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HERBAL DRUG IS BETTER THAN ALLOPATHIC DRUG IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT: Rheumatoid arthritis (RA) is a chronic inflammatory and systemic autoimmune disease, affecting people predominantly between the ages of 20-60 years with an 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. This is a long-lasting disease that can affect joints in any part of the body, most commonly the hands, wrists, and knees. The popularity of medicinal plants is increasing day by day due to the side effects of allopathic medicines. Herbal medicinal plants have been used as major sources of cure of human diseases since time immemorial. Today, one-fourth of the world population depends on traditional medicine, and 80% of the population relies on indigenous herbal medicinal plants. Even today most of the people live 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.

INTRODUCTION: Immune system of our body plays a crucial role, as an overactive immune system may lead to certain fatal disease because of various hypersensitive or allergic reactions which may cause numerous derangements; loss of normal capacity to differentiate self from non-self-resulting in immune reactions against our cells and tissues called autoimmune diseases. Certain common autoimmune diseases like myasthenia gravis, serum sickness, pernicious anaemia, reactive arthritis, *etc*., are the severe issues for medical and pharmaceutical community because of unknown aetiology [1].

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According to WHO, 0.3-1% of the world population is affected by rheumatoid arthritis (RA), and among them, females are three times more prone to the disease as compared to males [2]. RA is a chronic, inflammatory and systemic autoimmune disease [3]. The primary symptoms of RA include pain, swelling, and destruction of cartilage and bone as a result of which permanent disability occur. Although, the exact etiology is unknown several hypotheses said that it is triggered by the combination of genetic predisposition and exposure to environmental factors like viruses [4].

The exact pathophysiology is still unknown but the release of certain free radicals such as nitrous oxide and superoxide radicals generated as by-products of cellular metabolism. The release of such free radicals may induce the production of interleukins (IL) and tumor necrosis factor (TNF-α) from T-cells which ultimately influence the production of growth factors, cytokines and adhesive molecules

on immune cells as such factors may cause tissue destruction and inflammation **Fig. 1**. Pathological changes in RA are hyperplasia of the synovial membrane, infiltration of inflammatory cells and neovascularization, which results in cartilage erosion and articular destruction [5].

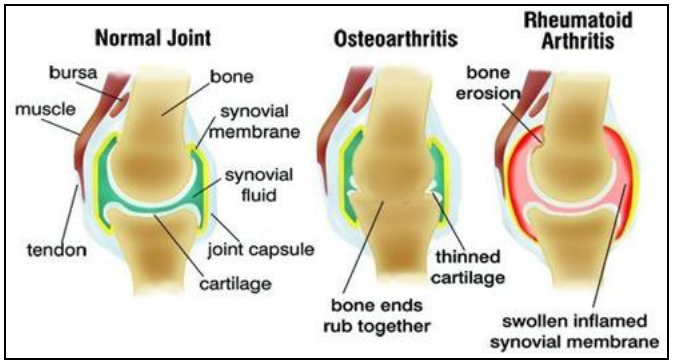

FIG. 1: NORMAL JOINT AND RHEUMATOID ARTHRITIS AFFECT JOINT

The goal of treatment for rheumatoid arthritis patients is to eliminate symptoms, slow disease progression, and optimize the quality of life [6]. Therefore, before starting the treatment of RA certain goals must be kept in minds such as relief of analgesia, reduction of inflammation, protection of articular structure, maintenance of function, and control of systemic involvement [7].

Rheumatoid Arthritis can be classified as:

1) Palindromic rheumatoid arthritis
2) Juvenile rheumatoid arthritis
3) Rheumatoid spondylitis
4) Other types of arthritis
5) Osteoarthritis:
a. Primary osteoarthritis - It occurs in older persons.
b. Secondary osteoarthritis - It occurs at any stage.
6) Ankylosing spondylarthritis
7) Infectious arthritis:
a. Supportive arthritis
b. Tuberculous arthritis
c. Lyme arthritis
d. Viral arthritis
8) Gout and gout arthritis

Etiology: Arthritis involves the breakdown of cartilage. Cartilage normally protects a joint, allowing it to move smoothly. The process produces an inflammatory response of the synovial (sinusitis) secondary to hyperplasia of synovial cells, excess synovial fluid, and the development of pain in the synovial. The pathology of the disease process often leads to the destruction of articular cartilage and alkalosis of the joints. Rheumatoid arthritis can also produce diffuse inflammation in the lungs, pericardium, pleura, and sclera and also nodular lesions, most common in subcutaneous tissue. Although, the cause of rheumatoid arthritis is unknown, autoimmunity plays a pivotal role in both its chronicity and progression and RA is considered a systemic autoimmune disease [8].

Epidemiology: About 1% of the world's population is afflicted by rheumatoid arthritis, women three times more often than men [9]. Arthritis represents one of the most prevalent chronic health problems and is a leading cause of disability. Arthritis affected 43 million U.S. adults in 2002 and by the year 2020, this number is expected to reach 60 million [10]. It is up to three times more common in smokers than non-smokers, particularly in men, heavy smokers, and those who are rheumatoid factor positive. A study in 2010 found that those who drank modest amounts of alcohol regularly were four times less likely to get rheumatoid arthritis than those who never drank [11].

Sign and 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 [12].

1. Symptoms of RA include.
2. Morning stiffness that lasts for at least 1 h.
3. Joint pain with warmth, swelling, tenderness, and stiffness of the joint after resting.
4. Low-grade fever.
5. Inflammation of small blood vessels can cause small nodules under the skin, but they are generally painless.

Pathophysiology of RA: RA is associated with several genetic and environmental factors that contribute the phenotype in different combinations **Fig. 2**. RA is initiated by immune complexes and the complement system, perpetuated by cytokines, and affected by metalloproteinase [13]. Antigen-activated CD4+ T cells stimulate monocytes, macrophages, and synovial fibroblasts which in turn lead to the production of cytokines interleukin-1, interleukin-6, and TNF*a* and secretion of matrix metalloproteinase through cell-surface signaling [14].

In early RA, a large amount of neutrophils are present in synovial fluid [15].

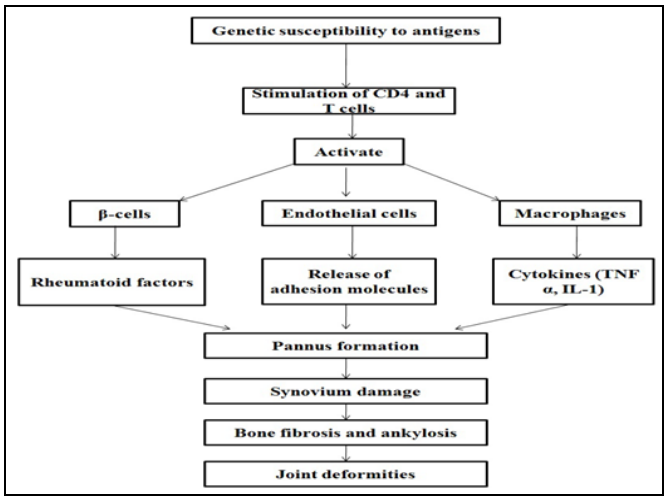

FIG. 2: POSSIBLE MOLECULAR MECHANISM FOR ARTHRITIS

Chronically, hypertrophy and hyperplasia form projections into the joint capsule. Immune complexes found in the synovial fluid often are IgG/anti-IgG antigen-antibody complex [16]. In RA bone erosions caused by osteoclasts and proteolytic enzymes causes cartilage dissolution [17]. Rheumatoid factors (IgM and IgA) are key pathogenic markers [18].

Diagnosis: Rheumatoid arthritis can be difficult to diagnose in its early stages because the early signs and symptoms mimic those of many other diseases. There is no one blood test or physical finding to confirm the diagnosis. During the physical exam, check joints for swelling, redness, and warmth. May also checked reflexes and muscle strength.

1. Blood Tests: People with rheumatoid arthritis often have an elevated erythrocyte sedimentation rate (ESR, or SED rate) or C-reactive protein (CRP), which may indicate the presence of an inflammatory process in the body. Other common blood tests look for rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies.

2. Imaging Tests: X-rays can help to track the progression of rheumatoid arthritis in joints over time. MRI and ultrasound tests can also help to judge the severity of the disease.

Treatment: The main aim of treatment is focused towards 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.

Medications may be prescribed along with lifestyle changes [19, 20]. The drug is available for the treatment of rheumatoid arthritis **Table 1**.

TABLE 1: DRUG IS AVAILABLE FOR TREATMENT OF RHEUMATOID ARTHRITIS

S. no.	Therapy	Drugs	Side effect
1	Over the Counter	Acetaminophen (tylenol), aspirin, ibuprofen, naproxen	Stomach upset or nausea, stomach pain, heartburn, diarrhoea, Stomach ulcer, and bleeding, increased blood pressure, allergic reaction - hives, facial swelling
2	Disease-modifying anti-rheumatic drugs (DMARDs)	Methotrexate, gold salts, penicillamine, sulfasalazine, and hydroxychloroquine. Common combinations of DMARDs include methotrexate - hydroxychloroquine, methotrexate sulfasalazine, Sulfasalazine – hydroxychloroquine and methotrexate – hydroxychloroquine – sulfasalazine.	Stomach upset, nausea, vomiting, or diarrhea liver problems, blood problems, muscle aches and pain
3	Non-steroidal anti-inflammatory drugs (NSAIDs)	Paracetamol, ibuprofen, naproxen, meloxicam, etodolac, nabumetone, sulindac, tolmetin, choline magnesium salicylate, diclofenac, diflunisal, indomethacin, ketoprofen, oxaprozin, and piroxicam	Stomach pain and heartburn, stomach ulcer, headache, dizziness, ringing in the ear, allergic reactions -rashes, wheezing, and throat swelling. Liver or kidney problem, high blood pressure
4	Biological agents	Tumor necrosis factor alpha (TNFα) blockers-etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi) Monoclonal antibodies against B cells – rituximab (Rituxan)	Peripheral edema, headache, fever, muscle aches and pain, decreased appetite, increased triglyceride level, insomnia, abdominal pain, back pain, dizziness, infusion reactions low blood pressure, anaphylaxis, cancer, serum sickness, autoimmune thyroiditis, arterial and venous blood clot, congestive heart failure

Surgery: If medications fail to prevent or slow joint damage, you and your doctor may consider surgery to repair damaged joints. Surgery may help restore your ability to use your joint. It can also reduce pain and correct deformities. Rheumatoid arthritis surgery may involve one or more of the following procedures:

1. Synovectomy: Surgery to remove the inflamed synovium (lining of the joint). Synovectomy can be performed on the knees, elbows, wrists, fingers, and hips.

2. Tendon Repair: Inflammation and joint damage may cause tendons around the joint to loosen or rupture. The surgeon may be able to repair the tendons around the joint.

3. Joint Fusion: Surgically fusing a joint may be recommended to stabilize or realign a joint and for pain relief when a joint replacement isn't an option.

4. Total Joint Replacement: During joint replacement surgery, the surgeon removes the damaged parts of the joint and inserts a prosthesis made of metal and plastic.

Herbal Drug Treatment of RA: Total of 15 plants with potential anti-arthritic activity has been discussed below.

***Harpagophytum procumbens*:** *Harpagophytum procumbens* (HP) known as "devils claws" is a plant, originated from Southern Africa, specifically, from the Kalahari Desert and Namibia steppes. Ethanolic extract of HP root has been evaluated for its anti-inflammatory and analgesic activity in the rat by Freund's adjuvant-induced arthritis both in the acute and chronic phases. Behavioral test, body weight, hot-plate test, and paw volume were measured. The results showed that the extract increased the animals 'latency of paws' withdrawal, indicating a protective effect against the pain induced by the thermal stimulus, both in acute and chronic treatments [21].

***Bauhinia variegata*:** The anti-inflammatory activity of the leaf extract of *Bauhinia variegata* using three *in-vivo* animal models: the carrageenan-induced rat paw edema, cotton pellets induced granuloma formation, and adjuvant-induced arthritis in the rat were evaluated. Both the ethanol extract and the petroleum ether fraction obtained from this extract demonstrated activity in all the three bioassays. The activity was found to be more pronounced in the petroleum ether fraction. These bioactivities compared favorably with diclofenac sodium, which was used as a positive control, and confirms the traditional use of this plant for the treatment of both acute and chronic inflammatory conditions [22].

***Leucas aspera*:** *Leucas aspera* (LA) is traditionally used for analgesic, antipyretic, anti-rheumatic, anti-inflammatory and anti-bacterial treatment and its paste is applied topically to inflamed areas. The chronic anti-inflammatory activity of ethanolic extract of LA was investigated using complete Freund's adjuvant arthritis model. A dose of 100 and 200 mg/kg exhibited significant anti-inflammatory activity ($p<0.001$). After the treatment, histopathological studies confirmed complete cartilage regeneration and near normal joint [23].

***Phyllanthus amarus*:** The aqueous extract of *Phyllanthus amarus* extract (PAE) (2.5% phyllanthin and hypophyllanthin) was tested against Freund's complete adjuvant-induced arthritic rats. Arthritis assessment, paw volume, joint diameter, mechanical hyperalgesia, and nociceptive threshold were measured. PAE significantly decreased arthritis which was evident with arthritis index, paw volume, and joint diameter. It also significantly increased the mechanical hyperalgesia and nociceptive threshold. The histopathology also revealed the control in inflammation with PAE [24].

***Acalypha indica*:** *Acalypha indica* (AI) methanol extract was evaluated using three different *in-vitro* models to explore anti-arthritic potentials such as inhibition of protein denaturation, proteinase inhibitory action, and anti-hyaluronidase activity. The concentrations of 10 to 200 µg/ml of AI methanol extract were prepared using DMSO. Diclofenac was used as positive control. All *in-vitro* determinations were done in triplicate. A dose-dependent increase in percentage inhibition was observed for all the three models. The inhibitory concentration (IC_{50}) was found to be 52 µg/ml for protein denaturation assay, 37µg/ml in proteinase inhibitory action and 18 µg/ml for anti-hyaluronidase activity.

Diclofenac offered protective activity at even much lower concentrations compared to AI methanol extract producing IC_{50} values of 40 and 13 µg/ml for protein denaturation and proteinase inhibitory assays. AI exhibited a very good anti-arthritic activity in all the methods checked confirming its traditional use [25].

***Cassia uniflora*:** Petroleum ether, ethyl acetate and methanolic extract of *Cassia uniflora* (CU) were screened for analgesic by Eddy's hot plate and acetic acid-induced writhing, anti-inflammatory by carrageenan-induced paw edema and anti-arthritic activity by complete Freund's adjuvant (CFA) induced arthritis. In complete Freund's adjuvant arthritis model, degree of inflammation was evaluated by hind paw swelling, body weight, and biochemical parameters, and supported by radiological analysis. Treatment with extracts of CU showed a significant and dose-dependent increase in paw licking time in Eddy's hot plate method. In writhing test, extracts significantly reduced the number of writhes. A dose-dependent and significant inhibition of edema were observed in carrageenan-induced paw edema. Petroleum ether extract at a dose of 100 mg/kg showed the most potent and significant activity which was supported by the result of body weight, biochemical parameters and radiological analysis in CFA arthritic model [26].

***Asystasia dalzelliana*:** Anti-arthritic activity of ethanolic extract of *Asystasia dalzelliana* (AD) leaves was evaluated by Freund's adjuvant-induced arthritis model in rats. Paw edema, changes in organ weight, serum parameters such as SGOT, SGPT and ALP were estimated. Hind paw of experimental rats was also subjected to radiographic and histopathological examination for assessing the anti-arthritis potential of ethanolic extract of AD leaves. The results of the current investigation concluded that the extract of a dose of 800 mg/kg possess is a significant anti-arthritic activity than the lower doses of 200 mg/kg and 400 mg/kg. The observed anti-arthritis activity of extract may be due to the presence of phytoconstituents such as alkaloid and flavonoids. AD for its possible anti-arthritic activity by HRBC membrane stabilization and inhibition of protein denaturation method was evaluated. Methanolic extract upon the column chromatography yielded five fractions named (AD-01, AD-02, AD-03, AD-04, and AD-05) and was screened for their anti-arthritic activity. Among the five fractions tested, AD-3 and AD-4 shown good anti-arthritic activity when compared with standard diclofenac sodium. The maximum membrane stabilization of AD-3 and AD-4 fraction was found to be at 71.64% and 94.68% (average) respectively. The protein denaturation inhibition of AD-3 and AD-4 fraction was found to be 52.84% and 64.56% respectively. Therefore, the studies supported the use of active constituents from AD leaves in treating rheumatoid arthritis [27].

***Asparagus racemosus*:** The hydroalcoholic extract of *Asparagus racemosus* (AR) roots *in-vivo* 200 and 400mg/kg were tested for its anti-inflammatory and anti-arthritic activity by carrageenan-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 hydroalcoholic extract of AR roots showed significant anti-inflammatory and anti-arthritic activity [28].

***Sida rhombifolia*:** *Sida rhombifolia* (SR) has been used from prehistoric times for the treatment of gout in Indonesia. Effect of SR stem and root extracts using adjuvant-induced arthritis model in experimental rats were evaluated. The extract was found to normalize the altered levels of hematological parameters. The elevated rate of erythrocyte sedimentation was also significantly reduced by [29].

***Genkwa flos*:** Antioxidant effect of *Genkwa flos* (GF) flavonoids on Freund's adjuvant-induced rheumatoid arthritis in rats. To evaluate the anti-oxidative effects of flavonoids aglycones (FA) isolated from the GF were tested for its anti-arthritic activity by adjuvant-induced arthritis. FA significantly decreased paw edema, arthritic score, and increased body weight. The results conclude that FA significantly decreased arthritis in a rat model through the anti-oxidant and hematological modulatory mechanism. The GF flavonoids may have clinical potential for the treatment of rheumatoid arthritis [30].

***Hemidesmus indicus*:** The protective effects of hydroalcoholic and its fractions from roots of *Hemidesmus indicus* (HI) has been investigated by complete Freund's adjuvant model. Rats treated with the hydroalcoholic extract (450 mg/kg), ethyl acetate (75 mg/kg), chloroform (60 mg/kg) and a residual fraction (270 mg/kg) showed a significant decrease in physical and biochemical parameters compared with arthritic model rats. Hydroalcoholic extract and its ethyl acetate fraction of HI showed significantly higher anti-arthritic activity than chloroform and residual fraction. Histopathological analysis demonstrated that both of hydroalcoholic extract and its ethyl acetate fraction had comparable anti-arthritic activity with methotrexate [31].

***Azima tetracantha*:** *Azima tetracantha* (AT) is known as Kundali in Ayurvedic medicine and also called uppimullu in Kannada. There are reports that the leaves juice is efficient against toothache and earache. In Indian tribes, leaves paste of AT is used to treat snakebites. Friedelin, a compound isolated from AT. Leaves were investigated for adjuvant-induced arthritis activity in Wistar rats and 54.5% of paw thickness in rats [32].

***Cinnamomum zeyllanicum*:** Anti-inflammatory and anti-arthritic activity of type-A procyanidins polyphenols (TAPP) from the bark of *Cinnamomum zeyllanicum* (CZ) in rats. TAPP showed significant anti-inflammatory effect in the carrageenan-induced paw edema model. TAPP treatment in established arthritic rats showed the significant reversal of changes induced in adjuvant-induced arthritis concerning body weight drop, ankle diameter, arthritic score, and serum C-reactive protein levels and evaluated hematological parameters like RBC, WBC, ESR, Hb% for assessing anti-arthritic activity. Their investigation concluded that TAPP from CZ has potential anti-inflammatory and anti-arthritic activity [33].

***Wedelia calendulacea*:** The effect of *Wedelia calendulacea* (WC) leaves has been investigated alone or in combination with a subtherapeutic dose of methotrexate (1 mg/kg) is salvaging, oxidative stress, anti-arthritic action and cardioprotective actin with methotrexate. Rats were induced arthritis by subplantar injection of 0.1 ml Complete Freund's adjuvant (CFA). Various hematological (RBC, WBC, Hb, ESR, and RA Factor), biochemical parameters (Homocecytein, TNF-α, IL-2, and CRP) and tissue parameters (SOD, catalase and lipid peroxidation of the aorta) were measured before initiation and after completion of treatment in all groups. The methanolic fraction of methanolic extract (Me-OH / Me-OH) of WC showed significant anti-arthritic activity in CFA induced arthritic animals [34].

***Holarrhena pubescens*:** *Holarrhena pubescens* (HP) is an Indian traditional medicinal plant, is commonly known as 'kurchi' in India. Ethanolic extract of dried seeds of HP was investigated for their anti-inflammatory and anti-arthritic activity. HP (400 mg/kg p.o.) extract showed maximum (74.07 %) inhibition of carrageenan-induced rat paw edema, 62.63% inhibition of granuloma formation and 77.95% inhibition of adjuvant-induced arthritic edema in rats when compared with indomethacin [35].

CONCLUSION: Traditional herbal medicines used for the treatment of rheumatoid arthritis are used in various tribal/rural cultures worldwide. The herbal medicinal plants, which have been discussed, show promising role as anti-arthritic agents. The presently available synthetic drugs in the market are not only economic exploitation but also associated with adverse effects. The synthetic drugs include NSAIDS and DMARDS like cyclophosphamide, intramuscular gold, sulfasalazine, methotrexate had the side effects of stomach ulcers, GIT bleeding, kidney, liver damage, and hypertension. There is a need to identify the active principals of these herbal medicines as potential chemotherapeutic agents and monitor the safety of these active constituents. A large number of herbal plants described in this review article demonstrated the importance of herbal plants in the treatment of rheumatoid arthritis.

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