inflammation induced by

carrageenan in rats in a dose dependent manner. At dose of 10 %, *L. stoechas* produced a significant inhibition of inflammation at  $74 \pm 7$  % compared to  $69 \pm 10.3$  % for diclofenac at 1 %. Flavonoid and mucilage extracts showed significant effect in reduction of edema<sup>[13]</sup>.

*L. stoechas* essential oil is found rich in fenchone (37.0 %) and camphor (27.3 %). *L. stoechas* is active against dermatophyte strains and showed potential anti-inflammatory activity at concentrations without affecting cell viability<sup>[77]</sup>.

Anti-inflammatory properties of *L. stoechas* extracts in two inflammatory experimental models: 2,4,6-Trinitrobenzenesulfonic acid model of rat colitis and the carrageenan-induced paw edema in mice were studied. *L. stoechas* extracts displayed immunomodulatory properties *in vitro* down-regulating different mediators of inflammation like cytokines and NO. They also showed anti-inflammatory effects in the TNBS model of colitis as evidenced by reduced myeloperoxidase activity and increased total glutathione content indicating a decrease of neutrophil infiltration and an improvement of the oxidative state. They also displayed anti-inflammatory effects in the carrageenan-induced paw edema in mice, since a significant reduction of the paw thickness was observed<sup>[77,78]</sup>.

### ***Moringa oleifera* Lam.:**

It is an ornamental tree belonging to the family Moringaceae. Its seeds can be used to treat RA and the whole plant can be used as an anti-microbial agent, in venomous bites. The seeds powder is defatted with petroleum ether and then extracted with 95 % ethanol. The phyto-constituents present are alkaloids, flavonoids, glycosides, tannins and terpenoids. The effect of *M. oleifera* on CFA induced arthritis in rats showed that the percentage weight reduction was significantly less. Similarly, when paw edema volume was measured, there was significant, very significant and highly significant decrease in the primary lesion in the *M. oleifera* 1 (100 mg) (MO1), *M. oleifera* 2 (200 mg) (MO2) and standard drug dexamethasone treated groups respectively. The serum parameters reflected the significantly increased level of Rheumatoid factor in arthritic diseased group which was reversed by MO1 and MO2 treatment for 21 d. Also, TNF- $\alpha$ , IL-1 and IL-6 was restored to nearly normal levels. This protective effect of the extract is thought to be brought about by the presence of flavonoid and antioxidants. Additionally, flavonoid prevents osteoporosis by increasing the bone mineral density. Furthermore,

to explain the mechanism of action of the extract, the *M. oleifera* treatment interferes with the formation of either IL-1 or IL-6 or TNF- $\alpha$  and reduces the development of RA in rats due to adjuvant treatment<sup>[79]</sup>. In another study, the effect of the methanolic extract on turpentine oil induced arthritis (acute model) showed 70.25 %, 90.46 % and 91.33 % at 125, 250 and 500 mg/kg p.o percent inhibition respectively<sup>[80]</sup>.

### ***Oryza sativa* Linn. Njavara Rice:**

*Oryza sativa* L. (Njavara) belongs to the family Oryzae. It is grown exclusively in Kerala, South India. Since ancient times, and is used mainly for ayurvedic treatments. Njavara rice is used to treat arthritis, cervical spondylitis, muscle wasting, skin diseases, certain neurological problems circulatory, respiratory and digestive systems. Njavara kizhi is a specialized Ayurvedic therapy for treatment of paralysis, arthritis and neurological problems<sup>[81]</sup>. Njavara was studied for its anti-arthritic activity and anti-denaturation study by using bovine serum albumin (BSA)<sup>[82]</sup>. Denaturation of protein is one of the causes of RA<sup>[83,84]</sup>. When BSA is heated it undergoes denaturation and express antigens associated with type- III hypersensitivity reaction and that is related to diseases such as serum sickness, glomerulonephritis, RA and system lupus erythematosus<sup>[85]</sup>.

The *in vitro* anti-arthritic activity was analyzed by BSA method. The sample Njavara rice extract showed 31.3, 43.6, 64.3, 77.6 % inhibition of denaturation of bovine serum at the concentration of 100, 250, 500 and 1000  $\mu$ l whereas standard diclofenac at 250  $\mu$ l showed 51.7 % inhibition of denaturation activities. Production of auto-antigens in certain rheumatic diseases may be due to *in vivo* denaturation of proteins. Mechanism of denaturation probably involves alteration in electrostatic, hydrogen, hydrophobic and disulphide bonding. Ethanolic extract of *O. sativa* (Njavara) possess anti-arthritic activity due the presence of high number of bioactive compounds especially flavonoids. The higher oryzanol content, chemical indices, antioxidant and anti-inflammatory activity for Njavara compared with staple varieties corroborates with its medicinal use in Ayurveda<sup>[86]</sup>.

### ***Pinus lambertiana*:**

*Pinus lambertiana* commonly known as the sugar pine or sugar cone pine is the tallest and massive pine tree and the longest cones of any conifer. Anti-arthritic activity of pinitol (PIN) was evaluated in AIA rat model.

Pinitol is one of the major constituents and mainly isolated from *P. lambertiana*. PIN mimics the effects of insulin by acting downstream in the insulin signaling pathway. Inflammation was induced by injecting heat killed strain of *Mycobacterium tuberculosis* mixed in paraffin oil in the right hind paw of rats. PIN was administered orally at 1, 2, 4 and 8 mg/kg once daily to treat the inflammation. The experiment showed a dose-dependent decrease in edema and showed a suppression of mediators such as PGE2 and Leukotriene B4 (LTB4). PIN induced an inhibition of T cell mediated immune response causing suppression of CD4+ and CD8+ T cells by flow cytometer in arthritic animals. It also significantly lowered pro-inflammatory T helper type (Th)-1 cytokine levels in arthritic paw tissue homogenate supernatant viz. IL-2, IFN- $\gamma$ , and TNF- $\alpha$  with maximum inhibition at dose levels of 4 mg/kg p.o. and enhanced the production of anti-inflammatory (Th2) cytokines IL-4 and IL-5 estimated by cytometric bead array immunoassay. PIN at graded doses also significantly decreased the expression of IL-1 $\beta$  and nitric oxide levels showing significant inhibition of these parameters<sup>[87]</sup>.

#### ***Piper nigrum:***

It is commonly called black pepper and is a flowering vine that belongs to Piperaceae family. It has a wide application ranging from spice, preservative, perfume to its medicinal uses. The medicinal use is brought about by the phenolic component Piperine. As this plant has shown *in vitro* inhibition of enzymes that helps in bio-synthesis of leukotriene, PGs, 5-lipoxygenase and COX-1, it contributes the major role in treatment of RA. Specifically, IL6 and PGE2 production was inhibited when *in vitro* study was carried out taking IL1 $\beta$ -stimulated RA fibroblast like synoviocytes (FLS) derived from arthritic patients. Also MMP13 collagenase enzyme was significantly inhibited in IL-1 $\beta$  stimulated FLS<sup>[88]</sup>.

#### ***Premna serratifolia linn.:***

It belongs to the family Verbenaceae and is widely distributed shrubs in deciduous forest of India and other parts of Asia. The woods *P. serratifolia* is useful in the treatment of arthritis. It has been reported in the indigenous system of medicine. The shrub can be used to treat many conditions such as weakness of limbs, headaches, cold and fever. It has also certain activity such as anti-coagulant, anti-inflammatory, anti-oxidant, anti-parasitic, in treating rheumatism

and gonorrhoea. Phyto constituents such as alkaloids, steroids, flavonoids, phenolic compounds, tannins and glycosides present in the shrub was revealed by the preliminary screening of the ethanol extract of the plant.

In the Freund's AIA model, treatment with 300 mg/kg body weight p.o of the plant extract improved the chronic swelling in multiple joints caused by influence of inflammatory cells and erosion of joint cartilage. These inflammatory cell mediators such as cytokines and interferon released during chronic inflammation are responsible for pain, destruction of bone leading to disability. Also the percentage inhibition of rat paw edema was produced to be 68.32% with ethanolic extract which is a close value obtained to that of a standard drug (indomethacin=74.87 %) after 21 d of model induction. The extract can significantly increase the Red Blood Cells (RBC) count and body weight which is reduced in arthritic model. However, it can decrease the WBC count which gets increased in adjuvant model due to the release of IL-1 $\beta$ , in response to its release, the production of granulocyte and macrophage colony stimulating factors are also increased.

Therefore, the significant anti-arthritic activity is exhibited by the several phyto constituents particularly Iridoid glycosides present in this plant which proves it to possess medicinal value suitably<sup>[89]</sup>.

#### ***Ranunculus sceleratus Linn.:***

*Ranunculus sceleratus* belong to family Ranunculaceae commonly known as blister buttercup, celery leaved crowfoot (English); jal dhaniyaa (folk). The whole plant is capable of promoting blood circulation by removing blood stasis, expelling cold, relieving swelling, and removing excessive heat from the liver and the gall bladder. It can also cure internal abscess, malaria, scrofula, snake or scorpion venom, and acute icteric hepatitis<sup>[90]</sup>.

Plants chemically constitute 5-hydroxy tryptamine, apigenin, apigenin 4'-O- $\alpha$ -rhamnopyranoside, apigenin 7-O- $\beta$ -glucopyranosyl-4'-O- $\alpha$ -rhamnopyranoside, tricetin 7-O- $\beta$ -glucopyranoside, isoscapoletin, tricetin, Protocatechuyaldehyde, Protoanemonin<sup>[91]</sup>. *R. sceleratus* aerial are known to have anti-inflammatory activity investigated in rats *in vivo* and *in vitro*, non-polar extract were able to inhibit eicosanoid production whereas polar extract enhanced the synthesis of 5(S)-HETE, LTB4 and 12(S)-HHTre aerial part<sup>[92]</sup>.

#### ***Randia dumetorum:***



It is a large thorny shrub belonging to the family Rubiaceae and is spread all over India upto 4000 ft. height. The phyto constituents present in this shrub include glycosides, triterpenoids, randianin, saponins and steroids. It is useful against bacteria, allergy, inflammation and algesia. Its fruit treat abscess, ulcers, inflammation and other skin related disorders. However, the main anti-arthritis activity is exhibited by the fruit of this shrub<sup>[93]</sup>. *R. dumetorum* at a dose of 100, 200 and 300 mg/kg reduces paw volume edema in rats which signifies the anti-inflammatory property of the plant. Arthritic score is decreased dose dependently from d 12 onward of CFA induction in rats. In collagen induced rats, bone destruction was observed by radiological analysis and it was seen that there was development of narrowing of the spaces in the inter-tarsal joints. Also, the soft tissue was swollen and severe erosions of all joint space were observed. But the extract treated group of rats revealed the improvement in these abnormalities characterized by small erosions with rare asymmetric soft tissue swelling and minimum narrowing of the joint space. Histopathological results strengthens the anti-arthritis activity of this plant<sup>[94]</sup>.

#### ***Santalum album:***

*Santalum album* Linn. belongs to family Santalaceae is commonly known as white sandalwood (English), safed chandan (Hindi) and srigandha (Sanskrit). It is found widely and cultivated in southern states of India. Traditionally, this plant is used in headache, fever and inflammation. The wood oil is used as diuretic, stimulant and disinfectant. Sandalwood contains a volatile oil 2.5-6 %. The main constituents of volatile oil are santalol, isovaleric aldehyde, santanone, santalone and tannic acid. The plant was evaluated for anti-inflammatory activity. The methanolic extract of wood was also evaluated for anti-inflammatory activities at various doses (100, 250 & 500 mg/kg) and compared with Diclofenac sodium (7 mg/kg) taken as standard. The extract showed maximum effect at 500 mg/kg<sup>[95]</sup>. Flavonoid extracted from the leaves of *S. album* for determining their anti-inflammatory and immunosuppressive activity<sup>[96]</sup>.

#### ***Salvia mellifera:***

*Salvia mellifera*, is used as a topical preparation to relieve minor to moderate pain. The plant also contains diterpenoids such as rosmanol and carnosic acid that are analgesic and anti-inflammatory agents<sup>[97]</sup>.

#### ***Sida rhombifolia* Linn.:**

*Sida rhombifolia* Linn. belong to the family Malvaceae. The *Sida* species is one of the most important families of medicinal plants in India. Plants aerial part extracts were screened for various parameters of anti-arthritis activity, such as adjuvant-induced arthritis, motor performance, mean distance travelled, and histopathological study. It showed that the polar constituents (ethanol and aqueous extracts) of the plant *S. rhombifolia* were useful in the treatment of arthritis<sup>[98]</sup>. Anti-oxidant potential of *S. rhombifolia* extracts for 30 d on AIA in experimental rats was investigated. The altered levels of haematological parameters were reverted to near normal levels; especially the elevated rate of erythrocyte sedimentation was significantly reduced by *S. rhombifolia* extracts in experimental rats. Oral administration of root and stem of *S. rhombifolia* extracts significantly increased the levels of thiobarbituric acid reactive substances and activities of catalase and glutathione peroxidase and decreased the levels of reduced glutathione and superoxide dismutase activity in arthritis induced rats<sup>[99]</sup>.

#### ***Swertia chirata* Buch.Ham:**

*Swertia chirata* Buch.Ham (Fam. Gentianaceae) is widely used in India to treat fever, malaria and liver diseases<sup>[100]</sup>. In addition, it is reported to have anti-inflammatory activity<sup>[101]</sup>. Xanthone derivatives like mangostin, isomangostin and mangostin triacetate are known to possess significant anti-inflammatory activities. The total xanthones of *Swertia* species produce significant CNS stimulant action<sup>[102,103]</sup>.

Anti-inflammatory effect of xanthone derivative (1, 5-dihydroxy-3,8-dimethoxy xanthone) of *S. chirata* (SC-I) in acute, sub-acute and chronic experimental models in male albino rats was studied<sup>[100]</sup>.

Aqueous extract of *S. chirayita* stem was studied on the anti-inflammatory cytokines balance in primary joint synovium of adjuvant-induced arthritic mice. The level of pro-inflammatory cytokines was found elevated in the joint synovium of arthritic mice in comparison to normal joints. Administration of *S. chirayita* extract in varying doses through the oral route, a dose dependent (0, 11.86 and 23.72 mg/kg body weight) reduction of TNF- $\alpha$ , interleukin-1 $\beta$ , (IL-1 $\beta$ ) and interferon- $\gamma$ , (IFN- $\gamma$ ) and elevation of Interleukin- 10 (IL-10) was observed in the joint homogenates of arthritic mice. Interleukin-6 (IL-6) was not down regulated in joint homogenate of arthritic mice at the dose 11.86 mg/kg but at higher doses (23.72 and 35.58 mg/kg) significant reduction

was observed. The aqueous extract was found to possess two polar compounds, amerogetin and mangiferin but was devoid of swerchirin, chiratol, methyl swetianin, and swertanone. Mangiferin possess potent anti-inflammatory property and presumed its presence in the aqueous extract of *S. chirayita* is responsible for reducing TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IFN- $\gamma$  and/or elevating IL-10 in the joint homogenates of arthritic mice on d 12<sup>[104]</sup>.

### ***Syzygium cumini*:**

*Syzygium cumini* (Family: Myrtaceae) is a folklore plant traditionally indicated to treat various inflammatory disorders. Phytochemical screening of the ethyl acetate and methanolic extracts of *S. cumini* seed used in this study revealed that the crude extract contained alkaloids, amino acids, flavonoids, glycosides, phytosterols, saponins, steroid, tannins and triterpenoids. *S. cumini* seeds can also have various medicinal values such as anti-inflammatory, anti-diabetic and analgesic activities and also for central nervous system activity<sup>[105]</sup>. Anti-rheumatic activity of petroleum ether extract of *S. cumini* stem bark at the doses of 50, 500, 750, 1000 mg/kg on CFA AIA has been studied in rats. The treatment is assessed by measuring the paw volume, body weight, arthritic index, and rheumatoid factor. The result showed that the extract inhibited the CFA induced arthritis in dose dependent manner and this effect was more significant ( $p < 0.05$ ) with 1000 mg/kg dose. The standard drugs Indomethacin (10 mg/kg), dexamethasone (0.1 mg/kg) also produce significant anti-rheumatic effect in rats and are compared with test drug<sup>[106]</sup>. The anti-arthritic effect of oral administration of methanolic extract of *S. cumini* seeds (SME) on Freund's complete adjuvant (FCA) induced arthritis has been studied in rats. The treatment is assessed by measuring the paw volume and by using various hematological parameters like hemoglobin (Hb) content, total RBC count, WBC count and erythrocyte sedimentation rate (ESR). The extract inhibited the CFA induced arthritis in a dose dependent manner and this effect was more significant ( $p < 0.001$ ) with 500 mg/kg dose. SME showed significant effect in preventing the rat paw edema volume and improved the RBC count, Hb level and the ESR to a near normal level when compared to CFA induced arthritis rats. In addition, SME also significantly decreased the WBC count in CFA induced arthritis rats. Administration of extract improved the body weight significantly when compared to CFA induced arthritis rats. The anti-

arthritic effect of SME was compared to that of standard drug Indomethacin<sup>[107]</sup>.

### ***Tripterygium wilfordii*:**

*Tripterygium wilfordii* Hook (TWH), an herbal plant growing mainly in South China, was described in ancient Chinese medical texts and has been used widely in China for treatment of joint pain<sup>[107]</sup>. *Tripterygium wilfordii* Hook F (TwHF) is effective for treating active RA patients and is superior to placebo and sulphasalazine according to American College of Rheumatology Criterion (ACR) 20, 50, and 70. TwHF is superior to conventional synthetic Disease-modifying Anti-rheumatic Drugs (DMARDs) such as MTX, leflunomide, sulphasalazine<sup>[108]</sup>. Extracts of *T. wilfordii* Hook suppress both immune and inflammatory responses and also effectively treat a number of models of autoimmune disease<sup>[109]</sup>. The ethanol/ethyl acetate extract of TwHF shows therapeutic benefit in patients with treatment-refractory RA<sup>[110]</sup>. Extracts of TwHF, in combination with MTX reduced swollen and tender joint counts, shortened the duration of morning stiffness, decreased the ESR, and decreased the level of C-reactive protein and rheumatoid factor<sup>[111]</sup>.

### ***Urtica dioica*:**

*Urtica dioica* (Urticaceae) is also called Stinging Nettle. In a folklore medicine, it has been used to treat arthritis and rheumatism and as a diuretic agent. It has been called a potent medicinal plant based upon the information on traditional knowledge, ethno biological and ethno medicinal issues and also by identification and studies of pharmacologically important molecules of this plant. In RA the inflammatory events are inhibited by the leaf extracts of *U. dioica* by switching TH1 derived responses to Th-2<sup>[112]</sup>. When the experiment was carried out, it was found that the 50 mg dried powdered extract of the plant combined with 50 mg of Diclofenac sodium had similar effect to 200 mg of Diclofenac sodium alone. Hence, *U. dioica* reduces the NSAID dose by 50 %<sup>[113]</sup>. Recent studies conclude that RA is elevated by NF- $\kappa$ B which is responsible for enhanced expression of many pro-inflammatory gene products. The different cell lines (the human T-cell line Jurkat, the macrophage cell line monomac6, the epithelial cell line HeLa) were treated with the extract that inhibited the NF- $\kappa$ B activation<sup>[114]</sup>.

### ***Withania somnifera*:**

*Withania somnifera* has been used in Unani Medicine

as an anti-inflammatory and to treat rheumatism beside other ailments. Administration of *W. somnifera* root powder (600 mg/kg) to the arthritic rats significantly decreased the severity of arthritis by effectively suppressing the symptoms of arthritis and improving the functional recovery of motor activity and radiological score<sup>[115]</sup>. WS extract inhibited liposaccharide induced synthesis of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$  and IL-12) in peripheral and synovial fluid mononuclear cells from RA subjects *in vitro*<sup>[116]</sup>. The WS extract also showed inhibitory effects on collagenase activity that may be useful in joint disease treatment<sup>[117]</sup>. Oral administration of *Withenia somnifera* Linn., root powder showed the anti-arthritic effect in adjuvant induced arthritic rats<sup>[118]</sup>.

### *Zingiber officinale*:

Ginger is obtained from rhizomes of *Zingiber officinale*. The plant belongs to Zingiberaceae family. It has been widely used as a medicinal herb and spice<sup>[119]</sup>. Because of containing phytochemical ingredients and as a beneficial therapeutic agent, *Z. officinale* has been contributing against a broad range of diseases like asthma, diabetes, stroke and constipation<sup>[58,120]</sup>. Anti-inflammatory effect of ginger was scientifically proven<sup>[121]</sup>.

The activity of *Z. officinale* as an anti-inflammatory agent was investigated in rats<sup>[122]</sup>. Experimental rats were treated with aqueous extract of *Z. officinale* either orally or intraperitoneally daily for 4 w. Though at low dose ginger did not reduce PGE2 concentrations, at high doses it significantly lowered PGE2 levels. Therefore, ginger could reduce inflammation associated with RA. Both *in vivo* and *in vitro* experiments were conducted to evaluate the effect of 6-gingerol as an inflammatory agent<sup>[123]</sup>.

Monosodium urate crystal-induced inflammation was developed in mice as a model of gouty arthritis. They found that 6-gingerol significantly reduced the lysosomal enzymes level as well as inhibiting lactate dehydrogenase and acid phosphate. These results show clear indication of anti-inflammatory activity of this ginger phytochemical.

### *Zingiber zerumbet*:

The rhizomes of *Zingiber zerumbet* belong to family Zingiberaceae. The essential oil of the rhizomes of *Z. zerumbet* was reported for the acute and chronic anti-inflammatory activities using the carrageenan-induced paw edema and cotton pellet-induced granuloma tests, respectively. The effect of the essential oil on inflammatory and non-inflammatory mediated pain was also assessed using the formalin test. Essential oil of *Z. zerumbet*, at doses of 30, 100, and 300 mg/kg, was administered intra-peritoneally to rats. The substance exhibited significant anti-inflammatory activity both in acute and chronic animal models. The essential oil also inhibited inflammatory and non-inflammatory mediated pain when assessed using the formalin test<sup>[124]</sup>. Anti-inflammatory constituents of *Z. zerumbet* like zerumbone, 3-O-methyl kaempferol, kaempferol-3-O-(2, 4-di-O-acetyl- $\alpha$ -L-rhamnopyranoside), and kaempferol-3-O-(3,4-di-O-acetyl- $\alpha$ -L-rhamnopyranoside) were isolated from the rhizome of *Z. zerumbet*<sup>[125]</sup>. The anti-inflammatory activity of zerumbone, a natural cyclic sesquiterpene isolated from *Z. zerumbet* Smith was investigated using carrageenan-induced paw edema and cotton pellet-induced granuloma tissue formation test in mice. It was demonstrated that intraperitoneal administration of zerumbone at a dose of 5, 10, 50 and 100 mg/kg produced significant dose-dependent inhibition of paw edema induced by carrageenan. It was also demonstrated that zerumbone at similar

**TABLE 1: LIST OF THE PLANT -DERIVED ACTIVE PRINCIPLE REPORTED FOR ANTI-INFLAMMATORY EFFECT**

SL NO.	NAME OF COMPOUNDS	PLANT SOURCE	MECHANISM OF ACTION	REFERENCE
1	Pyrrroquinazoline	<i>Adhatoda vasica</i> Nees	Toll like receptor (TLR-2) suppression in collagen of arthritic mice	18
2	Ajugarin-I, Lupulin-A, Withaferin-A, Reptoside & 6-deoxyharpazide	<i>Ajuga bracteosa</i> Wall	Inhibition of COX-1 and COX-2 enzymes	19
3	Aconitines, Benzoylaconine	<i>Aconitum carmechaeli</i> Debeaux	Inhibitory effects on- acute inflammation (by inhibiting increased vascular permeability) and proliferative inflammation (granulation tissue)	24
4	Calycosin	<i>Angelica sinensis</i>	-Inhibition of inflammatory mediator- interleukin-6 receptor (IL-6R)	32,33
	Ferrulic acid		-Inhibition of IL- $\beta$ , matrix metalloproteinase (MMP-1), COX-2 & PGE-2 production	

5	Diarylheptanoids	<i>Alpina officinarum</i>	-Inhibitors of the production of multi-functional NO by iNOS which is involved in inflammation -Reduction of abnormal expression of c-Fos antigen protein in the hippocampus which causes mental disturbances in long term arthritis	12
6	Triterpenoid Iridoid glycosides, Barlerin, Acetyl barlerin	<i>Barleria prionitis</i>	-Inhibits histamine release from mast cells and exert anti-inflammatory effect -inhibition of COX pathway(PGE-2 synthesis) and inhibition of LOX enzymes(leukotriene B4)	35,36
7	Cucurbitacin glucoside	<i>Bryonia alba</i>	Inhibits LT-B4 and 5-HETE (mediators of inflammation) and modulates corticosteroid secretion	126
8	Bartogenic acid	<i>Barringtonia racemosa</i> Roxb.	-Inhibits IL-1B (mediator of inflammation) and normalizes raised WBC count in RA -Reduction of C-reactive protein	39
9	Lycorine	<i>Crinum asiaticum</i>	inhibition of inducible nitric oxide synthase (iNOS) and the release of PGE2, IL-6, and IL-8	40,41
10	Curcumin	<i>Curcuma longa</i>	-Down-regulates the activity of COX-2, LOX, iNOS and NFK-B -inhibition of TNF- $\alpha$ , IL-6, monocyte chemo-attractant protein -Down-regulates mitogen-activated and janus kinases.	45,52
11	Cineole, linoleic acid	<i>Coriander sativum</i>	Reduction in pro-inflammatory cytokines such as IL-6, IL-1B and cytokine receptor-TNF-R1	57
12	Apigenin-7-O-glucuronide flavonoid	<i>Clerodendrum serratum</i>	-Acts during early phase of acute inflammation by inhibiting early release of histamine, serotonin and prostaglandins -Weak anti-proliferative effect by preventing formation of collagen fibre and suppression of mucopolysaccharides -Reduction of inflammatory markers i.e. CRP, IL-6	61127
13	Stigmasterol, Arbusculin A, Specioic acid	<i>Costus speciosus</i>	-Inhibition of NFK-B and MAP-kinase pathways -Inhibits COX-2 pathway	62,63,128
14	Deodarone, , isohemacholone, atlantone	<i>Cedrus deodara</i>	Inhibition of COX enzyme causing inhibition of prostaglandin synthesis	64,65
15	$\beta$ -sitosterol, ursolic acid, luteolin and apigenin	<i>Callicarpa macropophylla</i>	-Controls the production of auto-antigens as this auto-antigen production in arthritis causes protein denaturation -Inhibits histamine and prostaglandin synthesis	66,67
16	Quercetin	<i>Citrullus colocynthis</i>	Decreases IL-6, IL-1B and COX-2 expression whereas increases anti-inflammatory cytokine like IL-4	68,69
17	Gallic acid and polyphenols	<i>Cinnamomum zeylanicum</i>	Inhibits prostaglandin synthesis and its release Decreases TNF- $\alpha$ concentration	70
18	Celastrine, celapanine, Celapagine	<i>Celastrus paniculatus</i>	Inhibition of prostaglandin synthesis and IL-1B	129
19	Triterpenoids	<i>Euphorbia tirucalli</i>	Diminishes CRP level and inhibits IL-1, IL-6 and TNF- $\alpha$ Inhibits arthritis related joint destruction	75
20	Flavonoids and mucilage	<i>Lavandula stoechas</i>	-Synergistic action of flavonoid and mucilage on COX pathway inhibition -Immunomodulatory action- down-regulates inflammatory cytokines such as nitric oxide and cytokines	10,77
21	Benzylisothiocyanate	<i>Moringa oleifera</i>	-Prevents denaturation of proteins which causes inflammatory arthritic condition -Inhibits TNF- $\alpha$ , IL-1, IL-6	79,130

22	Flavonolignans [tricin 4 -O-(threo-b-guaiacylglyceryl)] & [tricin 4 -O- (erythro-b-guaiacylglyceryl)]	<i>Oryza sativa</i>	Protein denaturation is inhibited thereby inhibiting production of auto-antigen in arthritic condition	84,131
23	Pinitol	<i>Pinus lambertiana</i>	-Suppress PGE2 and LTB4, CD4, CD8 cells, IL-2, TNF- $\alpha$ and IFN-c	87
24	Piperine	<i>Piper nigrum</i>	-Enhances anti-inflammatory cytokines like IL-4 and IL-5 -Inhibition of IL-6 and PGE-2	88
25	Iridoid glycoside	<i>Premna serratifolia</i>	-Inhibition of MMP-13 collagenase enzyme in IL-1B stimulated model -Decreases WBC count which is increased due to release of IL-1B -Enhances production of granulocyte and macrophage colony stimulating factors	89
26	Phytol, B-sitosterol, Stigmasterol, Ranunculine	<i>Ranunculus sceleratus</i>	Inhibits eicosanoid production, PLA2, 12-LOX pathway	92
27	Randianin	<i>Randia dumetorum</i>	-Decrease in the inflammatory mediators including cytokines (IL-1B and TNF-alpha), MCSF, interferons and Platelet derived growth factor (PDGF). -Immune-stimulatory effect as it	93
	Triterpenoids		Increases the weight of spleen and decreases the weight of thymus.	
	Randioside A			
28	Santanone, santalone	<i>Santalum album</i>	Reduces the production of inflammatory nitric oxide and CD14 monocyte marker	96
29	Diterpenoids-Rosmanol, Carnosic acid and tanshinone	<i>Salvia mellifera</i>	-Inhibition of TRP channels -inhibition of the production of IL-17 and chemokines and down-regulates COX-2	132
30	B-Phenethylamine, N-methyl-B-phenethylamine, vasicinol, vasicinone, vasicine.	<i>Sida rhombifolia</i>	-inhibition of induction of reactive oxygen species by inhibiting iNOS.	98
31	Xanthone derivative (1, 5-dihydroxy-3,8-dimethoxy xanthone), Mangostin, Mangiferin Isomangostin and Mangostin triacetate	<i>Swertia chirata</i>	-Reduction of TNF- $\alpha$ , interleukin-1B, (IL-B) and interferon- $\gamma$ , (IFN- $\gamma$ ) and elevation of Interleukin- 10 (IL-10)	1,03,104
32	Rutin, B-sitosterol, quercetin	<i>Syzygium cumini</i>	-Elevation of anti-inflammatory mediator- IL-10 -Increases the plasma protein such as fibrinogen, $\alpha$ and $\beta$ globulins and obscure the disease -Controls the IL-1B release -Inhibits TNF- $\alpha$ and IL-1	105
33	Triptolide, triptolide and triptonide	<i>Tripterygium wilfordii</i>	-Decreases C-reactive protein and rheumatoid factor	108,111
34	Carvacrol, carvone chlorogenic acid, phaselic acid, rutin	<i>Urtica dioica</i>	Inhibits NFK-B activation, AP-1 activation Inhibits cytokines expression and eicosanoids formation	1,12,133 .
35	Withanolides, withaferinA, withanolide D	<i>Withania somnifera</i>	-Inhibits TNF-alpha, IL-1beta and IL-12	116
36	6-gingerol	<i>Zingiber officinale</i>	-Inhibitory effect on collagenase activity -inhibits prostaglandin synthesis at high dose -Reduces lysosomal enzymes	Pragasam et al. 2011.
37	Sesquiterpene-Zerumbone.	<i>Zingiber zerumbet</i>	Suppresses granulomatous tissue formation	125

**TABLE 2: LIST OF THE PLANT MARKETED HERBAL PRODUCT AVAILABLE FOR THE TREATMENT OF RHEUMATOID ARTHRITIS**

Sl. No.	Name of marketed/ commercial product	Make	Name of the Plants used in formulations
1.	Shigru	The Himalaya Drug Company, Makali, Bengaluru 562 162.	<i>Moringa oleifera</i> Lam. (Shigru)
	Flexibility 60	Organic India private limited, Office no -03, Ground floor,	<i>Cyperus rotundus</i> (Nagarmotha)
2.	Capsules Bottle	Uppals Plaza M6, Jasola District Center, New Delhi - 110025	<i>Withania somnifera</i> (Ashwagandha) <i>Tinospora cordifolia</i> (Guruchi) <i>Ocimum sanctum</i> (Rama Tulsi)
	Osteoseal 60 capsules bottle	Organic India private limited, Office no -03, Ground floor, Uppals Plaza M6, Jasola District Center, New Delhi - 110025	<i>Cissus quadrangularis</i> (Harjor)
	Allen A28 Rheumatism Drop		<i>Moringa oleifera</i> (Sahijan) <i>Asparagus racemosus</i> (Shatavari) <i>Rhus toxicodendron</i> (poison ivy) <i>Arnica Montana</i> (mountain tobacco) <i>Ruta graveolens</i> (rue)
4.		Allen homoeo & herbal products ltd., Allen Estate, Krishnapur Road, Kolkata-700 102, India	<i>Gaultheria procumbans</i> (eastern teaberry) <i>Hypericum perforatum</i> (perforate St John's wort) <i>Guaiacum officinale</i> (roughbark lignum-vitae) <i>Curcuma longa</i> (Turmeric)
5.	GNC triflex fast acting (supports joint health and flexibility - 120 tablets)	Apres flex GNC nutraceuticals, 300 6th Avenue 14th Floor Pittsburgh, PA 15222 United States.	<i>Boswellia serrata</i> (Shallaki)
	Dhanwantaram thailam pre-post natal treatment oil		<i>Sesamum indicum</i> L. (Til Tail) <i>Rubia cordifolia</i> (Manjeeth)
6.		Kama ayurveda product ltd., India	<i>Elettaria cardamomum</i> (Elayachi) <i>Withania somnifera</i> (Ashwagandha) <i>Phyllanthus emblica</i> (Amla)
7.	Cissus tvs0038	TVS biotech., 4 355, Ramagounder, Thottam, Annadanapatti, Salem - 636002, Tamil Nadu, India	<i>Cissus quadrangularis</i> (Harjor)
	Dr Ortho Combo Pack of Ayurvedic Oil 120ml & Ayurvedic Capsules 30	Dr Ortho Mouza Rampur Jattan, Kala-Amb, Distt. Sirmour, Himachal Pradesh - 173030	<i>Mentha piperita</i> (Peppermint) <i>Cinnamomum camphor</i> (Kapoor) <i>Pinus roxburghii</i> (Sarla) <i>Linum usitatissimum</i> (Flax)
8.			
9.	Ortho Balm and Tablets Combo - Deemark	Deemark Health Care Pvt Ltd., 4-H-1, Garg Tower, Netaji Subhash Place, Pitam Pura, Delhi - 110034, India.	<i>Gaultheria procumbens</i> (gandhpura) <i>Mentha arvensis</i> (pudina) <i>Cinnamomum tamala</i> (tejpatha)
10.	Nutmeg Pure and Natural Essential Oil	Naturoman Near Nandan Cinema Bahind Yadu Hotel Meerut 250002	<i>Myristica fragrans</i> (Nutmeg)
11.	Biotrex rose hip extract	Biotrex 1106-1107, Matrix Tower, Near Divya Bhaskar, Corporate Road, Prahlad Nagar, Ahmedabad 380015 Gujarat, INDIA	<i>Rosa canina</i> (The seed pods of roses)
	New life rheumacin drop	New Life Laboratories Pvt. Ltd., 16, Bal Vihar Road Ghora Nakkas, Bhopal-462001, Madhya Pradesh, India	<i>Bryonia alba</i> (wild hop) <i>Colchicum autumnale</i> (meadow saffron) <i>Guaiacum sanctum</i> (roughbark lignum-vitae) <i>stellaria media</i> (chickweed)

- |     |                               |  |  |
|-----|-------------------------------|--|--|
| 13. | Rumartho                      | Shree Baidyanath Ayurved Bhawan Pvt. Ltd.,<br>1, Gupta Lane, Kolkata 700006, India | <p><i>Vanda Roxburghii</i> (Rasna)</p> <p><i>Commiphora wightii</i> (Guggulu)</p> <p><i>Withania somnifera</i> (L.) Dunal (Ashwagandha)</p> <p><i>Eucalyptus globules</i> (southern blue gum)</p> <p><i>Withania somnifera</i> (L.) Dunal (Ashwagandha)</p>  |
| 14. | Rhuma gel                     | Shree Baidyanath Ayurved Bhawan Pvt. Ltd.,<br>1, Gupta Lane, Kolkata 700006, India | <p><i>Asparagus racemosus</i> (Shatavari)</p> <p><i>Curcuma amada</i> (mango ginger)</p> <p><i>Sesamum indicum</i> L. (Til Taila)</p> <p><i>Plumbago zeylanica</i> (Ceylon leadwort)</p> <p><i>Piper longum</i> (Long Pepper)</p> <p><i>Embelia Ribes</i> (Vidang)</p> <p><i>Cuminum cyminum</i> (Cumin)</p> <p><i>Commiphora wightii</i> (Guggulu)</p>  |
| 15. | Yograj guggulu                | Shree Baidyanath Ayurved Bhawan Pvt. Ltd.,<br>1, Gupta Lane, Kolkata 700006, India | <p><i>Cedrus deodara</i> (Devdaru)</p> <p><i>Piper chaba</i> (Chui Jhal)</p> <p><i>Elettaria cardamomum</i> (Elayachi)</p> <p><i>Tribulus terrestris</i> (Gokhru)</p> <p><i>Cyperus rotundus</i> (Nagarmotha)</p> <p><i>Cinamomum tamala</i> (Indian cassia)</p> <p><i>Zingiber officinale</i> (Ginger)</p> <p><i>Ficus religiosa</i> (Pipal)</p> <p><i>Piper retrofractum</i> (Balinese long pepper)</p> <p><i>Piper longum</i> (Long Pepper)</p> <p><i>Plumbago indica</i> (Leadwort)</p> <p><i>Ferula assa-foetida</i> (Ferula)</p> <p><i>Apium graveolens</i> (Celery)</p> |
| 16. | Mahayograj Guggulu<br>40 tabs | Shree Baidyanath Ayurved Bhawan Pvt. Ltd.,<br>1, Gupta Lane, Kolkata 700006, India | <p><i>Foeniculum vulgare</i> (Fennel flower)</p> <p><i>Nigella sativa</i> (Kajonji)</p> <p><i>Holarrhena pubescens</i> (Indrajav)</p> <p><i>Embelia Ribes</i> (Vidang)</p> <p><i>Picrorhiza kurrooa</i> (Kutki)</p> <p><i>Annona squamosa</i> (Atis)</p> <p><i>Commiphora wightii</i> (Guggulu)</p> <p>Blend of <i>Terminalia bellirica</i>, <i>Terminalia chebula</i>, <i>Phyllanthus emblica</i> (Triphala)</p>  |

	Patanjali, Patanjali Ayurved Limited, Haridwar, Uttarakhand - 249401, India.	<i>Pluchelanceolata</i> (Rasna) <i>Alhagicamelorum</i> (Javaśa) <i>Sidacordifolia</i> (Bariyara) <i>Ricinuscommunis</i> (Eranda) <i>Cedrusdeodara</i> (Devdaru) <i>Curcuma zedoaria</i> (Kachur) <i>Acorus calamus</i> (Bach) <i>Adhatodavasica</i> (Adusa) <i>Tribulus terrestris</i> (Gokhru) <i>Withania somnifera</i> (Ashwagandha) <i>Aconitum heterophyllum</i> (Atish) <i>Cassia fistula</i> (Amaltas ) <i>Asparagus racemosus</i> (Shatavari) <i>Ficus religiosa</i> (Pipal) <i>Barleriaprionitis</i> (Kat-sareya) <i>Coriandrum sativum</i> (Dhaniya) <i>Zingiber officinale</i> (Ginger) <i>Terminalia chebula</i> (Harad) <i>Piper retrofractum</i> (Chavya) <i>Cyperusscariosus</i> (Nagarmotha) <i>Boerhaaviadiffusa</i> (Punarnava) <i>Tinospora cordifolia</i> (Giloy) <i>Argyreiaspeciosa</i> (Vidhara) <i>Foeniculum vulgare</i> (Sounf) <i>Solanum surattense</i> (KateliChhoti) <i>Solanum indicum</i> (KateliBadi) <i>Syzygium aromaticum</i> (Lavang) <i>Mentha × piperita</i> (Pudina) <i>Eucalyptus L'Hér</i> (Neelgiri) <i>Commiphora wightii</i> (Guggulu) <i>Gaultheria</i> (Gandhapuro) <i>Zingiber officinale</i> (Ginger) <i>Plectranthus amboinicus</i> (Njavara) <i>Moringa oleifera</i> Lam. (Shigru, Drumstick) <i>Tinospora cordifolia</i> (Thunb.) Miers (Guduchi) <i>Curcuma longa</i> (Haladi) <i>Boswellia serrata</i> (Shallaki) <i>Ocimum Sanctrum/Ocimum tenuiflorum</i> (Tulsi)
17.	Maharasandi kwath	
18.	Dabur rheumatil oil	Dabur, 8/3, Asaf Ali Road, New Delhi-110002, India.
19.	Organic navara red rice	Hishopie Natural, Kerala, India.
20.	Himalaya rumalaya tablets	The Himalaya Drug Company, Makali, Bengaluru 562 162.
21.	Artho care - joint pain relief	Artho Care, 3/10, Kirti Nagar Ind. Area, New Delhi - 110015, India
22.	Guaiacum mt	Dr. Willmar Schwabe India Pvt. Ltd., A-36, Sector 60, Noida, Uttar Pradesh, India.
23.	Aamvatari ras	Patanjali Ayurved Limited, Haridwar, Uttarakhand - 249401, India.
		<i>Blend of Terminalia bellirica, Terminalia chebula</i> (Harad), <i>Phyllanthus emblica</i> (Triphala) <i>Plumbago indica</i> (Chitrakmool) <i>Commiphora wightii</i> (Guggul) <i>Ricinus communis</i> (Eranda Tail)



24.

Peedantak oil

Patanjali Ayurved Limited, Haridwar,  
Uttarakhand - 249401, India.

*Aconitum ferox* (Vatsanabha)  
*Glycyrrhiza glabra* (liquorice)  
*Piper longum* (Long Pepper)  
*Acorus calamus* (Bach)  
*Scindapsus officinalis* Schoott. (Badi pippali)  
*Nardostachys jatamansi* (Jatamansi )  
*Curcuma longa* (Haldi)  
*Cinnamomum tamala* (Tejpata)  
*Eclipta prostrate* L.(Bhrngaraja)  
*Rubia cordifolia* (Manjeeth)  
*Butea monosperma* (Palasha)  
*Inula racemosa* (Pushkarmool )  
*Pavonia Odorata* (Valaka)  
*Asparagus racemosus* (shatavari)  
*Zingiber officinale* (Ginger)  
*Pimpinella anisum* (aniseed)  
*Plumbago zeylanica* Linn. (Ceylon leadwort)  
*Foeniculum vulgare* (Fennel flower)  
*Ricinus communis* (Erاند Tail)  
*Calotropis procera* (Aak)  
*Datura stramonium* (jimson weed)  
*Trachyspermum ammi* (Ajwain)  
*Strychnos nux-vomica* (kuchla)  
*Celastrus paniculatus*(mal-kangani)  
*Paederia foetida* (Gandh Prasarini)  
*Pluchea lanceolata* (Rasna)  
*Vitex negundo* (chaste tree)  
*Allium sativum* (garlic)  
*Solanum Xanthocarpum*(Kantakari)  
*Habenaria intermedia* (rein orchids)  
*Lilium polyphyllum* (White Lily)  
*Sesamum indicum* L.(Til Taila)  
*Terminalia bellirica* (Bibhitaki)  
*Terminalia chebula* (Harad)  
*Phyllanthus emblica* (myrobalan)  
*Ricinus communis* (Erاند Tail)  
*Commiphora wightii* (Guggulu)

25. Singhnad guggul

Patanjali Ayurved Limited, Haridwar,  
Uttarakhand - 249401, India.

*Commiphora wightii* (Guggulu)

26. Divya peedantak vati Patanjali Ayurved Limited, Haridwar, Uttarakhand - 249401, India.
- Commiphora wightii* (Guggulu)  
*Colchicum luteum* (meadow saffron)  
*Withania somnifera* (L.) Dunal (Ashwagandha)  
*Asphaltum* (Shilajeet shuddha)  
*Strychnos nux-vomica* (kuchla)  
*Cyperus scariosus* (Nagarmotha)  
*Pluchea lanceolata* (Rasna)  
*Vitex negundo*(Nirgundi)  
*Boerhaavia diffusa* (punarnava mool)  
*Trigonella foenumgraecum* (methi)  
*Operculina turpethum* (nisoth)  
*Asparagus racemosus* (shatavari)  
*Cissus quadrangularis* (harjard)  
*Curcuma longa* (Haldi)  
*Zingiber officinale* (Ginger)  
*Picrorhiza kurroa* (Kutki)  
*Trachyspermum ammi* (Ajwain)  
*Corallium rubrum* (praval pishti)  
*Vitex nigundo* (Nirgundi)  
*Tinospora cordifolia* (giloy)  
*Apium graveolens*(Celery)  
*Embelia ribes* Burm.f. (VaiVidang)  
*Cedrus deodara* (Devdaru)  
*Plumbago indica* (ChitrakMool)  
*Rock salt* (Sendha Namak)  
*Terminalia chebula* (Chhoti Harad)  
*Argyreia nervosa* (vidhara )  
*Piper nigrum* L.(Kali Mirch)  
*Piper longum* (Long Pepper)  
*Glycine max* (soya bean)
27. Ajmodadi churna Patanjali Ayurved Limited, Haridwar, Uttarakhand - 249401, India.

28. Bala taila 100ml

Patanjali Ayurved Limited, Haridwar,  
Uttarakhand - 249401, India.

*Sida cordifolia* (Bala)  
*Tinospora cordifolia* (Giloy)  
*Pluchea lanceolata* (Rasna)  
*Curcuma zedoaria* (Kachur)  
*Pinus roxburghii* (Sarla)  
*Cedrus deodara* (Devdaru)  
*Elettaria cardamomum* (Elayachi)  
*Rubia cordifolia* (Manjeeth)  
*Aquilaria malaccensis* (Agaru)  
*Pterocarpus santalinus* (Rakta Chandan)  
*Prunus pudum* Roxb. (Padmaka)  
*Abutilon indicum* (Atibala)  
*Cyperus scariosus* (Nagarmotha)  
*Vigna trilobata* (jungle mat bean)  
*Teramnus labialis*. Spreng (mashavan)  
*Vitex negundo* Linn. (chaste tree)  
*Glycyrrhiza glabra* (liquorice)  
*Ocimum tenuiflorum* (Tulsi)  
*Malaxis muscifera* (Rishbhak)  
*Butea monosperma* (Palasha)  
*Abelmoschus moschatus*(Lata kasturi) *Mesua ferrea* (Nagkesar)  
*Indigofera tinctoria* Linn. (Jayphal)  
*Saxifraga aizoon* (rockfoils)  
*Crocus sativus* (Kunkuma)  
*Parmelia perlata* (Huds)  
*Aegle marmelos* (Bel Chhal)  
*Myrica esculenta*(Bayberry)  
*Coccinia grandis* (kanduri)  
*Cinnamomum camphor* (Kapoor)  
*Syzygium aromaticum*(Clove)  
*Pimenta dioica* (Clove Pepper)  
*Saussurea costus* (kuth)  
*Nardostachys jatamansi* (Jatamansi )  
*Callicarpa macrophylla* Vahl. (PriyanguPhool)  
*Tabernaemontana divaricata*  
(Dhayma)  
*Justicia adhatoda* (Vasa)  
*Sesamum indicum* L.(Til Tail)

29.	Mahanarayan taila 100ml	Shree Baidyanath Ayurved Bhawan Pvt. Ltd., 1, Gupta Lane, Kolkata 700006, India	<p> <i>Sesamum indicum</i> L. (Til Tail)  <i>Andrographis paniculata</i> (Godugdha)  <i>Aegle marmelos</i> (Bel Chhal)  <i>Withania somnifera</i> (Ashwagandha)  <i>Solanum indicum</i> (Bari Kateri)  <i>Tribulus terrestris</i> (Gokhru)  <i>Oroxylum indicum</i> (Sona patha)  <i>Sida cordifolia</i> (Bala Panchang)  <i>Erythrina variegata</i>  <i>Farhad Chhal</i> (Paribhadra)  <i>Solanum surattense</i> (Chhoti kateri)  <i>Boerhaavia diffusa</i> (Punarnava Mool)  <i>Clerodendrum plomidis</i> (Ganiyari)  <i>Abutilon asiaticum</i> (Kangh)  <i>Paederia foetida</i> (Gandh Prasarini)  <i>Stereospermum suaveolens</i> Patla)  <i>Sesamum indicum</i> (Murchhit Til Tel)  <i>Asparagus racemosus</i> (Shatavari)  <i>Pluchea lanceolata</i> (Rasna)  <i>Foeniculum vulgare</i> (Sounf)  <i>Cedrus deodara</i> (Devdaru)  <i>Saussurea lappa</i> (Kuth)  <i>Desmodium gangeticum</i> (Shalparn)  <i>Phaseolus trilobus</i> (Mugdhparni)  <i>Aquilaria agallocha</i> (Agar)  <i>Mesua ferra</i> (Nagkeshar)  <i>Nardostachys jatamansi</i> (Jatamansi )  <i>Curcuma longa</i> (Haldi)  <i>Berberis aristata</i> (Daruhaldi )  <i>Parmelia perlata</i> (Chharila )  <i>Santalum album</i> (Safed Chandan )  <i>Elettaria cardamomum</i> (Elaichi)  <i>Rubia cordifolia</i> (Manjith)  <i>Glycyrrhiza glabra</i> (Mulethi)  <i>Valeriana wallichii</i> (Tagar)  <i>Cyperus rotundus</i> (Nagarmotha)  <i>Cinnamomum tamala</i> (Tejpata)  <i>Eclipta alba</i> (Bhringraj)  <i>Pueraria tuberosa</i> (Bidarikand)  <i>Dioscorea alata</i> (Bridhi)  <i>Valeriana wallichii</i> (Sugandhabala)  <i>Acorus calamus</i> (Bach)  <i>Butea monosperma</i> (Palasmool)  <i>Leonotis nepetaefolia</i> (Gathiwan)  <i>Cinnamomum camphor</i> (K Kapoor)  <i>Crocus sativus</i> (Keshar)  <i>Abelmoschus moschatus</i> (Lata kasturi) </p>
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30. Saindhavadi taila

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Rock salt (Sandha Namak)  
*Calotropis gigantean* (L.) Dryand. (Arka)  
*Piper nigrum* L. (Kali Mirch)  
*Plumbago indica* L. (Citrakamool)  
*Eclipta prostrata* L. (Bhrngaraja)  
*Curcuma longa* Linnaeus (Haladi)  
*Berberis aristata* DC. (DaruHaladi)  
*Sesamum indicum* L. (Til Taila)

doses significantly suppressed granulomatous tissue formation in cotton pellet-induced granuloma test<sup>[126]</sup>.

The bioactive principles reported for anti-arthritis properties have been listed in Table 1 along with their respective plant source and mechanism of action. Also listed are the commercial anti-arthritis herbal products available in the market in Table 2. The compiled information regarding plants and their role in treatment of RA has been justified here as the perspective of plant derived medicine in the therapy of RA in near future.

## CONCLUSION

In India, 45 % rheumatic diseases patients are having comorbidities such as hypertension, hypothyroidism and diabetes mellitus. Hence, timely diagnosis of associated comorbid conditions is very much necessary for efficient management of rheumatic diseases. The presently available synthetic drugs used for management of rheumatic diseases have fatal side effect on prolonged uses. However, several medicinal plants and their bioactive phytochemicals exhibited potential responses on experimental rheumatic diseases. Several medicinal plants products (extracts/fractions) and their bioactive phytochemicals such as Epigallocatechin-3-gallate exhibited inhibitory effect on the biomarkers namely TNF- $\alpha$ , TNF- $\gamma$ , NFK $\beta$ , iNOS and COX which those are responsible for rheumatic diseases. In the present review, a list of medicinal plants reported for anti-arthritis properties, their bioactive phytochemicals and mechanism of action will be useful for research scholars, scientists, and industrialist. Though, several herbal formulations are available in market for management of RA and listed in the present review. But, there are huge scopes, for more and more research for invention of potent traditional knowledge based phyto-pharmaceutical drugs for treatment of RA.

## Conflict of interests:

The authors declared no conflict of interest.

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