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PHYTOCHEMICAL PROFILING AND ASSESSMENT OF ANTI-ARTHRITIC POTENTIAL OF *CAESALPINIA CRISTA* EXTRACT

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Abstract

Arthritis is a chronic inflammatory and autoimmune disorder that primarily affects the joints, causing pain, swelling, stiffness, and progressive destruction of cartilage and bone. Among the different forms of arthritis, rheumatoid arthritis and osteoarthritis are the most prevalent and debilitating conditions worldwide. Conventional treatment approaches such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs), and biological agents provide symptomatic relief but are often associated with adverse effects including gastrointestinal irritation, cardiovascular complications, renal toxicity, and immunosuppression. Therefore, there is an increasing interest in the exploration of natural products and phytochemicals as safer and effective alternatives for the management of arthritis. Various medicinal plants and their bioactive constituents such as alkaloids, terpenoids, flavonoids, glycosides, and polyphenols have demonstrated significant anti-arthritic and anti-inflammatory activities through modulation of inflammatory mediators, cytokines, oxidative stress, and immune responses. Phytochemicals including piperine, quercetin, kaempferol, resveratrol, sanguinarine, eugenol, nimbolide, and chebulanin have shown promising therapeutic potential in experimental arthritis models. The present review highlights the epidemiology, etiology, symptoms, diagnosis, and conventional treatment strategies of arthritis along with the therapeutic importance of medicinal plants and phytochemicals possessing anti-arthritic activity. The study suggests that plant-derived bioactive compounds may serve as potential candidates for the development of safer and more effective anti-arthritic therapies in the future.

Keywords: Arthritis, Rheumatoid Arthritis, Osteoarthritis, Anti-arthritic Activity, Medicinal Plants, Phytochemicals, Inflammation, Herbal Medicine, Rheumatoid Factors.

Introduction

Arthritis is a chronic, inflammatory and systemic auto-immune disease that mainly affect the joints of human body. It may affect other tissues and organs such as heart, skin and muscles. Osteoarthritis (OA), Rheumatoid Arthritis (RA) are the forms of arthritis which exists. The onset and severity of disease is variable and usually insidious. The initial symptoms of this disease are fatigue, musculoskeletal pain and stiffness and after some weeks to months it progress to involve joints. At first the small joints are affected, particularly the small bones of the hands. Later larger joints are affected, become swollen, warm and painful. One of the most important symptoms of the disease is morning stiffness or stiffness. The slowness or difficulty in moving is seen in the patient in the time of getting out of bed or after staying in one position too long. Here both sides of the body are involved and this symptom decrease with movement (Lineker *et al*., 1999).

Arthritis is one of the most deceptive diseases globally, with 350 million individuals are currently affected. As per a recent report, one in four adults in the USA suffer from arthritis with severe joint pain. Arthritis leads to the breakdown of cartilage which normally protects joints. Arthritis produces an inflammatory riposte as well as hyperplasia of synovial cells. Consequently, extra deposition of synovial fluid in the joints develops the sheets in the synovial cells that cause inflammation at joint sites. The pathology of the disease process often indicates that it also damages the articular cartilage and alkalosis of the joints. Ankylosing spondylitis, juvenile idiopathic arthritis, reactive arthritis, psoriatic arthritis, rheumatoid arthritis, septic arthritis, osteoarthritis, and gout are the commonly reported types of arthritis (Laev and Salakhutdinov, 2015; Katz *et al*., 2021).

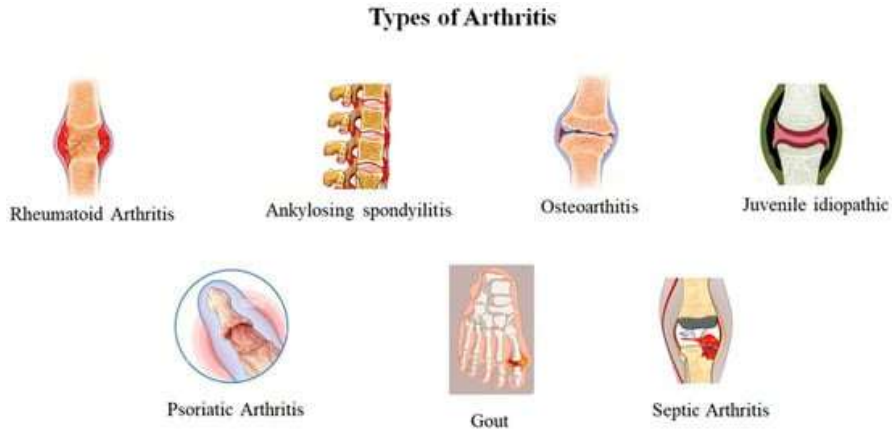

Figure 1: Common types of arthritis reported in the literatures

Epidemiology

The prevalence of rheumatoid arthritis (RA) varies between 0.3% and 1% worldwide and is more in developed countries. It mainly affects women than men (3:1). Generally, it strikes between 30 and 55 years. It affects 0.5-1.0% of adults, Rheumatoid arthritis (RA) is a chronic systemic inflammatory illness with prevalence of approximately 0.75% in India (Gabriel *et al*., 2003).

Etiology

The etiology of RA is still not known, a genetic susceptibility in combination with the influence of environmental factors are probably prerequisites for the onset of RA. The factors are:

Environmental factors: There are consistent data indicating that smoking may contribute to the development of RF positive, destructive RA in HLADRBI/ SE-positive individuals. The onset of RA has been associated with mineral oils, silica exposure, diet factors, and blood transfusion.

Impact of sex and sex hormones: More women than men are affected by RA, particularly at younger ages this implicates a plausible role for sex hormones in susceptibility and pathogenesis. In women, peak incidence is observed in the peri menopausal, postpartum period and pregnancy.

Genetic factors: Rheumatoid arthritis has a genetic link, and the disease can run in families. People with specific human leukocyte antigen (HLA) genes have a greater chance of developing rheumatoid arthritis than people who do not have the HLA genes. Still, not everyone with the HLA genes develops rheumatoid arthritis (Kumar and Cortan, 2005).

Symptoms

Symptoms of arthritis are gradually developed. The first symptoms are often felt in small joints, i.e. fingers and toes, although shoulders and knees can be affected early, and muscle stiffness can be a prominent early feature.

- Symptoms of RA includes
- Morning stiffness that last for at least 1 hr
- Joint pain with warmth, swelling, tenderness and stiffness of the joint after resting
- Low-grade fever

- Inflammation of small blood vessels can cause small nodules under the skin, but they are generally painless (Scott *et al*., 2010).

Diagnosis

Diagnosing rheumatoid arthritis (RA) in the early stages can be difficult. There is no single test that can clearly identify rheumatoid arthritis. Instead, doctors diagnose rheumatoid arthritis based on factors that are strongly associated with the disease. The American College of Rheumatology uses this list of criteria:

- Morning stiffness in and around the joints for at least one hour.
- Swelling or fluid around three or more joints simultaneously.
- At least one swollen area in the wrist, hand, or finger joints.
- Arthritis involving the same joint on both sides of the body (symmetric arthritis).
- Antinuclear antibody (ANA) – antibodies.
- X-ray changes in the hands and wrists typical of rheumatoid arthritis.
- Other tests, including X-rays, MRI, ultrasound, and other scan (Firestein *et al*., 2005).

Treatment

Treatments employed for treating arthritis:

The main aim of treatment is focused towards decreasing the disease activity or decreasing the inflamed condition with some remission if possible, along with a minimization of joint destruction and finally improving the physical condition and quality of life (Vane, 1971).

Pharmacological Strategies:

Generally, a strategic treatment plan is employed for the treatment of the disease which includes four different classes of drugs: non-steroidal antiinflammatory agents (NSAIDs), corticosteroids, disease modifying anti-rheumatic drugs (DMARDs) and biological agents. As the disease is more prevalent among the females, therefore the treatment strategies for females in the child bearing age need special caution as the treatment employed for curing their arthritic condition can have negative impact on their potential for conceiving and also during pregnancy (Chen *et al*., 2008).

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

Analgesics reduce pain, and NSAIDS lessen pain and stiffness. Both drugs are used widely to control symptoms of rheumatoid arthritis, evidence for use of analgesics is modest but

uncontroversial; support for use of NSAIDS is considerably stronger. The mode of action of these drugs was not known until JR Vane for the first time published the observations showing that these drugs work by blocking cyclooxygenase enzym. NSAIDS have lost their historical role as first line treatment because of concern about their limited effectiveness, inability to modify the longterm course of disease. One of the most common toxicity observed in case of regular use of these drugs is gastrointestinal disturbances or toxicity which generally includes the condition of burning, belching or irritation further leading to the development of gastric ulcers followed by bleeding During long term usage, NSAIDs also impair the renal as well as liver function of the body, predisposing the patients towards the cardiovascular diseases with their additional adverse effects on blood pressure (Schaffer, 2006).

Ex: parcetamol, opiates, Diproqualone

Corticosteroids

Corticosteroids like glucocorticoids have been used on large scale since last 60 years for the treatment of arthritis. Some of the commonly used glucocorticoids in disease remission are prednisone, methyl prednisolone etc. short term glucocorticoids reduce synovitis. Long term they decrease joint damage, but develops various infections, and osteoporosis, and their overall risk/ benefit ratio is deemed to be highly unfavorable. Glucocorticoids can be especially useful in two conditions. Firstly, in treating the short term flare ups can lead to rapid improvement and allow other treatment DMARDS which have slower onset of actionto be adjusted. Use of steroids in this way is low risk. Oral or intramuscular glucocorticoids are administered by many centers in this setting. Second, intra articular glucocorticoids are highly effective local treatment for individual active joint (Ravindran, 2009).

Ex: prednisone, prednisolone, methyl prednisolone

Cytotoxic drugs

Cyclophosphamide produces cytotoxic effects on both B and T cells and selectively suppresses the B lymphocyte activity. Decreased immunoglobulin secretion has been described in patients treated with low dose Cyclophosphamide for auto immune diseases.

The drug is Cytotoxic to many tissues, including the kidneys and the heart. This drug is teratogenic and should be avoided during pregnancy and breast feeding.

Ex: Cyclophosphamide

Phytochemicals with anti arthritic activity

Herbal products have been widely used as medicine since ancient eras. These natural products have broad chemical diversity, pharmacological specificity, and molecular properties that make them potential candidates for lead structure identification. Thousands of plant isolates possessing antiarthritic (AA) properties have been investigated and reported. These plant isolates have been categorized into alkaloids, glycosides, terpenoids, flavonoids, etc. In recent years, herbal products showing anti-inflammatory-mediated AA properties have been isolated. These plants have been used either solely, or their extracts or isolates have been used for the treatment of RA or OA. Plant isolate is a pure compound obtained from a plant extract, having a defined structure which is responsible for particular biological activity, and helps to develop new potent compounds. These plant isolates act through different mechanisms (Siddiqui *et al*., 2014; Sultan *et al*., 2009).

1] Alkaloids

Montanine

Plants belonging to the *Amaryllidaceae* family have a long history of usage globally, and are found to be a promising therapeutic tool for several human diseases. The plants belonging to this family have long been used as an alternative medicine in developing countries. The *Amaryllidaceae* alkaloids are secondary metabolites (alkaloids) of the *Amaryllidaceae* family, native to Argentina, Brazil and Uruguay. Montanine has structural similarities to *Amaryllidaceae* alkaloids, and its pleiotropic pharmacologic activity raises the possibility of montanine possessing anti-arthritic properties (Otterlo *et al*., 2018).

Recently, montanine has received the considerable attention due to its strong anti-inflammatory action, which was isolated from the bulb of the plant *Rhodophiala bifida* (Herb.) through maceration in sulfuric acid 2% (*v*/*v*). The authors reported its significant AA activity by using in vitro effects on lymphocyte proliferation and on invasiveness of fibroblast-like synoviocytes (FLS). Later, the activity of isolate was evaluated on antigen-induced arthritis (AIA) Balb/c mice and collagen-induced arthritis (CIA) DBA/1J mice models (Koutová *et al*., 2020).

Study results revealed that montanine administration decreased nociception and leukocyte articular migration in the AIA model, and reduced the severity of arthritis and joint damage in CIA model. Histological results revealed considerable improvements in arthritis. The

authors proposed that the inhibition of lymphocyte proliferation and decreased FLS invasion was responsible for AA activity. A median lethal dose (LD50) of montanine was reported to be 64.7 mg/kg for male mice, and the occurrence of side effects as altered motor activity, decreased respiratory rate, violent body tremors, and clonic convulsions (Farino *et al*., 2017).

3-Acetylaconitine

3-Acetylaconitine (AAc) is a nitrogen-containing alkaloid, obtained from *Aconitum flavum* and *Aconitum pendulum* (*Ranunculaceae*). Tang *et al*. isolated AAc from the root of *Aconitum flavum*, and reported its AA activity in mouse and rat models. An oral dose of 0.3–0.5 mg/kg of AAc impeded swelling of the hind paw in the formaldehyde-induced rat model, and inhibited the carrageenan-induced edema in the adrenalectomized rat model. Although AAc inhibited acetic acid and histamine-induced vascular permeability, it did not reduce the ascorbic acid content of the adrenal in rats, indicating that AAc did not act through stimulation of the pituitary adrenal axis (Tang *et al*., 1984).

Sanguinarine

Sanguinarine (SA) is a natural plant benzylisoquinoline alkaloid isolated from *Argemone mexicana, Bocconia frutescens, Bocconia frutescens, Chelidonium majus, Macleaya cordata, and Sanguinaria Canadensis*. SA is U.S.A Food and Drug Administration (FDA) approved; it inhibits osteoclast formation, and is recommended for inflammation. Ma *et al*. isolated SA from the roots of *Sanguinaria Canadensis,* and investigated the therapeutic effect of SA against OA. Results revealed that SA suppressed catabolic proteases expression in in vitro, in vivo, and ex vivo models. SA suppressed NF-κB and JNK activation, which presented a high level of specificity in repressing the production of catabolic factors. Additionally, SA also inhibited IL-1β-induced expression of matrix metalloproteinase (MMPs) 1, 3, and 13. It also suppressed a metalloproteinase and disintegrin with thrombospondin motifs-5 in chondrocytes. These results supported the potential application of SA in OA treatment (Huang *et al*., 2017).

Jatrorrhizine

Jatrorrhizine hydrochloride (JH) is a protoberberine alkaloid reported in many medicinal plants, including *Berberis aristata* and *Coptis chinensis*. Qiu and colleagues recently investigated and reported the AA potential of commercially available isolate JH in a CIA rat model. The results revealed the suppression of RA in the CIA rat model via an anti-inflammation action, and suppression of bone destruction. Furthermore, the in vitro assay

showed inhibition of production of inflammatory mediators, and inhibition of proliferation and migration in MH7A cells. JH was found to suppress tumor necrosis factor-α (TNF-α)-stimulated activation of nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), leading to suppression of proinflammatory mediators. These results suggested JH as potential compound for AA treatment (Slobodníková *et al*., 2004).

Piperine

Piperine is another alkaloid obtained from black pepper (*Piper nigrum* L.), responsible for the pungent taste, and found in the members of the *Piperaceae* family. *Piper nigrum* L. contains the highest amount of piperine, i.e., from 2% to 9%. *Piper nigrum* L. has been well reported in Ayurvedic and Chinese medicine. Bang and colleagues in 2009 reported anti-inflammatory, nociceptive, and AA activities of piperine. The AA activity was measured in a CI arthritis model in vivo by measuring the paw volume and weight distribution ratio. The results showed significant reduction of paw volume and weight distribution ratio. The authors also evaluated the levels of IL6, MMPs, COX-2, and PGE2 by ELISA and RT-PCR. An oral dose of piperine between 20 and 100 mg/kg/day for 8 days, inhibited the IL6 and MMP13 expression and PGE2 production. Surprisingly, piperine did not inhibit the expression of NFκB, but did suppress the migration of activator protein 1 (AP-1). Ultimately, on the fourth day, piperine reduced arthritic symptoms. These results suggested the potential of piperine in arthritis treatment (Stojanović *et al*., 2019).

Capsaicin

Capsaicin is an active component of chili peppers (genus Capsicum), and is produced as a secondary metabolite. It is a chemical irritant for mammals, including humans. Ahmed and colleagues investigated capsaicin effects on substrate P (SP) and calcitonin gene-related peptide (CGRP) in the ankle joints and dorsal root ganglia (L2–L6) of adult female Lewis rats.

Subcutaneous injection of capsaicin in a dose of 200 mg/kg significantly reduced the level of substrate P (19%) and CGRP (42 %) in dorsal root ganglia of adjuvant-induced arthritic rats. In the ankle joint, capsaicin reduced the SP level by 40%, accompanied by a 40% reduction in inflammatory response. Furthermore, the capsaicin administration reduced the up-regulated levels of sensory neuropeptides in dorsal root ganglia and ankle joints in adjuvant-induced arthritis rats. These findings suggested that capsaicin is useful in arthritis treatment (Gamse *et al*., 1981).

Tubastrine

The alkaloid tubastrine, obtained from the marine organism *Aplidium orthium* (Ascidiacea), possesses anti-inflammatory properties. Tubastrine isolated from the frozen specimen of *Aplidium orthium* with methanolic acid, followed by chloroform, reduced superoxide synthesis in phorbol-12-myristate 13-acetate (PMA)-stimulated neutrophils in vitro and, in an in vivo study, reduced superoxide levels in a gouty arthritis model. Additionally, tubastrine further showed an inhibitory effect on neutrophil infiltration in an in vivo model (Pearce *et al*., 2008).

Orthidines

The orthidines (A–F) are a group of marine alkaloids isolated from the same ascidian *Aplidium orthium.* Orthidines (A–D) are benzodioxane, orthidine E (a cyclobutane dimer of tubastrine), and orthidine F (a biosynthetically unrelated dihomovanillamide derivative of spermine). Pearce and colleagues isolated orthidines (A–F) from the frozen specimen of New Zealand *ascidian Aplidium orthium* with methanolic acid, followed by chloroform, and evaluated anti-inflammatory and anti-arthritic activity in a gouty arthritis model. Isolated orthidines (A–F) showed the in vitro production of superoxide by PMA-stimulated human neutrophils in a dose-dependent manner with IC_{50s} of 10–36 μM, and this was associated within the inhibition of superoxide production by neutrophils in vivo in a murine model of gouty inflammation.

2] Terpenoids

Terpenoids are plant secondary metabolites, extracted from various parts of the plant, such as stalks, fruits, flowers, leaves, and roots. They are colorless liquids with a pleasant smell, and have a high refractive index. The pharmaceutical importance of terpenoids has been proved and well documented in its anti-inflammatory, antibacterial, antiviral, antioxidant, and anti-carcinogenic properties. Recently, Carvalho *et al*., identified and reported 24 terpenoids which were effective in the treatment of inflammation and arthritis (Ali *et al*., 2015).

Eugenol

Eugenol is a major phenolic component obtained from the clove bud (*Eugenia caryophyllata*), and constitutes 80–90% of clove bud oil. Sharma *et al*. first reported the suppressive effects of eugenol on arthritic symptoms. A study was further carried out by Grespan *et al*. to estimate the AA activity of eugenol in a CIA mouse model. The arthritic symptoms were

induced with 100 μg of bovine collagen type II (CII) in male DBA1/J mice, and treated with orally administered eugenol (100 μg/mouse) from day 25 to day 40. Eugenol administration significantly decreased the levels of cytokines (i.e., TNF-α, tumor growth factor (TGF)-β, and interferon (IFN)-γ) within the ankle joints. Furthermore, the results indicated that eugenol also inhibited mononuclear cell infiltration into the knee joints of arthritic mice (Grespan *et al*., 2012).

Nimbolide

Nimbolide is a triterpene, which is isolated from the leaves and flowers of the neem plant (*Azadirachta indica*), and has been widely used in treating numerous human ailments. Several bioactive compounds have been isolated from this plant species which exhibit multiple pharmacological effects. Cui *et al*. performed the AA activity of nimbolide on male albino rats against Freund's adjuvant-induced arthritis. A study was carried out to access the AA activities of nimbolide using different in vitro and in vivo analytical methods. AA activity of nimbolide (at a dose of 20 mg/kg per day, which was given orally) exhibited a noticeable reduction in edema formation, paw volume, organ indices, and arthritic score, along with considerable improvement in body weight. Histopathological studies revealed the protecting effects of nimbolide towards joints and inflammation.

The outcomes of the study showed that nimbolide treatment inhibited inflammation by decreasing the proinflammatory cytokines (i.e., TNF-a, IL-6, IL-1b, and IL-10) manifestation in arthritic rats. Furthermore, nimbolide normalized the increased levels of iNOS, P-IkBa, Nf-kb, cox-2, and IKKa in treated rats (Cui *et al*., 2019).

Bartogenic Acid

Bartogenic acid (BA) is isolated from the fruits of the *Barringtonia racemosa* Roxb. (Lecythidaceae) plant. A study was performed by Patil *et al*. in order to evaluate the AA activity of BA. BA was isolated from the methanolic extract of fruits of *Barringtonia racemosa*. The in vivo results revealed noteworthy AA activity of BA against CFA-induced arthritis in rats by reducing serum markers, such as rheumatoid factor and C-reactive protein. BA protected against primary and secondary arthritis lesions with a dose of 2, 5, and 10 mg kg^{-1} day^{-1}. It also normalized the raised WBC counts and increased hemoglobin counts, and reduced erythrocyte sedimentation rate in arthritic conditions. The possible mechanism to improve Hb count by BA was due to increased response of the bone marrow erythropoietin. BA also protected the rats from CFA-induced radiographic changes (Patil *et al*., 2011).

Cannabidiol

Cannabidiol (CBD) are meroterpenoids, terpenophenolic compounds which are isolated from the plant *Cannabis sativa* L., belonging to the *Cannabaceae* family, and cultivated worldwide. This plant contains a number of phytoconstituents including amides, amines, phytosterols, phenolic compounds, carbohydrates, terpenes, and fatty acids and their esters, along with CBD as main active constitute (Pellati *et al*., 2018).

3] Flavonoids

Flavonoids are polyphenolic compounds isolated from plants and found in grains, fruits, flowers, vegetables, bark, stems, and roots. Flavonoids have been shown to possess anti-inflammatory properties, and these plant products have been widely used traditionally in the treatment of arthritis (Elisha *et al*., 2016).

Quercetin or 3,5,7,3′,4′-Pentahydroxy Flavone

Quercetin (QTN) is a flavonoid obtained from apples, buckwheat, onions, and citrus fruits. Recently, Yuan *et al*. investigated and reported the mechanism of AA activity of QTN. QTN significantly reduced ankle diameter and arthritic scores in adjuvant-induced arthritis (A42A) in a mouse model.

The study revealed that QTN endorsed apoptosis of activated neutrophils, and inhibited neutrophil infiltration. Additionally, QTN inhibited ROS-mediated neutrophil extracellular traps (NETs) formation and autophagy. These findings suggested that QTN may be a potential agent for RA treatment by inhibiting neutrophil activities. QTN (30 mg/kg) oral administration showed a decrease in clinical sign of arthritis in a chronic rat (AA) model. Gardi *et al*. showed a decrease in IL-1b level, monocyte chemotactic protein-1 (MCP-1) level, and also restored plasma antioxidant capacity in rat adjuvant arthritis after oral administration of QTN (150 mg/kg) (Gardi *et al*., 2015).

Resveratrol

Resveratrol (Res), a natural flavone, is widely present in medicinal plants including grape, cranberry, mulberry, pistachio, and peanut. The AA activity of Res was evaluated against a CFA-induced rat model by Chen and colleagues in 2013. Res was showed to inhibit the mRNA expression of IL-1β and TNF-α and, ultimately, IL-1β and TNF-α level after given through intragastric gavage (i.e. 10 mL/kg/day). Res stimulated synoviocytes, and the protein expression levels of p-ERK1/2 via protein kinase C (PKC).

Co-administration of Res and piperine significantly decreased the paw swelling and ameliorated the histopathological changes. The combined treatment highly reduced the serum TNF-a, IL-1b, thiobarbituric acid reactive substances (TBARS), and nitrate/nitrite (NOx). Moreover, a nearly negative expression of NF-κB p65 in the synovial tissue was observed by co-administration of piperine with Res. Results of the combination treatment were comparable to that of diclofenac treatment (Ghazaly *et al*., 2020).

Kaempferol

Kaempferol (KAE), a natural flavanol, chemically known as 3,4′,5,7-tetrahydroxyflavone, is found in numbers of edible plants such as beans, tea, kale, broccoli, and spinach. KAE is used as a traditional medicine for numerous inflammatory disorders. Studies revealed that KAE reduces COX-2 levels in RAW 264.7 cells, and inhibits ROS production via inhibition of iNOS and TNF-α protein expression. KAE also inhibits IL-4, C-reactive protein (CRP) expression and NF-κB in liver cells. Yoon *et al*. reported that KAE produces AA activity by inhibiting the proliferation of both unstimulated and IL-1β-stimulated RASFs, in addition to the mRNA and protein expression of MMP-1, MMP-3, PGE2, and COX-2 induced by IL-1β (Yoon *et al*., 2013).

Chebulanin

Chebulanin is a natural polyphenolic compound isolated from the fruits of *Terminalia chebula retzius* (*TC*). *Terminalia chebula retzius* (*TC*) is widely used in medicine in Asian countries for its anti-microbial, anti-inflammatory, antioxidant, and AA properties. Zhao and colleagues investigated the chebulanin function as an AA agent in a CIA-animal model using DBA/1 mice. Chebulanin was isolated from dry fruits of *Terminalia chebula retzius* with a 70% acetone solution (1:10, *w*/*v*) at room temperature (23 ± 2 °C). The authors measured the expression of inflammatory cytokines by immunohistochemical staining, and also performed a histopathological evaluation of the joints. Micro-CT was also performed to detect bone destruction and erosion. Micro-CT results showed the dose-dependent reduction in cartilage destruction and bone erosion. These results confirm the potential role of chebulanin as a strong therapeutic agent for the treatment of RA. Recently, Liu *et al*. also confirmed the AA activity of chebulanin via inhibiting NF-κB and MAPK activation in a collagen-induced arthritis (CIA)mouse model. Chebulanin significantly decreased the arthritic scores, paw swelling and IL-6 and TNF-α level in mice after being orally gavaged (80 mg/kg) daily for a total of 21 days. Moreover, chebulanin reduced the levels of excised phosphorylated (p)-p38, c-JUN, p-p65, N-terminal kinase (p-JNK), and phosphorylated NF-

κB inhibitor alpha (p-IκBα), but did not alter extracellular-signal regulated kinase, which is implicated in many pathological conditions, including arthritis.

Ellagic Acid

Ellagic acid (EA) is a polyphenol bioactive compound richly existing in berries (strew berry, raspberry, and cloudberry), almonds, grapes, walnuts, and pomegranates. Shruthi *et al*. isolated the ellagic acid from the methanol leaf extract of the plant *Kirganelia reticulate,* and tested its AA activity via in vitro, in vivo, and in silico assays. The in vitro assay of EA showed maximum percentage inhibition of protein denaturation, membrane stabilization, and proteinase inhibitory action, which were observed at 250µg/mL. The in vivo studies of EA against the formaldehyde-induced paw edema showed inhibition of cytokines and leukotriene infiltration, reduced paw edema volume, protected synovial membranes, and cartilage damage at both 100 µg/mL and 250 µg/mL concentration. The possible proposed mechanism was inhibition of hypoxia-inducible factor (HIF-2α). Other parameters including body weight, paw edema volume, and the movements of rats, were also studied, which showed a protective effect of EA similar to standard aspirin (Shruthi *et al*., 2014).

Medicinal plants with Anti-arthritic activity

Table 1: List of medicinal plants with Anti-arthritic activity

Sl.No	Plant name & family	Plant part used	Reference
1.	Sophora flavescens (Fabaceae)	Rhizomes	Jin *et al*., (2010)
2.	Commiphora caudata (Burseraceae)	Leaves	Eggadi *et al*., (2014)
3.	Cinnamomum zeylanicum (Lauraceae)	Bark	Vetal *et al*., (2013)
4.	Glycyrrhiza glabra L. (Fabaceae)	rhizomes	Mishra *et al*., (2011)
5.	Monocellate cobra (Bungarinae)	venom	Gomes *et al*., (2010)
6.	Euphorbia tirucalli (Euphorbiaceae)	Whole plant	Chandrasenan *et al*., (2016)
7.	Saussurea lappa (Asteraceae)	roots	Gokhale *et al*., (2002)

8.	Boswellia serrata (Burseraceae)	Gum resin	Umar *et al*., (2014)
9.	Xanthium strumarium L. (Astereaceae)	Fruit	Rashmi *et al*., (2021)
10.	Merremia tridentata Linn.(Convulvulaceae)	Whole plant	Lin *et al*., (2014)
11.	Tridax procumbens (Asteraceae)	Whole plant	Jain *et al*., (2012)
12.	Barringtonia racemosa (Lecythideceae)	fruit	Patil *et al*., (2011)
13.	Glycirrhizaglabra (Fabaceae)	Rhizomes	Mishra, (2011)
14.	Glycosmispentaphylla (Rutaceae)	Stem bark	Ramesh, (2012)
15.	LawsoniaInnermis (Lythraceae)	Leaves	Kore and Shete, (2011)
16.	Machalis macrantha (Lauraceae)	Bark	Tatiya *et al*., (2011)
17.	Phyllanthusamarus (Euphorbiaceae)	Herbs	Mali, (2011)
18.	Pistiostratios (Araceae)	Leaf	Samuel, (2012)
19.	Pongammiapinnata (Fabaceae)	Leaves	Arote, (2011)
20.	Punica grantum (Punicaceae)	Seeds	Kothari, (2011)
21.	Randiadumetorum (Rubiaceae)	Fruit	Patel, (2012)
22.	Ricinuscommunis (Euphorbiaceae)	Leaves	Kabra and Rachhadiya, (2011)
23.	Strychnospotatorum Linn (Loganiaceae)	Seeds	Ekambaram, (2010)
24.	Saussaurealappa (Compositae)	Roots	Chandur, (2011)
25.	Sidarhombifolia (Malvaceae)	Aerial parts	Gupta, (2009)

26.	Tinosporacardifolia (Menispermaceae)	Leaves	Paval *et al*., (2011)
27.	Urticapilulifera (Urticaceae)	Leaves	Abudoleh and Disi, (2011)
28.	Urgeniaindica (Liliaceae)	Bulb	Rahman, (2011)
29.	Vernoniaanthelmintica (Asteraceae)	Seeds	Otari, (2010)
30.	Wedeliacalendulaceae (Asteraceae)	Leaves	Panchal, (2011)

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