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A REVIEW ON ANTI-ARTHRITIC ACTIVITY OF SOME MEDICINAL PLANTS

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory and systemic auto immune disease affecting people predominantly between the ages of 20-50 years with unpredictable course. About 1% of the world's population is afflicted by rheumatoid arthritis and is two to three times more common in women than men. There are different types of arthritis. The rheumatoid arthritis due to the presence of pro-inflammatory markers, cytokines and leukotrines. The primary inflammatory markers are IL-1, TNF-α, IL-6, IL-15, IL-16, IL-17, IL-18, IFN-γ, and granulocyte macrophage-colony stimulating factor, chemokines such as IL-8, macrophage inflammatory protein-1 and monocyte chemo attractant protein-1. TNF-α blockade, IL-1 blockade, B cells therapy, IL-6 blockade and Angiogenesis blockade, these are therapeutic target for its treatment. There are different animal models are used to induce arthritis in rats to evaluate the anti-arthritic activity ofthe plants. Medicinal plants have been used as major sources of pure of human diseases since time immemorial. Today, one fourth of world population depends on traditional medicine and 80% of the population relies on indigenous medicinal plants. Even today most of the people lives in different developing countries depend on the plant derived medicines for the first line of primary health care because of least or no side effects. Review in this area has explored the potential research on plants for their anti-arthritic activity.

Keywords: Rheumatoid arthritis, animal models, Anti-arthritic potential, cytokines.

INTRODUCTION

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease predominantly affecting the joints and periarticular tissue. RA still remains a formidable disease, being capable of producing severe cripplingdeformities and functional disabilities and cartilage destruction and commonly leads to significant disability, caused by no. of proinfalmmatory molecules released by macrophages including reactive oxygen species and ecosanoids such as prostaglandins, leukotrines and cytokines .The regulation of these mediators secreted by macrophages and other immune cells[1]and modulation of arachidonic acid metabolism by inhibiting enzymes like Cox and LOX are the potential target for chronic inflammatory conditions[2].

RA is a complex process, involving synovial cell proliferation and fibrosis, pannus formation and cartilage and bone erosion. This process is mediated by an interdependent network of cytokines, prostanoids and proteolytic enzymes.

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Proinfalmmatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF-α), are central mediators in RA. This is illustrated in patients with RA, who experience an initial cell-mediated response that leads to the presence of elevated levels of IL-1 in the synovial fluid. Furthermore, IL-1 concentrations in the plasma have been reported to correlate with disease activity. It has also been demonstrated that patients with erosive RA have higher synovial and circulating levels of IL-1 than patients without erosions. Interleukin-6 (IL-6) is an inflammatory cytokine that is characterized by pleiotropy and redundancy of action, involved in inflammation, bone metabolism, immunity, endocrine functions and in particular it is a major regulator of the synthesis of acute phase reactants by the liver. IL-6 is produced by many different cells in the body including lymphocytes, monocyte, fibroblasts and endothelial cells. Adipose tissue is another major source of IL-6, accounting for about 30% of total circulating concentrations of IL-6 in healthy subjects**.** Excessive adipose tissue deposition leads to excessive production of IL-6, a high risk factor to the RA.Body mass index (BMI) is an established risk factor for knee osteoarthritis (OA).Weight loss can help to reduce the incidence of symptomatic knee OA [3].

GENERAL CONSIDERATION OF ARTHRITIS

RA can be classified as [4]

- Palindromic rheumatoid arthritis
- Juvenile rheumatoid arthritis
- Rheumatoid spondylitis
- Other types of arthritis
- Osteoarthritis

There are two types of osteoarthritis –

a) Primary osteoarthritis - It occurs in elderly.

b) Secondary osteoarthritis- It occurs at any stage.

- Ankylosing spondylarthritis
- Infectious arthritis
- It can be classified as fallows

a) Supportive arthritis

b) Tuberculous arthritis

c) Lyme arthritis

D) Viral arthritis

- Gout and Gout arthritis

Epidemiology[5]:

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**.**

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:

1. 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.

2. 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.

3. 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.

Symptoms[6]:

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.

Pathophysiology of rheumatoid arthritis

Pathogenesis process may develop in the following way:

RA starts in synovium, the membrane produces sac surrounding the joint. This sac containing synovial fluid which lubricate and cushioning the joints along with that supplies nutrients and oxygen to cartilage which coats the end of bones. Cartilage is made of collagen and gives support and flexibility to joints. In rheumatoid arthritis, destructive molecules produced by an abnormal immune system response which is responsible for continuous inflammation of the synovium. Collagen is gradually destroyed, narrowing the joint space and finally damaging bone. In a progressive rheumatoid arthritis, destruction of the cartilage accelerates. Further pannus (thickened synovial tissue) formation occurs due to the accumulation of fluid and immune system cells in the synovium. The pannus produces more enzymes which destroy nearby cartilage, worsening the area and attracting more inflammatory white cells as shown in Figure No 1

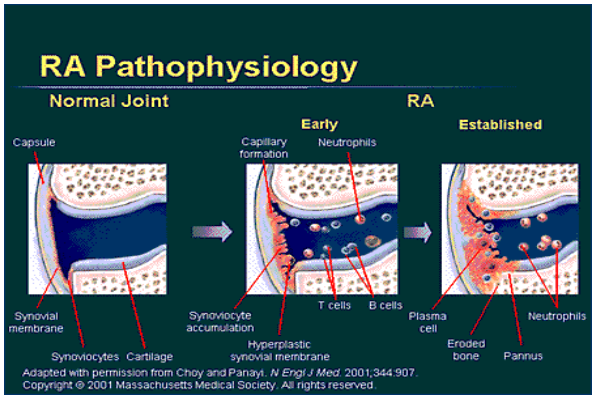
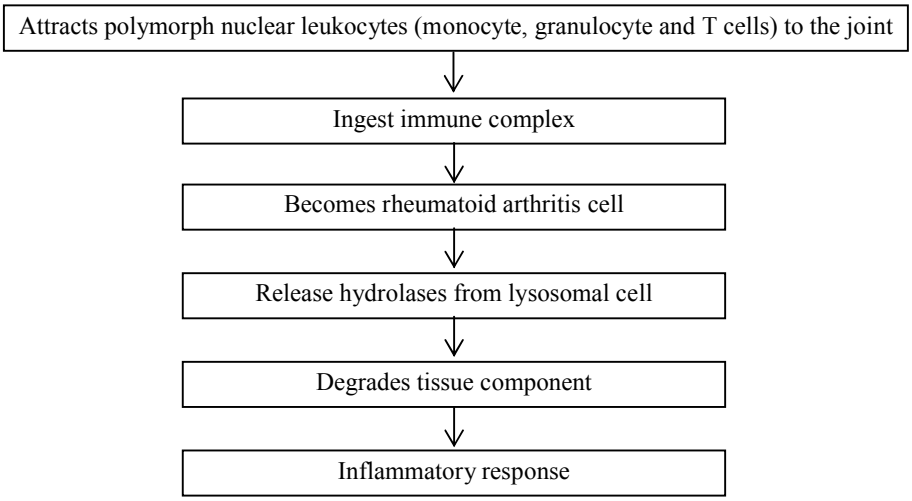


Figure 1: Pathophysiology of Rheumatoid arthritis

It shows Inflammation of Synovium in Rheumatoid arthritis.

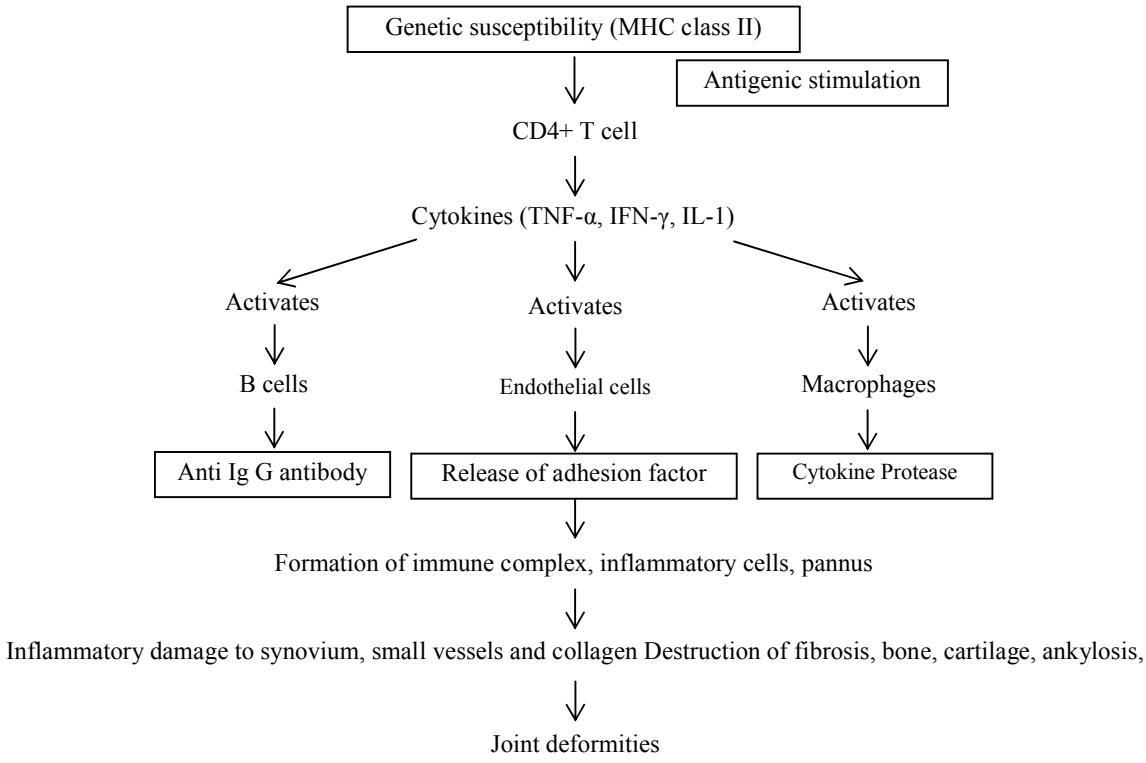
There are two most important components of immune system i.e. B cells and T cells lymphocytes that play important role in inflammation associated with rheumatoid arthritis. If the T cell recognizes an antigen as "non-self," it will produce chemicals (cytokines) which cause B cells to multiply and release antibodies circulate largely in the bloodstream, recognizing the foreign particles and triggering inflammation in order to rid the body of the invasion[7]. There are various steps involved in inflammatory responses in RA disease[8].



Steps involved in inflammation of RA

The rheumatoid joint contains a various pro-inflammatorycytokinesIL-1, IL-6, IL-8, IL-15, IL-16, IL-17, IL-18, IL-23, IFN-γ, TNF-α, granulocyte macrophage-colony stimulating factor, macrophage inflammatory protein-1 and monocyte chemo attractant protein-1, Anti-inflammatory cytokines, such as IL-4, IL-10, IL-11, andIL-13, and natural cytokine antagonists, including IL-1Receptor antagonist (IL-1ra), soluble type 2 IL-1 receptor, soluble TNF receptor (TNF-RI), and IL-18 binding protein are responsible for maintenance of balanced action of these pro-inflammatory cytokines, in normal physiological condition. In the rheumatoid joint, the balance swings towards the pro-inflammatory cytokines[9]. The recruitment of inflammatory cells to the inflammatory site can be up regulated by the expression of cell adhesion molecules on endothelial cells with the help of IL-1 and TNF-α. Both IL-1 and TNF-α activate a variety of inflammatory cell types found in the synovial, including macrophages, fibroblast, mast cell, neutrophils,chondrocytes, dendritic cells and osteoclasts, resulting in the release of other proinfalmmatory mediators and derivative enzymes. Both stimulate proliferation of synovial cells leading to pannus formation. Both cytokines influence immunological activity by causing T cell and B cell activation[10].

Step by step process in the pathogenesis of RA including various factors viz B cells, T cells, Cytokines etc.



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:

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

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.

Pharmacological Strategies:

Generally, a strategic treatment plan is employed for the treatment of the disease which includes four different classes of drugs: non-steroidal anti-inflammatory 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.

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

Ex: parcetamol, opiates, Diproqualone

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 enzyme[11].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[12]. 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[13]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.

Corticosteroids:

Ex: prednisone, prednisolone, methyl prednisolone

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[14]. Glucocorticoids can be especially useful in two conditions. Firstly, in treating the short term flare ups can lead to rapid improvement and allow other treatmentDMARDS 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.

Disease Modifying Anti-rheumatic Drugs (DMARDs):

Ex: Methotrexate, Leflunomide, Hydroxychloroquine, chloroquine, cyclosporine, sulfasalazine, gold salts.

Disease Modifying Anti-rheumatic Drugs commonly referred to as DMARDs do not, include any specific class of drugs but is a large and heterogeneous collection of various agents grouped together according to their use, convention and efficacy in treating arthritis[15].Their diverse mechanism of action are incompletely understood, they reduce joint swelling and pain, decrease acute phase markers, limit progressive joint damage, and improve function, When a patient is diagnosed with RA, the American college of rheumatology recommends initiation therapy with DMARDS within 3 months of diagnosis (in addition to NSAIDS, low –dose corticosteroids, physical therapy, and occupational therapy). Methotrexate is dominant DMARD, sulfasalazine and Leflunomide are widely used. Hydroxyl chloroquine and chloroquine have DMARDSlike properties, gold salts and cyclosporine are additional DMARDs, and their use is limited by toxic effects. DMARDs are sometimes combined, and several combinations of DMARDs have been proven efficacy. An example is methotrexate, sulfasalazine and hodroxy chloroquinetermed triple therapy. Use of DMARDs combinations varies across different countries; in some regions they are used rarely. Adverse effects of DMARDs include those that are minor e.g. (nausea) and serious e.g. (hepatotoxicity, blood dyscrasias, interstitial lung disease) monitoring of adverse effects requires pre-treatment screening and subsequent safety recording of blood counts and liver function tests[6].

Cytotoxic drugs:

Ex: Cyclophosphamide

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[16].

Biological therapies in rheumatoid arthritis:

Ex: Etanercept, infliximab, adalimumab, golimumab, anakinra, cetrolizumab, rituximab, abatecept

Biological agents for the treatment of disease includes the use of TNF-inhibitor, T- cell co-stimulatory blockers, B- cell depletion molecules, IL-1 receptor antagonist, etc. Interleukin -1 and TNF-α are proinfalmmatory cytokines involved in the pathogenesis of RA, when secreted by synovialmacrophages, IL1andTNFαstimulate synovial cell stoproliferate and syn thesize collagenase, thereby degradingcartilage,stimulatin gboneresorption,andinhibitingproteoglycosynthesis,TNFα inhibitors (Adalimumab, Etanercept, Golimumamab, Cetrolizumab and Infliximab). Have been shown to decrease signs and symptoms of RA, reduce progression of structural damage, and improves physical function clinical response can be seen within 2 weeks of therapy. If a patient has failed therapy with one TNF inhibitor, a trail with a different TNF inhibitor is appropriate. Many experts propose that a TNF plus methotrexate be considered as standard therapy for patients with rheumatoid and psoriatic arthritis. Indeed, TNF inhibitors can be administered with any of the other DMARDs, except for anakinra, IL-1receptor antagonist. Patients receiving TNF inhibitors are at increased risk for infections (tuberculosis and sepsis), fungal infections, and pancytopenia. Live vaccinations should not be administered while on TNF-α inhibitor therapy. Rarely demyelinating disorders and bone marrow suppression may occur. An increased risk of lymphoma and other cancers has been observed with the use of TNF-α.However, the risk of malignancies associated with these therapies has been hard to establish because the incidence is very low, and they are usually administered together with other treatments[16].

Complementary Alternative Medications (CAMs):

All the above mentioned therapies, which are employed heavily in the treatment of arthritis such as the use of NSAIDs, corticosteroids, DMARDs and biological agents are helpful in decreasing the joint stiffness, pain. But, one of the main drawbacks of using these drugs is that while they reduce the symptoms of the disease but the progression of the disease continues. All these drugs come with a line of side effects which includes gastrointestinal ulcers, osteoporosis, serious infections like sepsis, tuberculosis, development of various lymphomas etc. Hence, majority of the patients are seen to shift towards the CAMs[17] Once some remission in the disease is observed, which mainly includes meditation, yoga, exercises, dietary controls and phytochemical treatment approach etc.

New treatment:

New biological agents in development include drugs that target proximal effects on the immune response and growth factors for T-cell subsets(such as interleukin 17) new conventional drugs with DMARD like properties might also have important future roles. Clinical trials of inhibitors of the kinases JAK and SYK have provided promising data and other tother targets are under investigation[6].

Induction of arthritis in animal models

1. Complete Freunds Adjuvant Induced (CFA) Arthritis in Rats

Freund's complete adjuvant induced arthritis in rat model is the best and most widely used experimental model for arthritis. It is a T cell and neutrophil dependent and complement independent helper (Th) 1 and (Th) 17 inflammatory cytokines are associated CFA induced arthritis. Increased levels of TNFα, interferon γ (INFγ), IL1, IL6 and IL17A mRNA have been detected in this type of model. This model is sensitive to anti inflammatory and immune inhibiting medicines and best for the study of phathophysiological and pharmacological control of inflammation process as well as for the evaluation of anti-nociceptive potential of drug. AIA is not joint-specific but is associated with granuloma formation in various organs and tissues, such as the spleen, liver, bone marrow, skin and eyes[18].

Procedure

Animals are randomly divided into five groups of six animals. Group I served as controlled received normal saline. Standard and test groups are further divide into two sections of treatment i.e. Prophylactic (P) group (before induction of disease) and therapeutic (T) group (after induction of disease). Group II and Group III were standard group received Indomethacin (10 mg/kg p.o), Group IV and V were test group received the test drug[19]. On day zero animals are injected into the sub plantar region of the left hind paw with 0.1 ml of complete Freund's adjuvant (FA). This consists of 6mg Mycobacterium butyric suspended in heavy paraffin oil by through grinding with mortor and pestle to give a concentration of 6 mg/ml. Drug treatment is started from the 14th day i.e. from the day of adjuvant injection and continued till 28thday. The paw oedema and joint thickness is measured on 7th, 14th, 21stand 28thday by using digital verniercallipers or plethysmometer. The mean changes in injected paw oedema and joint thickness with respect to initial paw volume and joint thickness, are calculated on respective days and % inhibition of paw oedema and joint thickness with respect to untreated group are calculated using following formula.

Inhibition in paw edema / joint thickness = 100 x (1- Vt/ VC)

VC = Mean paw edema volume/ joint thickness in control group

VT = Mean paw edema volume/ joint thickness in the drug treated group

In radiological analysis, radiographs are taken by using X-ray apparatus. X-rays are taken at the joint of hind paw of the animal for evaluating the bone damage before sacrificing the animal. In histopathological analysis, the ankle joint of rats are removed and separated from the surrounding tissues. To examine the histopathological changes during the experimental period in all the groups under the light microscope, the joints are fixed in 10 % formalin and decalcified, sectioned and finally stained with eosin and hematoxyline[20].

2. Carrageenan Induced Paw edema in Rats

Carrageenan induced paw edema in rats (CRR) is most commonly used in animal model. CRR produces acute and chronic inflammatory responses. The acute response appears to be similar to rheumatoid arthritis lesion plens, which are characterized by sustained cellular emigration. Hydrolysed Carrageenan induces inflammation by inhibiting DNA synthesis, also effects on chromium release, and cell morphology retarded cell growth and eventually caused cell death[21].

Procedure

This method is simple and induced with 1% carrageen and measured paw volum within 6 h by plethysmometer. Acute inflammation is producing in all animals by sub plantar injection of freshly prepared suspension of 1% Carragenan an in 0.9 % normal saline on the left hind paw of rats. The paw volume of the tibio-tarsal articulation is measured by using plethysmometer. Increase in paw volume is determined at 0, 0.5, 1, 1.5,2, 3, 4, 5, 6h[22].

The % inhibition in paw volume is calculated by using following formula:

% inhibition in paw volume= 100 x (1-Vt/Vc)

VT: mean paw volume in control group

VC: mean paw volume in drug treated group

3. Formaldehyde Induced Arthritis

Principle

Swelling around the ankle joint and paw of arthritic rat is considered to be due to the oedema ofParticular tissue such as ligament and capsule[22]. The development of oedema in the paw of the rat after injection of formaldehyde is due to the release of histamine, serotonin and the prostaglandin like substances at the site of injection[2]. Formaldehyde induces arthritis by denaturing protein at the site of administration, which produces immunological reaction against the degraded product[23].

Procedure

Animals are divided into four groups of six animals, Group I served as controlled received 0.5% CMC, Group II received Indomethacin (10 mg/kg p.o.) served as standard, Group III and IV received the test drug. Rats are injected with 0.1 ml of a formaldehyde solution in the sub planter surface of a left hind paw, on 1st and 3rd day of a test. Test and standard are administered orally once a day for 10 days. The rat paw thickness is measured daily for 10 days. The present inhibition of mean increase in the paw oedema of each group is calculated on 10 th day and compared with the control. The paw oedema is measured using digital verniercallipers or plethysmometer[24].

4. Collagen Type II Induced Arthritis (CIA) In Rats

Principle

CIA model is standard animal model of RA. It is a complement dependent. There are three different cartilagederived proteins are responsible for induction of arthritis in rats i.e. collagen type II, collagen type XI, and cartilage oligomeric matrix protein. To study mechanism of immune response to auto antigen which are generally involved in human disease, it is an excellent model. Induction of collagen arthritis in many strains of rats by immunizing them with type II collagen emulsified in Incomplete Freund's Adjuvant (IFA). After the induction of disease there is development of both cellular and humoral immune response to type II collagen, which can be passively transferred by sensitized spleen and lymph node cells as well as IgG antibodies to type II collagen. Collagen arthritis is an immunologic hypersensitivity to type II collagen. After introduction of collagen type II into the dermis, immediately captured by antigen presenting cells (APCs). In this type of disease activation of both T & B cells are antigen-specific & auto reactive. T cell and T cell-derived cytokines promote differentiation and activation of macrophages, osteoclasts and fibroblast causes development of an aggressive erosive arthritis.18CIA is genetically controlled by expression of Class II major histocompatibility complex (MHC) molecules, specifically I-Aq and I-Ar in the mouse [18].

Procedure

Type II collagen is dissolved in a 10 mM (4 mg/ml) acetic acid overnight at 4°C. After that solution is emulsified in an equal volume of chilled Complete Freund's adjuvant and mixed for 30 minutes at 1000 rpm with homogenizer. Induction of arthritis is done by a subcutaneous injection of 100 µl of emulsion (BnCII 100 mg + CFA 100 mg) into the plantar surface of paw. On day 7 after the first adjuvant injection, rats are boosted intradermally into the base of tail with a same volume of the emulsion. Animals are dividing into 3 groups of 6 rats each. Control animals receive only the Complete Freund's adjuvant diluted with 10mM acetic acid. Standard group receive Indomethacin (10 mg/ kg) orally. Drug treatment to standard and test group started from the 18thday after chronic infection of disease and continued till 36th day. The volume of both hind paws is measured plethysmographically[25].

5. Pristane induced arthritis (PIA)

PIA in rats is a chronic, symmetrical model that mimics many of the aspects of the human disease. PIA is induced in susceptible rats with the mineral oil pristane. Disease symptoms start to appear after 7-10 days. The experiment can be terminated around day 30 after induction. PIA is T cell driven and dependent on MHC but thus far no antigen has been identified in PIA. This disease is also transferrable by T cells allowing direct studies of T cell arthritogenicity ex vivo[26].

6. Oil-induced arthritis (OIA)

OIA develops approximately 14 days after the intradermally injection of IFA.

In this a mild monophonic jointinflammation develops in the hind paw and ankle which can progress to front paws. Disease subsides before day 45[27].

7. Streptococcal cell wall-induced arthritis

A single intraperitoneal injection of an aqueous suspension of cell wall peptidoglycan-polysaccharide fragments from streptococci and several other types of bacteria into susceptible rat strain, male Lewis rats, induces severe erosive arthritis. An acute, thympicdependent,Compliment-dependent phase develops within 24h [28].

8. Aureus-induced septic arthritis

To induce arthritis the intravenous injection of live bacteria (S.aureus) suspension is given to susceptible strain of mice in lateral tail vein of each mouse. To evaluate the intensity of arthritis, a clinical scoring (arthritic index) is used as previously described[29].

Daphne genkwa

Cui-Ping Jiang et.al, (2014) reported that anti-rheumatoid arthritic activity of flavonoids from *Daphne genkwa* .Flavonoids of *Daphne genkwa*were extracted by refluxing with ethanol and purified by polyamide resin tested for its anti arthritic activity by various models namely Carragenan-induced paw oedema model ,tampongranuloma model and complete freunds adjuvant induced arthritis model.FFD significantly reduced the degree of acute inflammatory paw oedema in mice as a response to Carragenan administration.FFD also inhibited chronic inflammation in adjuvant induced arthritis rats when administered orally at the dose of 50mg/kg /day.FFD suppressed the production of NO and exhibited immunoregulatory function and revealed conspicuous antioxidant activity. Their investigation concluded that the FFD possesses significant anti-inflammatory and anti oxidant activity, which could be a potential therapeutic agent for rheumatoid arthritis[30].

Vitexnegundo

Cheng-jian zheng et.al, (2014) reported that therapeutic effects of standardized *vitex negundo* seeds extract on complete freunds adjuvant induced arthritis in rats. The ethanolic extract of *vitex negundo* seeds 85 and 340mg/kg were tested for its anti arthritic activity by adjuvant induced arthritis. The results suggest that the ethanolic extract of *vitex negundo* seeds possess a potential anti arthritic activity and therefore may be an effective cure for the treatment of human rheumatoid arthritis[31].

Genkwa flos

Chun-Feng Zhang et.al, (2014) reported that antioxidant effect of *Genkwa flos* flavonoids on freunds adjuvant-induced rheumatoid arthritis in rats. To evaluate the antioxidative effects of flavonoids aglycones (FA) isolated from the *Genkwa flos* were tested for its anti arthritic activity by adjuvant induced arthritis .FA significantly decreased paw oedema, arthritic score, and increased body weight .the results conclude that FA significantly decreased arthritis in a rat model through anti oxidant and haematological modulatory mechanisms .The *Genkwa flos* flavonoids may have clinical potential for the treatment of rheumatoid arthritis[32].

***Mentha arvensis* Linn**

Dhinek Prasath, Saranya Palanisamybb (2014) reported that anti inflammatory and anti arthritic activity of methanolic leaf extracts of *Mentha arvensis* Linn in arthritis induced male albino rats, the methanolic extract of mint leaves 150&200 mg/kg b.w were tested for its anti inflammatory and anti arthritic activity by complete freunds adjuvant induced arthritis. Evaluation of haematological parameters such as Hb%, WBC, ESR and RBC. Serum parameters and liver marker enzymes such as ALT, AST, ALP, urea, uric acid, and creatinine are also estimated for assessing the anti inflammatory and anti arthritic activity of methanolic extract of *Mentha arvensis* .their investigation conclude that the methanolic extract of *Mentha arvensis* posses a significant anti inflammatory and anti arthritic activity[33].

***Commiphora caudate* linn**

Girijapashikanti et.al, (2014) reported that the anti arthritic activity of ethanolic extract from the leaves of *commiphora caudate* linn in complete freunds adjuvant induced arthritic rats. The ethanolic extract of commiphora *caudate*leaves 200 and 400mg/kg were tested for its anti arthritic activity. Their investigation concluded that the ethanolic extract of *commiphora caudate*leaves have potential anti arthritic activity[34].

***Cynodandactylon* (L) pers**

Jitendra Bhang ale and Sanjeev Acharya (2014) reported that anti-arthritic activity of *Cynodan dactylon* (L) pers. The ethanolic extract of leaves of *Cynodan dactylon* (L) 100,200 and 400mg/kg were tested for its anti- arthritic activity by complete freunds adjuvant induced arthritis. The *Cynodan dactylon* (L) significantly reduces the ankle diameter, clinical severity and significantly increased body weight. Their investigation concluded that the ethanolic extract of leaves of *Cynodan dactylon* (L) at dose of 400mg/kg is effective in improving haematological level, CRP and reducing TNF-α level. The results support the traditional uses of the plant in the treatment of rheumatoid arthritis[35].

Jatropha curcas

Hanif Nasiatul Baroroh et.al (2014) reported that *Jatropha curcas* leaves exert anti-arthritic activity on adjuvant-induced arthritis in rats. The ethanolic extract of *J. curcas* leaves at doses of 150 mg/kg, 300 mg/kg and 600 mg/kg were tested for its anti- arthritic activity by adjuvant induced arthritis The *J. curcas* leaf extract at doses of 150, 300 and 600 mg/kg BW decreased mobility scores. Histopathology studies showed that the *J. curcas* extract reduced oedema and cartilage destruction in arthritic joints. The result suggests that *Jatropha curcas* leaves extract had potential anti arthritic activity[36].

Euphorbia thymifolia linn

G.C. Mamatha et.al, (2014) reported that anti-arthritic activity of *Euphorbia thymifolia linn* The Petroleum ether (40-60°C), Chloroform, Alcohol, Aqueous extract of *Euphorbia thymifolia* were tested for various preliminary phyto constituents and were screened for anti-arthritic activities using Freund's adjuvant arthritis in albino rats Lipid per oxidation in liver and effect of gastric mucosa were also estimated for assessing anti-arthritic activity the results suggest that the *Euphorbia thymifolia Linn* possess anti-arthritic activity[37].

***Colocasiaesculenta*linn**

Kumbhar C. M et.al, (2014) reported that Prophylactic effect of Hydro alcoholic extract of *Colocasia esculenta* leaves in CFA and Formaldehyde induced arthritic rats. The extract reduces the paw volume and paw diameter and increases body weight. Serum parameters such as SGOT,SGPT, ALP are also estimated for assessing anti arthritic. The observed anti arthritic activity may be due to the presence of phytoconstituents such as alkaloid and flavonoids[38].

***Sterculiatragacantha (*Lindl)**

Udegbunam Rita Ijeoma et.al, (2014) reported that evaluation of the anti arthritic effect of *Sterculiatragacantha (*Lindl) leaf extract in rats. Evaluation of haematological parameters such as RBC, WBC, Hb%, ESR. The Liver enzymes like ALT, ALP, AST and antioxidants SOD, CAT and GSH are also estimated for assessing anti arthritic activity. The results concluded that the methanolic leaf extract of *Sterculiatragacantha (*Lindl) have potential anti arthritic activity[39].

***Oroxylumindicum*(L.)**

Mamatha Karnatiet.al, (2013) reported that Anti-arthritic activity of root bark of *Oroxylum indicum* (L.) vent against adjuvant-induced arthritis. The chloroform, ethyl acetate and n-butanol extracts of root bark of *Oroxylum indicum* were tested for its anti-arthritic activity by freunds adjuvant induced arthritis. The relative percentage inhibition potential of paw volume in rats treated with various extracts of *Oroxylum indicum* was found to be ethyl acetate extract (67.69%) >chloroform extract (64.61%) >n-butanol extract (58.46%) respectively. The haematological parameters like RBC count, haemoglobin content showed significant increase while there was a significant decrease in total WBC count and ESR in all the groups of animals pre-treated with root bark extracts.The present study suggests that the chloroform, ethyl acetate and n-butanol extracts of root bark of *Oroxylum indicum* exhibit anti-arthritic activity. The order of activity of extracts was found to be ethyl acetate >chloroform >n-butanol respectively[40].

***Litsea cubeba* (lour)**

Lu-Ping Qin et al., (2013) proved that Inhibitory effects of the root extract of Litsea cubeba (lour.) person adjuvant arthritis in rats. Results indicate that extract of *Litseacubeba* root significantly attenuates adjuvant arthritis in rats by decreasing the levels of TNF-α, IL-1β andIL-6andincreasingofIL-10inserumaswellas down-regulate the levels of inflammatory enzymes such as COX-2 and 5-LOX. This suggests that *Litsea cubeba* root might be used as a therapeutic agent for the treatment of human arthritis[41].

Tripterygium wilfordii Hook.

Lidian Chen et al., (2013) reported that Therapeutic effects of total alkaloids of *Tripterygium wilfordii Hook f.* on collagen-induced arthritis in rats. ATW could significantly reduce paw swelling and suppresses articular cartilage degenerated. The results also found that there was a significant reduction level of IL-6, IL-8 andTNF-a in serum of CIA rats treated with ATW and ATW inhibited the expression of IL-6, IL-8, NF-kB, TNF in synovial tissue. ATW would be a drug as a novel botanical drug for the treatment of RA[42].

Cinnamomum zeyllanicum

SachinVetal et.al, (2013) reported that anti-inflammatory and anti-arthritic activity of type-A procyanidine polyphenols from bark of *Cinnamomum zeyllanicum* in rats. TAPP showed significant anti-inflammatory effect in CPE model. TAPP treatment in established arthritic rats showed significant reversal of changes induced in AIA with respect to body weight drop, ankle diameter, arthritic score, and serum C - reactive protein levels and evaluate hematological parameters like RBC, WBC, ESR, Hb% for assessing anti arthritic activity. Their investigation concluded that TAPP from CZ have potential anti-inflammatory and anti- arthritic activity[43].

Aconitum Vilmorianum ,Aconitum Radix, AconitiKusnezoffii Radix

Ming Li et.al, (2013) reported that the anti-arthritic effects of *Aconitum Vilmorianum*, a folk herbal medicine in south western china .The ethanolic extract of *Aconitum Vilmorianum*(10 and100mg/kg)*Aconitum Radix* (100mg/kg))*AconitiKusnezoffii Radix*(100mg/kg)were tested for its anti arthritic activity by complete freunds adjuvant induced arthritis. The results showed that *Aconitum Vilmorianum* (10 and100mg/kg)*Aconitum Radix* (100mg/kg)*AconitiKusnezoffii Radix*(100mg/kg) suppressed joint allodynia*Aconitum Vilmorianum* (10 and100mg/kg)*AconitiKusnezoffii Radix*(100mg/kg) significantly reduced joint swelling and hyperaemia while*Aconitum Radix* (100mg/kg)did not*Aconitum Vilmorianum* (100mg/kg) attenuated vascular permeability while *Aconitum Radix* (100mg/kg)*AconitiKusnezoffii Radix*(100mg/kg) showed no improvement. Their investigation concluded that the ethanolic extract of *Aconitum Vilmorianum*possess a potential anti arthritic activity compare to other herbs[44].

Asparagus racemosus

Suchita Mittal and Praveen K. Dixit (2013) reported that anti-inflammatory and anti-arthritic activity of *asparagus racemosus* roots. The hydro alcoholic extract of *Asparagus racemosus* roots (ARHE) *in-vivo* 200 and 400mg/kg were tested for its anti-inflammatory and anti-arthritic activity by Carragenan induced paw edema methodology is used to induce inflammation whereas Freund's Complete adjuvant used to induce arthritis .The extract reduces paw volume, joint diameter, arthritic score and estimate the hematological parameters like RBC, WBC, ESR Hb% for assessing arthritic activity. Their investigation concluded that the hydro alcoholic extract of *Asparagus racemosus* roots (ARHE) showed significant anti-inflammatory and anti-arthritic activity[45].

Luffaechinata Roxb

Sanjeev sing et.al, (2013) reported the Evaluation of antiarthritic activity on *Luffaechinata Roxb.* Fruits on rats the aqueous extract (LEFAE) and the alcoholic extract (LEFEE) of *Luffaechinata Roxb.* Fruits were tested for its anti arthritic activity by Freund's complete adjuvant (FCA) induced arthritis. The LEFEE and LEFAE treated groups, showed significant reduction in paw volume and normal gain in body weight and altered the hematological parameters (Hb, RBC, WBC and ESR) in the arthritic rats were significantly brought back to near normal by the LEFEE and LEFAE treatment at the dose of 250 mg/kg/p.o in both developing and developed phases of arthritis.The results of the current investigation concluded, ethanol extract of *Luffaechinata Roxb.* Fruits, extract possess a significant anti-arthritic activity against adjuvant induced arthritis[46].

Barringtoniaacutangula (L) Gaertn

M. Thirumal et.al,(2013) reported that anti arthritic activity of chloroform extract of *Barringtonia acutangula (L) Gaertn*. Leaves on Wister rats. The chloroform extract of the leaves of *Barringtonia acutangula (L) Gaertn* 200 and 400mg/kg were tested for its anti-arthritic activity. The CEBA significantly reduces the paw oedema and decreases the levels of inflammatory mediators. This suggests that *Barringtonia acutangula (L*) leaves are mightbe usedfor the treatment of human arthritis[47].

Hybanthusenneaspermus.

S.Tripathy et.al, (2013) reported that evaluation of anti arthritic potential of *Hybanthusenneaspermus.* The alcoholic and aqueous extract of whole plant of *Hybanthusenneaspermus* were tested for its anti arthritic activity. The percentage yield was found to be 12.8% and 10.6% for alcoholic and aqueous extracts respectively. Both the extracts significantly decrease the paw thickness. Though in acute phase inflammation both of them show the same potency in chronic phase alcoholic extract exhibit more potency than the aqueous extract. The results concluded that the alcoholic extract shows more pronounce effect on arthritis as comparable to aqueous extract[48].

Tribulus terrestris

N. K. Mishra et. al, (2013) reported that anti-arthritic activity of Tribulus terrestris studied in freunds adjuvant induced arthritic rats. The methanolic extract of Tribulus terrestris fruit200and 300mg/kg were tested for its anti arthritic activity by complete freunds adjuvant induced arthritis. The herbal extract significantly reduces the paw volume and estimated the haematological parameters like WBC, Hb%, ESR, alkaline phosphate and acid phosphate for assessing anti arthritic activity. The results indicated that the methanolic extract of Tribulus terrestris at dose300mg/kg has better anti arthritic activity[49].

***Lipidiumsativum*Linn**

Raval Nita D et. al, (2013) reported that evaluation of anti arthritic activity of *Lipidiumsativum* Linn seeds against freunds adjuvant induced arthritis in rats .The suspension of*Lipidiumsativum L*inn seed powder was made with sufficient quantity of distilled water, the suspension of 550and 110mg/kg were tested for its anti arthritic activity . The rat paw oedema, histopathological and radiological studies were evaluated for assessing anti arthritic activity. Their investigation concludes that the lower dose, moderate dose anti arthritic effect was produced by the test drug while at a higher dose it had a tendency to produce inconsistent effect[50].

Boerhaaviadiffusa

Gyanesh Kumar et. al, (2013) reported that anti arthritic activity of root extract of *Boerhaaviadiffusa* in adjuvant induced arthritis in rats. The petroleum ether extract of root of the *Boerhaaviadiffusa*500 and 1000mg/kg p.o were tested for its anti arthritic activity by complete freunds adjuvant induced arthritis .Administration of the extract reported significant reduction in paw swelling and paw diameter using digital plethysmometer. The results concluded that the extract of *Boerhaaviadiffusa* possess a potential anti arthritic activity[51].

Cissusquadrangularis*and *Justiciatranquebariensis

S. Akilandeswari et. al, (2013) reported that Anti Arthritic Activity of *Cissus quadrangularis*and *Justiciatranquebariensis*in the Treatment of Rheumatism. The ethanolic plant extract of *Cissusquadrangularis*and *Justiciatranquebariensis*100 and 200mg/kg were tested for its anti- arthritic activity by Freund's adjuvant induced arthritis model; the plant extracts significantly reduced the arthritis of affected joint. The biochemical parameters like SGOT.SGPT.ALP are evaluated haematological parameters such as RBC, WBC, ESR, Hb% are also estimated for assessing anti arthritic activity. The results revealed the potential ofplant extract in the management of inflammation and arthritis confirming the folk core use of medicinal plants[52].

***Hibiscus plantifolius* Linn.**

Marri Praveen, M. Janarthan et. al, (2013) reported that evaluation of anti arthritic activity of aqueous extract of *Hibiscus plantifolius* Linn in albino rats. The aqueous extract leaves of *Hibiscus plantifolius* Linn 200 and400 mg/kg were tested for its anti arthritic activity by turpentine oil and complete freunds adjuvant induced arthritis. The results indicated that AEHP reduces the degree of inflammation .the haematological parameters such as RBC, WBC, ESR, Hb% are evaluated. It also estimated by liver marker enzymes like ALT, AST,ALP, creatinine urea and uric acid for assessing the anti arthritic activity. Their investigation concluded that the aqueous extract leaves of *Hibiscus plantifolius* Linn possess a potential anti-arthritic activity[53].

Asystasia Dalzelliana

Vishal Babushetty al., (2012) reported that Evaluation of Anti-Arthritis Activity of Asystasia Dalzelliana Leaves. Paw edema, changes in organ weight, serum parameters such as SGOT, SGPT and ALP were estimated. Hind paw of experimental rats were also subjected for radiographic and histopathological examination for assessing the anti-arthritis potential of ethanolic extract of *Asystasia Dalzelliana*leaves. Their investigation concluded that extract of dose of 800mg/kg possess a significant anti-arthritis activity than the lower doses of 200mg/kg and 400mg/kg[54].

Costus speciosus

Shruti Srivastava et.al, (2012) reported that Evaluation of anti-arthritic potential of the methanolic extract of the aerial parts of Costus speciosus. The methanolic extract of the aerial parts of Costus speciosus were tested for its anti arthritic activity by complete freunds adjuvant induced arthritis.. The methanolic extract of CS in doses of 400 and 800mg/kg showed 75.80%and 68.33% protection against increase in paw edema. Evaluation of hematological parameters Like hemoglobin content, total WBC count, Differential WBC count, ESR, RBC, and serum parameters SGOT, SGPT, ALP are also estimated for assessing anti-arthritic activity The results indicated that CS have potential anti- arthritic properties[55].

Barlerialupulina

Papaya Mitra Mazumder *et.al, (*2012) reported that evaluation of anti arthritic and immunomodulatory activity of *Barleria lupulina*leaves. The methanolic extract of *barlerialupulina*leaves 300 and 600mg/kg b.w

were tested for its anti arthritic activity by various inducing models namely, formalin –induced arthritis, complete freunds adjuvant induced arthritis and collagen type II induced arthritis. Immunomodulatory activity of the same was evaluated by haematological parameters Hb%, WBC count, ESR, DTH, spleen weight. It also estimated by serum parameters such as serum albumin, total protein, calcium and phosphorus levels and antioxidants like SOD, CAT, GSH are also estimated for assessing the anti arthritic potential of methanol extract of *Barlerialupulina.* Their investigation concluded that the methanol extract of *Barlerialupulina* possess a significant anti arthritic activity[56].

***Merremiaemarginata*Burm. F.**

Purushoth Prabhu et. al, (2012) reported that anti-inflammatory, anti arthritis, analgesic effect of ethanolic extract of whole plant of *Merremia emarginata* Burm.F. The results concluded that the ethanolic extract of whole plant of400 mg/kg *Merremia emarginata* Burm.F showed potent anti-arthritic activity[57].

***Portulacaoleracea*Linn.**

B. Mallikarjun Rao et. al, (2012) reported that evaluation of anti- arthritic activity of petroleum -ether extract of *Portulaca oleracea*Linn. The petroleum-ether extract of *Portulaca oleracea*Linn100, 200 and 300mg/kg were tested for its anti- arthritic activity by freunds adjuvant arthritis model. The*Portulaca oleracea significantly* suppress the IL-1, IL-6, and TNF-α, paw swelling and increases the body weight. The haematological parameters such as WBC, RBC, Hb%, ESR are also estimated for assessing anti-arthritic activity. The results concluded that the petroleum-ether extract of *Portulaca oleracea*Linn has a potential anti-arthritic activity can be used as anti-arthritic drug[58].

***Hemidesmusindicus*R.Br. (Anantmul)**

Alka Mehta et.al (2012) reported that Anti-arthritis activity of roots of *Hemidesmusindicus*R.Br. (Anantmul)in rats. The hydro alcoholicextract and its three fractions namely ethyl acetate, chloroform fraction and residual fraction ofroots of *Hemidesmusindicus* were tested for its anti arthritic activity by freunds adjuvant induced arthritis. Rats treated hydro alcoholic, ethyl acetate fraction, chloroform fraction and residual fraction significantly decrease the paw edema and increase body weight. The hematological parameters like RBC, WBC, ESR, Hb% are evaluated and serum parameters such as ALT, AST, ALP, and C - reactive protein and serum nitrite are also estimated for assessing anti arthritic activity. The results showed that the roots of Hemidesmusindicus have potential anti arthritic activity and the activity might be presence of Terpenoids in hydro alcoholic, as well as in ethyl acetate fraction[59].

LIST OF HERBS USED IN RHEUMATOID ARTHRITS

S. No	Name of the plant	Family	Part used	Experimental model	References
1.	*Aristolochiabraceata*	Aristolochiaceae	Whole plant	FCA	Chitme, H.R., Patel, N.P.,[60]
2.	*Ammaniabacifera*	Lytraceae	Wholeplant	CFA	Tripathy S etal.,[61]
3.	*Boswellia serrata*	Burseraceae	Whole plant	CFA	Mishra NKet al.,[62]
4.	*Capparisspinosa*	Capparidaceae	Fruit	AIA	Feng X et al.,[63]
5.	*Cassia uniflora*	Caesalpiniaceous	Stem	CFA	Sheetal SC etal.,[64]
6.	*Centellaasiatica*	Mackinlayaceae	Leaves	PD	Chippada SC, MeenaV[65]
7.	*Cleome rutidosperma*	Capparidaceae	Aerial parts	CFA	Chakraborty AK, Roy HK[66]
8.	*Cocculus hirsutus*	Menispermaceae	roots	FCA	Bothara SB etal.,[67]
9.	*Delonixelata*	Fabaceae	Bark	CFA	MuruganantanG,Mohan S[68]
10.	*Elaeocarpus*sphaericus	Elaeocarpaceae	fruit	FCA	Ramasamy, S etal.,[69]
11.	*Euphorbia atiquorum*	Euphorbiaceae	Whole plant	CFA	Harpalani AN etal.,[70]
12.	*Ficusbengalensis*	Moraceae	Stem bark	FCA	Manocha, N et al[71]
13	*Glycirrhizaglabra*	Fabaceae	Rhizomes	CFA	Mishra NK etal.,[62]
14	*Glycosmispentaphylla*	Rutaceae	Stem bark	FCA	Ramesh, P.R., Vijaya, C[72]
15	*LawsoniaInnermis*	Lythraceae	Leaves	FIA,CFA	Kore KJ et al.,[2]
16	*Machalis macrantha*	Lauraceae	Bark	FCA	Tatiya, A.U., Saluja, A.K[73]
17	*Phyllanthusamarus*	Euphorbiaceae	Herbs	CFA	Mali SM et al.,[74]
18	*Pistiostratios*	Araceae	Leaf	CFA	Samuel K et al.,[75]
19	*Pongammiapinnata*	Fabaceae	Leaves	FCA	Arote, S.R., Yeole, P.G[76]
20	*Punica grantum*	Punicaceae	Seeds	FCA	Kothari A etal.,[77]
21	*Randiadumetorum*	Rubiaceae	Fruit	FCA	Patel, R.G. etal.,[78]
22	*Ricinuscommunis*	Euphorbiaceae	Leaves	CFA	Kabra MP et al.,[79]
23	*Strychnospotatorum Linn*	Loganiaceae	Seeds	CFA	Ekambaram etal.,[80]
24	*Saussaurealappa*	Compositae	Roots	CFA	Uma Chandur, S etal.,[81]
25	*Sidarhombifolia*	Malvaceae	Aerial parts	AIA	Gupta, S.Retal.,[82]
26	*Tinosporacardifolia*	Menispermaceae	Leaves	FCA	Paval j etal.,[83]
27	*Urticapilulifera*	Urticaceae	Leaves	FCA	Abudoleh S etal.,[84]
28	*Urgeniaindica*	Liliaceae	Bulb	CPM	Rehman MM etal.,[85]
29.	*Vernoniaanthelmintica*	Asteraceae	Seeds	FCA	Otari KV etal.,[86]
30.	*Wedeliacalendulaceae*	Asteraceae	Leaves	CFA	Panchal AH etal.,[87]

CONCLUSION:

Indian sub-continent is a rich source of plant & animal wealth which is due to its varied geographical and agro climate regions. It is a well known fact that traditional system of medicines always played important role in meeting the global health care needs. Arthritis is one of the most common auto-immune inflammatory disorders, foremost cause of disability in western and developing countries. The presently available synthetic drugs in the market are not only economical exploitation but also associated with adverse effects. The synthetic drugs includes NSAIDS and DMARDS like Cyclophosphamide, intramuscular gold, sulfasalazine, Metho-trexate had the side effects of stomach ulcers, GIT bleeding, kidney, liver damage and hypertension.

The given plant provides essential compounds with active principles, having no or minimum side effects and may be useful for arthritis control. From the above review it should be manifest that there are many medicinal plants which exert anti-arthritic activity at a particular dose. It is conclude that isolation of lead compound which is responsible for improving the better treatment of the arthritis

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