International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1363-1371 www.ijprajournal.com ISSN: 2249-7781

Rheumatoid Arthritis

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Submitted:25-07-2023 Accepted: 05-08-2023

ABSTRACT
Rheumatoid arthritis (RA) is a chronic inflammatory and systemic autoimmune disease that primarily affects adults aged 20 to 50 years old and has an unpredictable course. It affects around 1% of the world's population and is two to three times more frequent in women than males. There are several forms of arthritis. The presence of pro-inflammatory markers, cytokines, and leukotrienes causes rheumatoid arthritis. IL-1, TNF-, IL-6, IL-15, IL-16, IL-17, IL-18, IFN-, and granulocyte macrophage-colony stimulating factors are the key inflammatory indicators, as are chemokines such as IL-8, macrophage inflammatory protein-1, and monocyte chemoattractant protein-1. TNF-blockade, IL-1 blockade, B cell therapy, IL-6 blockage, and Angiogenesis blockade are some of the therapeutic targets for its treatment. To assess the anti-arthritic efficacy of plants, various animal models are employed to generate arthritis in rats. From time immemorial, medicinal plants have been employed as primary sources of clean cures for human ailments. Nowadays, traditional medicine is used by one-fourth of the world's population, while indigenous medicinal herbs are used by 80% of the population. Even today, owing to the low or no adverse effects, most people in underdeveloped nations rely on plant-derived medications as the first line of primary health care. A review of the prospective study on plants for antiarthritic activity has been conducted.
Keywords: Rheumatoid arthritis, animal models, Anti-arthritic potential, cytokines

I. INTRODUCTION

Rheumatoid arthritis is a chronic, systemic inflammatory disease that primarily affects the joints and periarticular tissue. RA is still a formidable disease, capable of causing severe crippling deformities, functional disabilities, and cartilage destruction, and frequently results in significant disability, caused by several pro-inflammatory molecules released by macrophages, including reactive oxygen species and eicosanoids such as prostaglandins, leukotrienes, and cytokines. Chronic inflammatory disorders may benefit from the control of these mediators released by macrophages and other immune cells, as well as the manipulation of arachidonic acid metabolism by blocking enzymes such as Cox and LOX . RA is a complicated condition characterized by synovial cell proliferation and fibrosis, pannus development, and cartilage and bone degradation. An interconnected network of cytokines, prostanoids, and proteolytic enzymes mediates this process. Proinflammatory cytokines including interleukin-1 (IL-1) and tumor necrosis factor (TNF-) are key players in RA.

This is seen in RA patients, who have an initial cell-mediated response that results in higher levels of IL-1 in synovial fluid. Additionally, IL-1 concentrations in the blood have been linked to disease activity. It has also been shown that patients with erosive RA had greater levels of IL-1 in their synovium and blood than individuals without erosions. Interleukin-6 (IL-6) is an inflammatory cytokine with pleiotropy and redundancy of functions involved in inflammation, bone metabolism, immunity, and 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 for Rheumatoid arthritis. Body mass index (BMI) is an e3stablished risk factor for knee osteoarthritis (OA). Weight loss can help to reduce the incidence of symptomatic knee OA .

General Consideration of Arthritis

RA can be classified as

- 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

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1363-1371 www.ijprajournal.com ISSN: 2249-7781

people.
b) Secondary osteoarthritis- It occurs at any stage.

- Ankylosing spondylarthritis
- Infectious arthritis

It can be classified as follows
a) Supportive arthritis.
b) Tuberculous arthritis.
c) Lyme arthritis.
d) Viral arthritis

Epidemiology:

The prevalence of rheumatoid arthritis (RA) varies between 0.3% and 1% worldwide and is more in developed countries. It mainly affects women more 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 a 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 is probably a prerequisite for the onset of RA. The factors are:

Environmental factors:

Consistent data are 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, the peak incidence is observed in the perimenopausal, 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.

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 include

- Morning stiffness that lasts 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

The pathogenesis process may develop in the following way :

RA starts in the synovium, the membrane produces a sac surrounding the joint. This sac contains synovial fluid which lubricates and cushions the joints along with that supplies nutrients and oxygen to the cartilage which coats the end of bones. Cartilage is made of collagen and gives support and flexibility to joints. In rheumatoid arthritis, destructive molecules are 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 progressive rheumatoid arthritis, the 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 that destroy nearby cartilage, worsening the area and attracting more inflammatory white cells.

It shows the Inflammation of Synovium in Rheumatoid arthritis.

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

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Attracts polymorph nuclease leukocytes (Monocyte, granulocyte & T-Cells) to the joint

Injest immune complex

Becomes rheumatoid arthritic cell

Release hydrolases from lysosomal cell

Degrades tissue component

Inflammatory response

The rheumatoid joint contains a various proinflammatorycytokinesIL-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 chemoattractant 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, 9in normal physiological condition. In the rheumatoid joint, the balance swings towards the pro-inflammatory cytokines . The recruitment of inflammatory cells to the inflammatory site can be upregulated 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, fibroblasts, mast cells, neutrophils, chondrocytes, dendritic cells, and osteoclasts, resulting in the release of other proinflammatory mediators and derivative enzymes. Both stimulate the proliferation of synovial cells leading to pannus formation. Both cytokines influenceimmunological activity by causing T cell and B cells activation.

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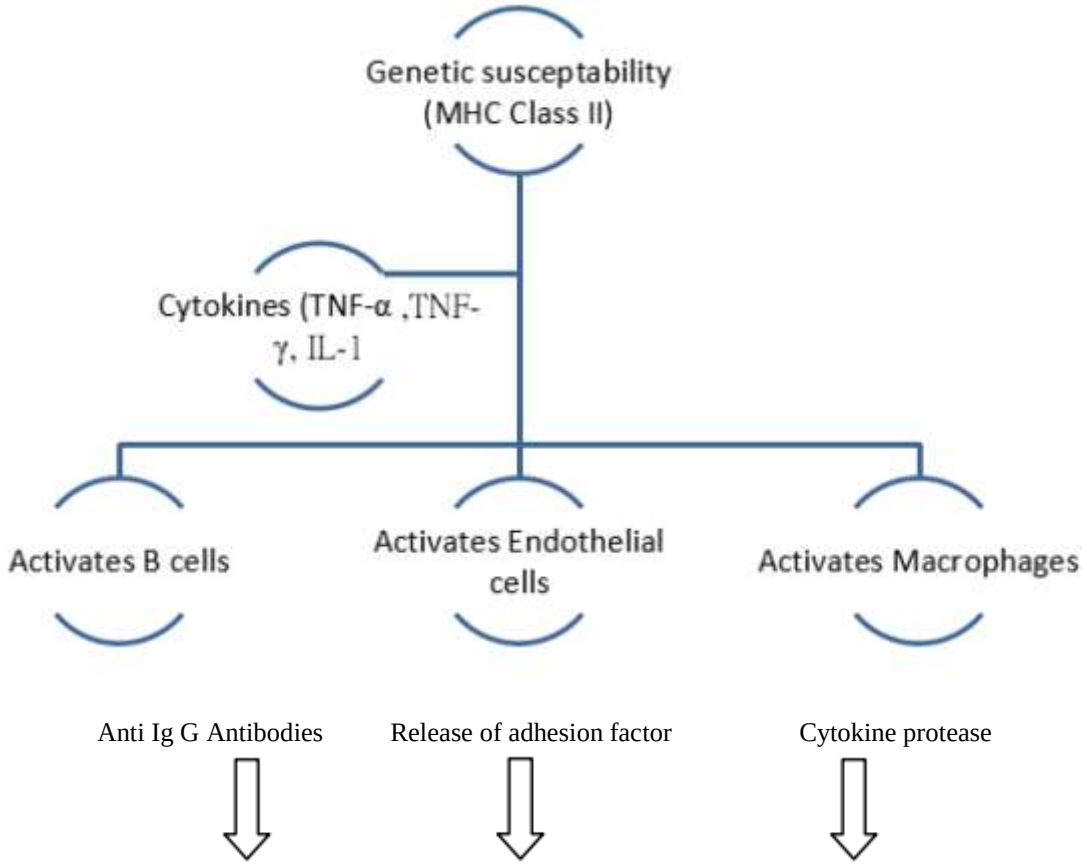

FORMATION OF IMMUNE COMPLEX

Diagnosis:

Diagnosing rheumatoid arthritis (RA) in the early stages can be difficult. There is no single test that can 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 scans

Treatment:

Treatments employed for treating arthritis:

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

Pharmacological Strategies:

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)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 females, therefore the treatment strategies for females of childbearing age need special caution as the treatment employed for curing their arthritic condition can harm their potential for conceiving and also during pregnancy. Ex: paracetamol, opiates, Diproqualone Analgesics

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reduce pain, and NSAIDs lessen pain and stiffness. Both drugs are used widely to control symptoms of rheumatoid arthritis, evidence for the use of analgesics is modest but uncontroversial; support for the use of NSAIDS is considerably stronger. The mode of action of these drugs was not known unti1l1 JR Vane for the first time published the observations showing that these drugs work by blocking cyclooxygenase enzyme . NSAIDS have lost their historical role as 1f2irst-line treatment because of concern about their limited effectiveness, and inability to modify the long-term course of disease . One of the most common toxicities observed in the case of regular use of these drugs is gastrointestinal disturbances or toxicity which generally includes t1h3e 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 cardiovascular diseases with their additional adverse effects on blood pressure.

Corticosteroids:

Ex: prednisone, prednisolone, methylprednisolone Corticosteroids like glucocorticoids have been used on a large scale for the last 60 years for the treatment of arthritis. Some of the commonly used glucocorticoids in disease remission are prednisone, methylprednisolone, etc. short term glucocorticoids reduce synovitis. Long term they decrease joint da14mage but develop 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, treating the short-term flare-ups can lead to rapid improvement and allow other treatmentDMARDS which have a slower onset of action to be adjusted. The 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 a highly effective local treatment for individual active joints.

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 a la1r5ge and heterogeneous collection of various agents grouped according to their use, convention, and efficacy in treating arthritis . Their diverse mechanism of action is 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 the 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 hydroxychloroquine termed triple therapy. The 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.

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 autoimmune 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 breastfeeding.

Biological therapies in rheumatoid arthritis:

Biological agents for the treatment of disease include the use of TNF-inhibitor, T-cEx: Etanercept, infliximab, adalimumab, golimumab, anakinra, certolizumab, rituximab, co-stimulatory blockers, B- cell depletion molecules, IL-1 receptor antagonist, etc. Interleukin -1 and TNF-α are proinflammatory cytokines involved in the pathogenesis of RA, when secreted by synovial macrophages, IL1 andTNFαstimulate synovial cells

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1363-1371 www.ijprajournal.com ISSN: 2249-7781

to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis, TNFαinhibitors (Adalimumab, Etanercept, Golimumamab, Certolizumab, and Infliximab). Have been shown to decrease signs and symptoms of RA, reduce the progression of structural damage, and improve physical function clinical response can be seen within 2 weeks of therapy. If a patient has failed therapy with one TNF inhibitor, a trial 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-1 receptor 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 therapies16has been hard to establish because the incidence is very low, and they are usually administered together with other treatments .

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 help to decrease joint stiffness and 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, tu17berculosis, development of various lymphomas, etc. Hence, the majority of the patients are seen to shift toward CAMs .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 targets are under investigation.

List of Herbs Used In Rheumatoid Arthritis

Abbreviations:

FCA- Functional complementation assay
CFA- Confirmatory factor analysis
FIA- Flow ejection analysis\

S.no	Name of the plant	Family	Part used	Experiment model
1	Aristolochiabraceata	Aristolochiaceae	Whole plant	FCA18
2	Ammannia baccifera	Lytraceae	Whole plant	CFA19
3	Boswellia serrata	Burseraceae	Whole plant	CFA20
4	Capparisspinosa	Capparidaceae	Fruit	AIA21
5	Cassia uniflora	Caesalpiniaceous	Stem	CFA22
6	Centellasiatica	Mackinlayaceae	Leaves	PD23
7	Cleome rutidosperma	Caapparidaceae	Aerial parts	CFA24
8	Cocculus hirsutus	Menispermaceae	Roots	FCA25
9	Delonixelata	Fabaceae	Bark	CFA26
10	Elaeocarpussphaericus	elaecarpaceae	Fruit	FCA27
11	Euphorbia antiquorum	Euphorbiaceae	Whole plant	CFA28

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12	Ficus bengalensis	Moraceae	Stem bark	FCA29
13	Glycyrrhiza glabra	Fabaceae	Rhizome	CFA20
14	Glycosmi spentaphylla	Rutaceae	Stem bark	FCA30
15	Lawsonialnnermis	Lythraceae	Leaves	FIA, CFA30
16	Machalis macrantha	Lauraceae	Bark	FCA31
17	Phyllanthus amarus	Euphorbiaceae	Herbs	CFA32
18	Pistiostratios	Araceae	Leaf	CFA33
19	Pongammia pinata	Fabaceae	Leaves	FCA34
20	Punica granatum	Punicaceae	Seeds	FCA35

21	Randiadum etorum	Rubiaceae	Fruid	FCA36
22	Ricinus communis	Euphorbiaceae	Leaves	CFA37
23	Tinospora cordifolia	Menispermaceae	Leaves	FCA38
24	Wedeliacalendulaceae	Asteraceae	Leaves	CFA39
25	Urginea indica	Liliaceae	Bulb	CPM40

II. 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 the traditional system of medicine always played an important role in meeting global healthcare needs. Arthritis is one of the most common auto-immune inflammatory disorders, the 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. Synthetic drugs including NSAIDS and DMARDS like Cyclophosphamide, intramuscular gold, sulfasalazine, and Methotrexate 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 many medicinal plants exert anti-arthritic activity at a particular dose. It is concluded that the isolation of lead compounds is responsible for improving the better treatment of the arthritis.

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