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Rheumatoid Arthritis and Herbal Therapy

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ABSTRACT

A persistent autoimmune condition called rheumatoid arthritis (RA) causes gradual joint damage and systemic inflammation. It is a systemic illness, which means that it may impact all of the body's internal organs, including the heart, lungs, and eyes. Despite the fact that many synthetic medications are utilized as the conventional treatment for rheumatoid arthritis, many drugs have side effects that can undermine the therapeutic approach. Unfortunately, there is still no proven medical cure for rheumatoid arthritis. Instead, modern medicine can only alleviate the symptoms of this condition, such as joint discomfort and inflammation. It is possible to employ herbs and plants in a variety of ways to treat joint pain and inflammation. The ability of numerous medicinal plants to treat rheumatoid arthritis has been demonstrated. So, for the treatment of rheumatoid arthritis, plants and plant products with notable advantages are utilized. The focus of the current review is on medicinal herbs with anti-rheumatoid arthritis action.

1. INTRODUCTION:

Rheumatoid arthritis (RA) is the most common multisystem inflammatory autoimmune disease which has affected approximately 1% of the world population.[1] Rheumatoid Arthritis has emerged as a major health problem in the current scenario. In India, the prevalence of RA is quite similar to that reported from the developed countries. China, Indonesia, Philippines and Rural Africa reported higher prevalence than India. These findings are in based on the fact that the North Indian Population is genetically closer to the Caucasians than to other ethnic groups.[2]

1.1PATHOPHYSIOLOGY

Primarily RA starts when autoimmunity and immune complexes occur in both joints and other organs because of persistent cellular activation. Immune cells cause infiltration in the synovial fluid which further leads to swelling and congestion as well as inflammation of synovial membrane. Three phases of progression of RA are an initiation phase(due to non-specific inflammation), an amplification phase(due to T cell activation) and chronic inflammatory phase with tissue injury (due to cytokines IL-1, TNF-alpha and IL-6).

2.SIGNS AND SYMPTOMS:

RA primarily affects joints, but it also affects other organs in more than 15–25% of individuals. Inflammation of synovial membrane occurs in the arthritis of joints. Synovitis can lead to tethering of tissue with loss of movement and erosion of the joint surface causing deformity and loss of function.[3]Lung fibrosis is a recognized complication of rheumatoid arthritis. It is also a rare but well-recognized consequence of therapy (for example with methotrexate and leflunomide.[4] People with RA are more prone to atherosclerosis, and risk of myocardial infarction (heart attack). Other possible complications that may arise include: pericarditis, endocarditis, left ventricular failure, valvulitis and fibrosis.[5]

Table 1 : A summary of the stages of Rheumatoid Arthritis: pathological process, symptoms[6] and radiographic changes.

Stage	Pathological Process	Symptoms	Physical Signs	Radiographic Changes
1	Presentation of Antigen to T cells	Probably none	-	-
2	T cell proliferation B cell proliferation Angiogenesis in synovial membrane	Malaise, mild joint stiffness and swelling	Swelling of small joints of hands or wrist, or pain in hands, wrists, knees and feet.	None
3	Accumulation of neutrophils in synovial fluid	Joint pain and swelling, morning stiffness, malaise and weakness	Warm, swollen joints, excess synovial fluid, soft tissue proliferation in the joints, pain and limitation of motion and rheumatoid nodules	Soft Tissue Swelling
4	Polarization of Synovitis into centripetally invasive pannus	Morning stiffness, swelling in joints and pain	Same as stage 3 but more pronounced swelling	MRI reveals proliferative pennus, radiographic evidence of periarticular osteopenia
5	Erosion of sub-chondral bone Chondrocyte proliferation, Stretched ligaments around joints	Ulnar deviation at metacarpophalangeal joints	Instability of joints, flexion contractures, decreased range of motion, extra-artricular complications	Early erosions and narrowing of joint spaces.

Dubey L et al,(2016) concluded long-term low-dose MTX is safe in RA patients in the Indian population. The patterns of adverse effects were similar to those documented in earlier studies. However, our study results

suggest that disease duration, cumulative MTX dose, concomitant DMARD intake are not risk factors associated with hepatic or hematological adverse effects.**Lawrence, R.C., et al.,(1998)** provided national estimates with important caveats regarding their interpretation, for self-reported arthritis and selected conditions. An estimated 15% (40 million) of Americans had some form of arthritis in 1995. By the year 2020, an estimated 18.2% (59.4 million) will be affected.**Turesson, C., et al.,(2003)** concluded there was no decrease in the incidence of extra-articular manifestations in patients with RA diagnosed up to 1995. Smoking and early disability are independent risk factors for extra-articular RA.**Vos, I., et al.,(2017)** resulted the manufacturer's cut-off point, 55/68 (80.9%) RA patients were positive for anti-CCP2, 53/68 (78.0%) for anti-CCP3 antibodies, and 45/68 (75.0%) for RF. In the control group, 18/59 (30.5%) were positive for anti-CCP2, 23/59 (39.0%) for anti-CCP3, and 19/57 (33.3%) for RF (In the RF-negative RA group (n = 15), 8/15 (53.3%) were positive for CCP2, and 9/15 (60.0%) were positive for CCP3. In the group of RA patients with a disease duration less than 2 years, 20/26 (76.9%) were positive for anti-CCP2 as well as for anti-CCP3. In the group of patients with disease duration between 2 and 5 years, 13/18 (72.2%) were positive for anti-CCP2 positive and 14/18 (77.8%) for anti-CCP3. In patients with disease duration more than 5 years, 22/25 (88.0%) were CCP2 positive, and 20/25 (80.0%) were CCP3 positive.[7].**Kim, E.J.,et al (2009)** explains Interstitial lung disease (ILD) is a frequent extraarticular manifestation of rheumatoid arthritis (RA). While the nonspecific interstitial pneumonia pattern predominates in most forms of connective tissue-associated ILD, studies in patients with RA-associated ILD (RA-ILD) suggest that the usual interstitial pneumonia (UIP) pattern is more common in this patient population. High-resolution CT (HRCT) scans appear accurate in identifying UIP pattern in many patients with RA-ILD. Although the data are limited, UIP pattern appears to predict worse survival in RA-ILD patients. Larger, prospective, multicenter studies are needed to confirm this finding. We propose that the evaluation of patients with RA-ILD should focus on identifying those with UIP pattern on HRCT scans, as these patients are likely to carry a worse prognosis. In patients in whom the underlying pattern cannot be determined by HRCT scanning, surgical lung biopsy should be considered.

GENETICS:

Over the past decades, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)-supported researchers have identified several genetic factors that predispose some people to develop rheumatoid arthritis. More than one gene is involved in determining whether a person develops rheumatoid arthritis and how severe the disease will become. New areas in the human genome are identified which are associated with rheumatoid arthritis and they give us a lead to cure the disease. Some of the genes thought to be responsible for RA are:

- HLA: The HLA gene site is responsible for distinguishing between your body's proteins and the proteins of the infecting organism. A person with the HLA genetic marker is five times more likely to develop rheumatoid arthritis than those who do not have this marker. This gene is one of the most significant genetic risk factors for RA.
- STAT4: This gene plays a role in regulating and activating the immune system.

- TRAF1 and C5: This gene has a part in causing chronic inflammation.
- PTPN22: This gene is associated with the onset of RA and the progression of the disease.[8]

3.TREATMENT OF RHEUMATOID ARTHRITIS

The treatment of rheumatoid arthritis (RA) has gone through many major changes in the past 100 years. A number of modern therapies and drugs are now employed for the treatment of arthritis. Symptom-modifying anti-rheumatic drugs (SMARDs) are widely used to control symptoms of rheumatoid arthritis. Analgesics are used to reduce pain, and non-steroidal anti-inflammatory drugs (NSAIDs) including traditional or non-selective NSAIDs as well as selective cyclooxygenase-2 (COX-2) inhibitors are used to lessen pain and stiffness in arthritic patients [9].

NSAIDs (Non steroidal anti-inflammatory drugs):

Traditional NSAIDs have been reported to cause several adverse effects, the most important being gastrointestinal toxicity and renal damage. Such undesirable side-effects of NSAIDs have been attributed to the inhibition of constitutive isoform of cycloxygenase enzyme, COX-1. Treatment with traditional NSAIDs is often prescribed with gastro protective agents or a combination therapy is accompanied. At the turn of this century two new highly selective COX-2 inhibitors, known as Coxibs (celecoxib and rofecoxib) were introduced both of which were claimed to have low gastrointestinal (GI) side effects. Coxibs were found to spare COX1 and so enhanced the safety profile in the gastrointestinal tract, but on the other side increased the risk of heart attack and stroke. In 2004, rofecoxib was withdrawn worldwide because of serious cardiovascular events [10].

DMARDs (Disease modifying anti-rheumatic drugs):

Disease-modifying anti-rheumatic drugs (DMARDs) are used to try to slow the course of the disease. These include hydroxychloroquine (malaria drug), leflunomide, methotrexate (MTX,anti cancer), and sulfasalazine. These are genetically engineered medications that help reduce inflammation and structural damage to the joints by interrupting the cascade of events that drive inflammation. Another DMARD, tofacitinib, from a new class of drugs call jak kinase (JAK) inhibitors, fights inflammation from inside the cell to reduce inflammation in people with rheumatoid arthritis.[11]

New therapeutic regimens are now employed in the treatment of RA with the introduction of new classes of therapeutic agents. (DMARDs) have the potential to reduce or prevent joint swelling, pain, decrease acute-phase markers, limit progressive joint damage and improve function [12]. Therapy with DMARDs should be initiated promptly in persistent synovitis and joint damage. DMARDs commonly used in RA include methotrexate (MTX), hydroxychloroquine (HCQ), sulfasalazine (SSZ).

leflunomide, cyclosporine, etanercept and infliximab (American college of Rheumatology subcommittee on rheumatoid arthritis guidelines, 2002). Methotrexate is recommended as first line treatment for rheumatoid arthritis, while biologic DMARDs are usually considered only when the former are not sufficiently effective

[13].Moreover, these drugs are associated with considerable toxicity, which makes careful patient monitoring necessary. Major toxicity includes gastrointestinal upset, oral ulceration and liver function abnormalities that appear to be dose-related and reversible, and hepatic fibrosis [14]. Unfortunately, MTX alone may not fully control disease activity. So combination therapy is extensively used with varying level of success [15]. In conclusion, the ideal outcome of combination DMARD therapeutic strategies is one that is synergistic for efficacy and lacking any additive effects of toxicity.

Table 2. : A summary of the small molecules of clinically used DMARDs [16]:-

S.No.	Name of the agent	First used	Remarks
1	Gold salts	1920	Relatively long period of administration, rarely used these days.
2	Sulphasalazine	1940	Second most common DMARD used in Europe in 1990s.
3	Chloroquine, Hydroxychloroquine	1950	Less efficacious and less toxic than other DMARDs
4	Methotrexate	1950	Gold-standard Therapy
5	Cyclosporin A	1960	Efficacious but relatively toxicity has recluded widespread use
6	Leflunomide	1990	Side effects are similar to sulphasalazine and methotrexate.

4. New therapies:

Researchers have identified molecules that appear to play a role in rheumatoid arthritis and thus are potential targets to identify more candidate drugs which will have fewer side effects or will cure more patients.

Tofacitinib*:*

It is approved for the treatment of rheumatoid arthritis in 2012, was from a new class of drugs developed to target Janus kinases. One member of this family, JAK3, was discovered in the early 1990s by a National Institutes of Health (NIH) laboratory. Subsequent studies carried out in collaboration with the NIAMS, showed that genetic defects in JAK3 can cause severe combined immunodeficiency. This discovery led to the drugs which block Janus kinases which further suppress the immune system and are protective against the damaging inflammation of rheumatoid arthritis and certain other autoimmune diseases.

HERBAL THERAPY FOR THE TREATMENT OF ARTHRITIS

Herbal medicines are used for the treatment of various ailments from ancient times and it is not an exaggeration to say that the use of the herbal drugs is as old as mankind [17]. Herbal medicines are synthesized from the therapeutic experience of generation of practicing physicians of ancient system of medicine for more than hundreds of years [18]. Nowadays, researcher shows a great interest in those medicinal agents that are derived from plants because the currently available drugs are either have certain side effects or are highly expensive [19]. Nature has blessed us with enormous wealth of herbal plants which are widely distributed all over the world as a source of therapeutic agents for the prevention and cure of various diseases [20]. According to WHO, world's 80% population uses herbal medicines for their primary health care needs. Herbal medicines will act as

parcels of human society to combat disease from the dawn of civilization [21]. The medicinally important parts of these herbal plants are chemical constituents that produce a desired physiological action on the body [22]. Since ancient time India uses herbal medicines in the officially alternative systems of health such as Ayurveda, Unani, Sidha, Homeopathy, and Naturopathy [23]. In India, there are more than 2500 plants species which are currently used as herbal medicaments. For than 3000 years, the herbal medicines are used either directly as folk medication or indirectly in the preparation of recent pharmaceuticals [24]. Thus, from the knowledge of traditional plants, one might be able to discover new effective and cheaper drugs [25]

CONCLUSION AND FUTURE ASPECTS

Rheumatoid arthritis (RA) is a chronic autoimmune condition characterized by systemic symptoms, increasing joint degeneration, and joint inflammation. Understanding its fundamental mechanisms and creating tailored medicines have advanced our knowledge of RA care significantly. There are still issues, though, and more study is required to improve the effectiveness of diagnostic procedures, the efficacy of treatment plans, and the long-term consequences for patients. The safety profile, mechanism of action, and toxicity investigations of plant extracts are the key topics of this review. Plant extracts and multi-herbal preparations would be used as an alternative medicine with fewer side effects for the treatment of arthritis.

REFERENCES

[1] Lawrence, R.C., et al., Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum, 1998. **41**(5): p. 778-99.

[2] Dubey, L., S. Chatterjee, and A. Ghosh, Hepatic and hematological adverse effects of long-term low-dose methotrexate therapy in rheumatoid arthritis: An observational study. Indian J Pharmacol, 2016. **48**(5): p. 591-594.

[3] Turesson, C., et al., Extra-articular disease manifestations in rheumatoid arthritis: incidenc trends and risk factors over 46 years. Ann Rheum Dis, 2003. **62**(8): p. 722-7.

[4] Kim, E.J., H.R. Collard, and T.E. King, Jr., Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. Chest, 2009. **136**(5): p.

a. 1397-1405.

[5] Alenghat, F.J., The Prevalence of Atherosclerosis in Those with Inflammatory Connective Tissue Disease by Race, Age, and Traditional Risk Factors. Sci Rep, 2016. **6**: p. 20303.

[6] .Harris, E.D., Jr., Rheumatoid arthritis. Pathophysiology and implications for therapy. N Engl J Med, 1990. **322**(18): p. 1277-89.

[7] Vos, I., et al., Anti-citrullinated protein antibodies in the diagnosis of rheumatoid arthritis(RA): diagnostic performance of automated anti-CCP-2 and anti-CCP-3 antibodies assays.Clinical Rheumatology, 2017. **36**(7): p. 1487-1492.

[8] De Vries, N., et al., No support for HLA-DQ encoded susceptibility in rheumatoid arthritis.Arthritis Rheum, 1999. **42**.

[9] Wilson, H. D., Toepfer, V. E., Senapati, A. K., Wilson, J. R., & Fuchs, P. N. (2007). Hyperbaric oxygen treatment is comparable to acetylsalicylic acid treatment in an animal model of arthritis. The Journal of Pain, 8(12), 924-930.

[10] .Suleyman, H., Albayrak, A., Bilici, M., Cadirci, E., & Halici, Z. (2010). Different mechanisms in formation and prevention of indomethacin-induced gastric ulcers. Inflammation, 33(4), 224-234.

a. .Dale, J., et al., Combination therapy for rheumatoid arthritis: methotrexate and sulfasalazine together or with other DMARDs. Nat Clin Pract Rheumatol, 2007. **3**(8): p. 450-8; quiz, following 478.

[11] .Fries, J. F., Spitz, P. W., Mitchell, D. M., Roth, S. H., Wolfe, F., & Bloch, D. A. (1986). Impact of specific therapy upon rheumatoid arthritis. Arthritis & Rheumatology, 29(5), 620-627.

[12] .Singh, J. A., Furst, D. E., Bharat, A., Curtis, J. R., Kavanaugh, A. F., Kremer, J. M., ... & Bridges, S. L. (2012). 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis care & research, 64(5), 625-639.

[13] Kumar, P., & Banik, S. (2013). Pharmacotherapy options in rheumatoid arthritis. Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders, 6, CMAMD-S5558.

[14] O'dell, J. R., Leff, R., Paulsen, G., Haire, C., Mallek, J., Eckhoff, P. J., ... & Hadley, S. (2002). Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two year, randomized, double blind, placebo controlled trial. Arthritis & Rheumatology, 46(5), 1164-1170.

a. Matsuno, H., Small Molecule DMARD Therapy and Its Position in RA Treatment, in Innovative Rheumatology, H. Matsuno, Editor. 2013, InTech: Rijeka. p. Ch. 08.

b. Tandon V, Gupta RK. Histomorphological changes induced by Vitex negundo in albino rats. Indian Pharmacol. 2004;36:176–7.

c. Vispute S, Khopade A. Glycyrrhiza glabra Linn.-“Klitaka”: A review. Int J Pharm Bio Sci. 2011;2:42–51.

[15] Badami S, Moorkoth S, Suresh B. Caesalpinia sappan a medicinal and dye yielding plant. Nat Prod Rad. 2004;3:75–82.

[16] . Kalaria P, Gheewala P, Chakraborty M, Kamath J. A phytopharmacological review of Alstonia scholaris: A panoramic herbal medicine. IJRAP. 2012;3:367–371.

[17] Sudha K, Mathanghi SK. Traditional underutilized green leafy vegetables and its curative properties. Int J Pharm. 2012;2:786–93.

[18] Singh V, Patel H, Suvagiya V, Singh K. Some traditionally used anti-arthritic herbs a review. Int Res J Pharm. 2011;2:43–5.

[19] Kiran D, Rohilla A, Rohilla S, Khan MU. Phyllanthus amarus: An ample therapeutic potential herb. Int J Res Ayur Pharm. 2011;2:1096–9.

[20] Thirumal M, Vadivelan R, Kishore G, Brahmaji VS. Aristolochia bracteolata: An overview on pharmacognostical, phytochemical and pharmacological properties. Earth J. 2012;1:66–78.

[21] Kalita S, Kumar G, Karthik L, Rao BV. A review on medicinal properties of Lantana camara Linn. Res J Pharm Technol. 2012;5:711–5