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ANTI-ARTHRITIC MEDICINAL PLANTS - A REVIEW

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Abstract: Rheumatoid arthritis (RA) is a chronic, inflammatory, and destructive polyarthritis with numerous autoimmune features and the potential for extra-articular and systemic complications. Its etiology is still unknown but much progress has occurred in defining important mechanistic components of RA, leading to significant advances in its treatment. RA is a multifactorial and multistage disease, beginning with preclinical autoimmunity that arises in a genetically predisposed individual who encounters one or more environmental triggers, progressing to the clinical appearance of inflammation in joints and sometimes in other organs, and leading (if effective treatment is unavailable) to destruction of the articular cartilage and adjacent bone. Medicinal plants are plants containing inherent active ingredients used to cure disease or relieve symptoms of arthritis. The aim of this review is to update information on RA including causes, epidemiology, prevalence, symptoms and diagnosis, classification, medications, toxicities of allopathic anti-rheumatic drugs and importance of herbal drugs for the management of RA. The present review also focuses on the medicinal plants that interact with the mediators of inflammation and are used in the treatment of rheumatoid arthritis (RA).

Keywords: Rheumatoid arthritis, Medicinal Plants.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disorder whereby the immune system promotes articular damage. It is a disabling and painful condition, which can lead to severe loss of mobility due to pain and joint destruction. RA is a systemic disease, often affecting extra-articular tissues throughout the body including the skin, heart, lungs, and muscles. With approximately 50% of RA patients are unable to work 10 years after the onset of their disease [1].

Materials and Methods:

In the present review, bibliographic investigation was done to retrieve articles for preclinical studies from worldwide scientific databases like Scopus, PubMed, SciELO, NISCAIR and Google Scholar available during 2005–2015.

Epidemiology and Historical Aspects of RA:

RA prevalence in developed countries is 0.5–2%, with an annual incidence of 12–1200 per 100,000 inhabitants. The female: male ratio is 2–3:1, and the peak age range of onset is 30–55 years old, but it could occur at any age [2]. The historical epidemiology of RA is recognizable descriptions in the medical literature recent, beginning about 200 years ago, but some earlier European paintings show what appear to be RA-like deformities. RA may have been present in ancient times but was likely rarer than at present. If this assessment is correct, it may indicate changes in the presence of environmental triggers and/or genetic changes in the human population over time that have increased propensity to RA [3].

Clinical manifestations:

RA can be hard to detect because it may begin with subtle symptoms, such as achy joints or a little stiffness. The stiffness seen in active RA is most often worst in the morning. It may last one to two hours (or even the whole day). Stiffness for a long time in the morning is a clue that one may have RA [4]. Most patients with RA note a gradual onset of joint inflammation over weeks to months; however, 10%- 20% may develop the classic joint stiffness, pain, and swelling of RA acutely. Systemic symptoms, such as malaise, fatigue, and weakness often accompany the signs and symptoms of joint inflammation [5].

Etiopathogenesis of RA:

The etiology of RA is still not known, a genetic susceptibility and influence of environmental factors are responsible for the onset of RA. The factors are:

Genetics of RA:

The most important genome in RA susceptibility is the major histocompatibility complex (MHC), which encodes for genes that are essential to immune responses, notably the HLA-A, HLA-B, HLA-C, and HLA-D proteins. These structures are expressed on the surface of antigen-

presenting cells and are required for recognition of peptide antigens by T lymphocytes, leading to initiation of immune responses [6].

Environmental Triggers of RA:

Smoking is the best-established environmental risk factor for RA and is a potential trigger for the development of RA-associated autoimmunity. Preliminary evidence suggests that cigarette smoking can induce expression in the lungs of the enzymes responsible for citrullination of various proteins, thus creating antigen targets of autoantibodies that are tightly associated with RA. Smoking is also associated with resistance to successful treatment of RA and more rapid disease progression. Thus, smoking cessation should be viewed as part of both prevention and treatment of RA [7].

Classification of RA:

The autoimmunity in RA proceeds with clinical onset of RA, and joint inflammation proceeds damage to the cartilage and bone. The sequence of systemic and articular events in RA can be classified as discrete stages of RA [8]. Classification criteria for RA were first proposed by the American Rheumatism Association (ARA) in 1958 [9]. The 1958 ARA criteria were revised in 1987 by the American College of Rheumatology (ACR) [10]. The 1987ARA criteria were revised in 1991 by American College of Rheumatology (ARC) [11].

Table 1

1991 American College of Rheumatology Revised Criteria for Classification of Functional Status in Rheumatoid Arthritis.

Class I Completely able to perform usual activities of daily living (self-care, vocational, and avocational)

Class II Able to perform usual self-care and vocational activities, but limited in avocational activities.

Class III Able to perform usual self-care activities, but limited in vocational and avocational activities

Class IV Limited in ability to perform usual self-care, vocational, and avocational activities.

Treatment:

RA therapy includes non-pharmacological and pharmacological options.

Non-Pharmacological Therapies:

Exercise

Joint pathology can reduce physical activity due to pain or joint dysfunction. A recent review has identified that an increase in aerobic exercise (moderate to high intensity, 3 times/week for 30 to 60 minutes) and strengthening exercise (moderate to hard resistance training 2 to 3 times/week) will result in better outcomes for patients with RA [12].

Diet

The role of diet remains controversial but recent evidence suggests that some dietary modifications may modestly reduce disease activity. A small study demonstrating that the Mediterranean diet (high consumption of fruit, vegetables, cereals, legumes, little red meat, more fish, olive oil, and moderate intake of wine) reduced disease activity in patients with RA. The Mediterranean diet has also been demonstrated to reduce cardiovascular risk in those not affected by RA and therefore would be a useful adjunct in RA patients [13].

Pharmacological Therapies:

Drugs used in the treatment of RA fall into two basic categories:

1. those which provide short-term symptomatic relief;
2. those which modify the course of the disease Process

Category 1 includes simple analgesic preparations and nonsteroidal anti-inflammatory drugs (NSAIDs). They are traditionally used early in the course of the disease and there is little controversy that an NSAID should be the first prescribed drug given to patients presenting with early arthritis. Category 2 represents a heterogeneous group of drugs that act very slowly via unknown mechanisms. Over a long period of time they can alter the course of persistently active or progressive disease. The appropriate time to initiate these 'second-line agents' or 'disease-modifying antirheumatic drugs' (DMARDs) [14].

Complications of medical treatment of RA:

RA itself confers an elevated risk of infection, and DMARD and biologic therapies suppress the immune system through various targets, also increasing this risk [15]. Bacterial infections, particularly pneumonia and soft-tissue infections, are increased with the use of methotrexate, and this is increased 2–4-fold with the addition of an anti-TNF medication [16]. Similar infectious risks have been found with other biologic DMARDs as well [17]. A significant risk of reactivation of tuberculosis has also been noted with anti-TNF medication [18]. An increased risk of viral infections with traditional or biologic DMARDs, including varicella zoster virus, Epstein-Barr virus and cytomegalovirus has been documented [19]. Hepatitis B and C reactivation have also occurred with biologic DMARDs, so screening prior to treatment and vaccination when possible is recommended [20].

Conventional treatments for rheumatoid arthritis (RA) present a number of problems, in terms of both safety and efficacy [21]. The side effects of shown in given table-2

Table 2

Toxicities of anti RA drugs [22]

Sr. No.	Drug	Toxicities
1.	Methotrexate (DMARD's)	Stomatitis, rash, alopecia, infrequent myelosuppression, hepatotoxicity, rare but potentially life-threatening pulmonary toxicity
2.	Oral Gold Salts	Diarrhoea
3.	Injectable Gold Salts	Stomatitis, myelosuppression, rash, thrombocytopenia.
4.	Cyclosporine	Renal impairment, hypertension, gingival overgrowth.
5.	D-penicillamine	Rash, stomatitis, dysgeusia, proteinuria, myelosuppression.
6.	Nonsteroidal Antiinflammatory Drugs	Gastrointestinal symptoms (indigestion, ulceration, hemorrhage, stomatitis); renal abnormalities; pulmonary neurological abnormalities; abnormalities; dermatologic abnormalities; hematologic abnormalities; hepatic abnormalities; displacement of protein-bound drugs; possible systemic complications

Research has indicated that people suffering from chronic pain, as in RA, and those dissatisfied with current treatment are very likely to seek alternative treatments, and an estimated 60–90% of persons with arthritis use alternative treatments. With the growing interest in herbal therapies among persons with rheumatoid arthritis, there exists a need for investigation into their safety and efficacy [23].

The management of rheumatoid arthritis is a multidisciplinary approach in order to lessen the pain, reduction of inflammation and restoration of joints function. In practical terms suppression of inflammation is the target intensive therapy. Herbal medicines have become popular for the treatment of rheumatoid arthritis worldwide recently [24]. Herbal medicinal drugs that interact with the mediators of inflammation are used in the treatment of rheumatoid arthritis (RA).

Medicinal plants of anti-arthritic potential:

Heliopsis longipes: This study assesses the anti-arthritic effect of the affinin-enriched hexane extract from the roots of *Heliopsis longipes*, on a Freund adjuvant-induced arthritis model in

rodents. The extract was orally administered at a dose of 2, 6.6, or 20 mg/kg; a significant edema-inhibitory activity in the acute and chronic phases was observed with a dose of 2 and 20 mg/kg, respectively. The extract showed higher anti-inflammatory and anti-arthritic effects than the reference drug phenylbutazone (80 mg/kg). Moreover, the extract prevented the occurrence of secondary lesions associated to this pharmacological model [25].

Barleria prionitis Linn: This study was designed to evaluate anti-arthritic potential of ethyl acetate fractions of chloroform extract from leaves of *Barleria prionitis*. This fraction was evaluated at two doses 125 and 250 mg/kg, against formaldehyde-induced acute non immunological and Freund's Complete Adjuvant-induced chronic immunological arthritis in rats. Arthritis assessment, paw volume, body weight, motor in coordination and nociceptive threshold were measured. Dose dependent and significant inhibition of oedema was observed in both acute as well as chronic models. The extract at dose 250 mg/kg showed most potent and significant (P 6 0.05–0.01) paw oedema inhibition which is supported by the results of body weight, biochemical parameters, motor in coordination and nociceptive threshold in Freund's Complete Adjuvant-induced arthritis model [26].

Fagopyrum cymosum: This study evaluated the anti-arthritic effect of 95% ethanol extract of EFC (extract of Fagopyrum cymosum). The anti-arthritic activity was investigated by adjuvant arthritic (AA) rat model induced by Freund's complete adjuvant (FCA). The AA rats were randomly separated into different groups and then treated with EFC (40, 80 and 160 mg/kg) from day 7 to day 28 after immunization. Arthritis was evaluated by hind paw swelling, polyarthritis index, body weight and index of immune organs. The levels of interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF-a) in the serum were assessed by ELISA. Result shows high dose level of EFC (160 mg/kg) significantly suppressed the swelling of hind paw of AA rats and inhibited their body weight loss. EFC (80 and 160 mg/kg) also decreased the plasma viscosity in different shear rates. Moreover, EFC significantly reduced the production of IL-1 and TNF-a in the serum of AA. This study provides a scientific basis for the claims that F. cymosum is effective in preventing and suppressing the development and progression of experimental arthritis, with reductions in inflammatory response [27].

Persea macrantha: This study evaluated the anti-inflammatory and anti-arthritic properties of different extracts of stem bark of *Persea macrantha* in rats. Anti-inflammatory activity was determined in albino rats in a model of acute plantar inflammation induced by carrageenan, while the serial extracts were tested for anti-arthritic activity in adjuvant-induced arthritis in rats. The petroleum ether extract (PE) and aqueous extract (AE) caused a significant inhibition of the carrageenan- induced paw edema at a dose of 200 mg/kg, when compared with control and reference drug, diclofenac. PE (200 mg/kg) significantly decreased primary lesions, secondary lesions and total radiological score in adjuvant induced arthritis. The findings of this experimental animal study indicate anti-inflammatory and anti-arthritic properties of *Persea*

macrantha and thus provide pharmacological support to the traditional use of *Persea macrantha* in the treatment and management of painful, arthritic inflammatory conditions [28].

Withania somnifera: In this paper author studied the effect of W. somnifera root powder on the behavioral and radiological changes in collagen-induced arthritic rats. The rats were randomly divided into five groups: normal control, arthritic control, arthritic rats treated with W. somnifera root powder (at dose levels 600 and 800 mg/kg) and arthritic rats treated with methotrexate (at dose level 0.3 mg/kg). The treatment with W. somnifera (daily) and methotrexate (weekly) was initiated from the 20th day post collagen immunization and continued up until the 45th day. Arthritis was assessed macroscopically by measuring paw thickness, ankle size and body weight. Arthritic pain was assessed by toe-spread and total print length of the affected paw. Result declared administration of W. somnifera root powder (600 mg/kg) to the arthritic rats significantly decreased the severity of arthritis by effectively suppressing the symptoms of arthritis and improving the functional recovery of motor activity and radiological score. The results suggest that W. somnifera root powder acts as an anti-inflammatory and antioxidant agent in decreasing the arthritic effects in collagen-induced arthritic rats [29].

Rhizopora mucronata: The present investigation was carried out the evaluation of the anti-arthritic property of *Rhizophora mucronata* by three different methods viz., membrane stabilization assay, protein denaturation assay and albumin denaturation assay. Four different concentration of test (100, 200, 300 and 400 mg) were using in this study. Action was observed in dose dependent manner. In protein denaturation method at 400 mg of chosen extract showed maximum protection (97.56%) and standard drug provided 99.2% protection. Similarly, in membrane stabilization test, the selected extract at concentration of 400 mg showed maximum protection (95%) and standard drug provided 97% protection. Moreover, albumin denaturation test showed maximum protection (90.12%) at concentration of 400 mg. The author concluded that, methanolic extract of Rhizophora mucronata shows strong anti-arthritic activity at different concentration when compared to standard drug of Diclofenac sodium [30].

Pterocephalus hookeri: The author evaluated the anti-arthritic activity of total glycosides from P. hookeri, and its possible mechanisms of action. Anti-arthritic activity of total glycosides from P. hookeri (oral administration for 30 days at 14–56mg/kg) was evaluated using paw swelling, arthritis scores and histopathological measurement in adjuvant-induced arthritis (AA) Sprague-Dawley rats. The serum superoxide dismutase (SOD) activity, malondialdehyde (MDA) and nitric oxide (NO) levels was measured in AA rats, respectively. The results shows total glycosides (56mg/kg) decreased the paw swelling (38.0%, $p<0.01$), arthritis scores (25.3%, $p<0.01$) and synovial inflammation in AA rats. The glycosides significantly ($p<0.05$–0.01) attenuated the inflammation induced by xylene, carrageenan, acetic acid and agar, increased the pain threshold in acetic acid-induced writhing in mice and mechanical stimuli-induced hyperalgia in AA rats [31]

Triphala: Triphala, an Indian Ayurvedic herbal formulation which contains Terminalia chebula, Terminalia bellerica and Emblica officinalis L. is used for treating bowel-related complications, inflammatory disorders, and gastritis. Arthritis was induced in Wistar albino rats by intradermal injection of complete Freund's adjuvant (0.1 ml) into the foot pad of right hind paw. Triphala (100 mg/ kg b wt, i.p.) was administered from day 11 to 18 after the administration of complete Freund's adjuvant. The activities/levels of lysosomal enzymes, glycoproteins, antioxidant status, and lipid peroxidation were determined in the paw tissues of arthritic rats. In addition, the inflammatory mediators were also measured in both the serum and the paw tissue of arthritic rats. The result shown the Triphala has a promising anti-inflammatory effect in the inflamed paw of arthritis-induced rats [32].

Oryza sativa Var: In this paper author studied the in-vitro anti-inflammatory and anti-arthritic activity of Joha Rice, an aromatic indigenous rice of Assam, India. The ethanolic extract of Oryza sativa Var. Joha rice (EEOS-JR) was studied for in-vitro anti-inflammatory activity by human red blood cell (HRBC) membrane stabilization method and In-Vitro anti-arthritic activity by bovine serum protein denaturation method and egg albumin denaturation method. The activity of ethanolic extract of Joha rice was compared with standard anti-inflammatory drug Diclofenec. In result it is found that EEOS-JR at concentration of 100, 250 and 500 mcg/ml showed 51.12, 58.75 and 63.77% protection of HRBC in hypotonic solution respectably, whereas, standard diclofenac at 50, 100 and 250 mcg/ml which showed 68.11, 73.83 and 76.17% protection of HRBC in hypotonic solution respectably. It also showed 39.29%, 52.78% and 60.47% inhibition of denaturation @ 100, 250 and 500 mcg/ml of bovine serum whereas, standard diclofenac@100, 250 and 500 mcg/ml showed 93.20, 95.41 and 96.91% inhibition of denaturation of bovine serum. In egg albumin denaturation method at concentration of 100, 250 and 500 mcg/ml showed 75.00, 80.31 and 84.15% inhibition of egg albumin denaturation whereas, standard diclofenac @100, 250 and 500 mcg/ml which showed 27.78, 45.84 and 69.77% inhibition of egg albumin denaturation. Finally it is concluded that Oryza sativa Var. Joha rice; an indigenous aromatic rice of Assam posses good in-vitro anti-inflammatory and anti-arthritic activities [33].

CONCLUSION:

Plants described in this review clearly demonstrated the importance of herbal plants in treatment of rheumatoid arthritis and also to consider one of good source for a new drug or a lead to make a new drug.

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