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A POTENTIAL ROLE OF SUPPLEMENTS IN THE THERAPY OF RHEUMATOID ARTHRITIS: A REVIEW ARTICLE

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Abstract:

Rheumatoid arthritis (RA) is a chronic inflammatory disorder affecting 1% of the adult population. The disease is characterised by inflammation of the synovial tissue of multiple joints leading to pain, deformities and a reduced quality of life. Rheumatoid arthritis is a chronic inflammatory disease which generally affects the joints of the body. It involves three forms of the bones which are getting affected majorly in the body. These three forms include focal bone loss affecting the immediate sub-chondral bone, peri-articular osteopenia adjacent to inflamed joints and the axial and appendicular skeleton. RA is associated with decreased life expectancy and quality of life. NSAIDs and conventional synthetic disease modifying agents (DMARDs) are used. The conventional DMARD, Methotrexate remains the anchor drug to induce and maintain remission. The herbal drug is a holistic therapy, integrating emotional, mental and spiritual levels. The life style, emotional, mental and spiritual considerations are part of any naturopathic approach. The use of herbs does not generally involve adverse effects. The herbal medicine has gained momentum and it is evident from the fact that certain herbal remedies are more effective as compare to synthetic drugs. As per ayurveda the supplement play vital role to treat the RA. Drug used for the treatment of RA along with supplement have beneficial effect as compare to only drug treatment.

Keywords: Rheumatoid Arthritis, Conventional therapy, Supplements.

Introduction:

Rheumatoid arthritis (RA) is a systemic inflammatory joint disease which is mainly characterised by various symptoms includes joint inflammation, bone erosion, destruction of cartilage and infiltration of immune cells by synovial. It is an autoimmune disease affects the joints in addition, it also affects the other organs of

the body like lungs, heart, skin, kidneys, eyes and nervous system etc. It is a very complex process which involves the proliferation of synovial cells, pannus formation along with cartilage and bone erosion. In the disease process of rheumatoid arthritis joints are the main target, patients may show some symptoms like extra articular features including subcutaneous nodules, vasculitis, fibrosis and pulmonary fibrosis but in more severe cases of the disease. There are various inflammatory cytokines which are involved in rheumatoid arthritis are IL-1, IL-6 and TNF-α (Tumour Necrosis Factor). This disease is generally triggered by the interaction of both genetic and environmental factors and formation of disease related autoantibodies. About 0.5-1% of the population of the world is affected with the rheumatoid arthritis, women's are more susceptible with RA due to gender bias[1]. Various therapy has been used for the treatment of rheumatoid arthritis such as Glucocorticoids, NSAID's (Non-steroidal anti-inflammatory drugs), DMARD's (Disease modifying anti-rheumatic drugs) but some patient's don't respond to these drugs appropriately for those patients additional treatment are used which involves biopharmaceuticals, TNF-α inhibitors. This treatment offers to be a greater opportunity for the management of the disease. However, all above therapy have adverse effects [2]. There are number herbs have been used as food and for medicinal purposes to past era. Research interesthas been focused on various herbs that possess the anti-arthritic effect which may be useful to protectthe risk of development of RA andless toxic effects. The purpose of this review article is to introduce the therapy for rheumatoid with less toxic effects.

Role of Immune System the in Development of RA:

Theauto immune antibodies leads to the development of RA which is associated with more severe symptoms and joint damage and increased mortality. It is due to formation of the immune complexes.The formation of immune complexes are generally formed by ACPAs (Anti-citrullinated peptide antibodies) with citrulline containing antigens and eventually binds with RF (Rheumatoid Factor) which leads to the complement activation system. The autoimmune response can be detectedto citrullinated self-proteins is a major advance research. The ACPAs can bind citrullinated and itsresidues on many self-proteins including vimentin, α-enolase, fibronectin, fibrinogen, histones, and type II collagen. The lung is the major tissue which is attracted more towards the autoimmune response, which is more compatible with the role of smoking in rheumatoid arthritis. The ACPAs has been diagnosed 10 year before RA, so it is called pre rheumatoid arthritis with the passage of time, theconcentration of the ACPAs increases, especially before the involvement of the articular.

ACPAs can be of IgG, IgA, IgMiso-type and these all are the indicative of the T-cell and have an altered glycosylation status that confers enhanced Fc-receptor and citrullinated antigen binding. B-cells which are produced by the ACPAs are generally present in the synovium and in the circulation. The ACPAs itself become a pathogenic by activating the macrophages or by activating osteoclasts via immune complex formation or Fc-receptor involvement or by binding membrane citrullinated residues and it further promoting the bone loss. Rheumatoid factor is the proteins which are produced by the immune system that can attack healthy tissue in the body. RF is directly involved in the mechanisms of activation of macrophage and induction of cytokines which cause the inflammation and joint destruction. The alteration of immune system various system are altered. Now a days for relief of the patientconventional treatment are used for RF and ACPAs concentration decreases but the patient rarely become ACPAs negative many drugs are used, however they have serious side effects throughout the body particularly in liver and kidney also damaged [3].

Role of Synovial Immunological In Rheumatoid Arthritis:

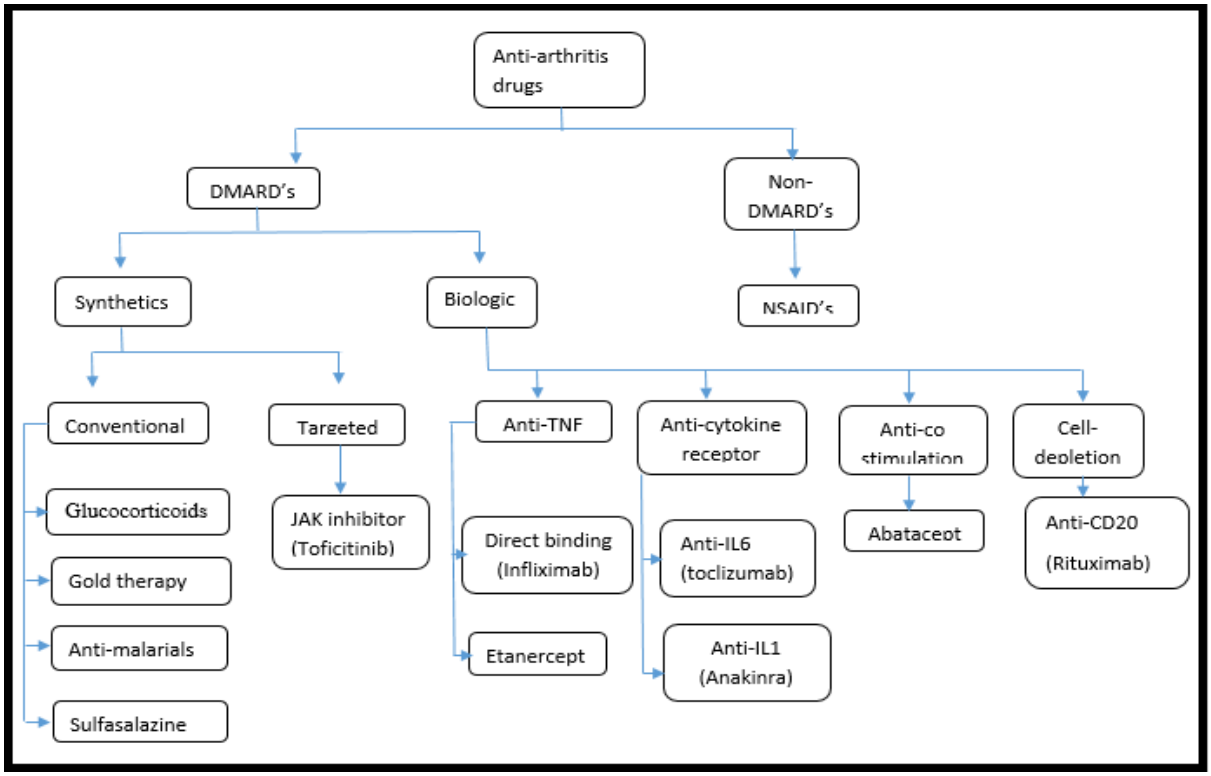
It is painful condition during the joint movement the leukocytes (WBC) infiltrate the synovial compartment, synovitis occurs. Accumulation of leukocyte are generally reflects migration instead of native proliferation. The activation of epithelial cells of synovial membrane enables the cell migration, which further increase the expression of chemokine's and adhesion molecules including immunoglobulin, integrin's, selectin etc. It is consequently induced neoangiogenesis by chemokine's and native hypoxic conditions are the distinctive features of the early synovitis. The micro-environmental are changed and build up the synovial inflammatory tissue in joint in condition of rheumatoid arthritis [4]. The patients have RA consequently inflammation is difficult to bear.

Role of Synovial Membrane in Inflammation:

The synovial membrane plays a vital role in inflammation during immune activation forms the swelling of the joint in rheumatoid arthritis and is characterised by the infiltration of leukocyte (WBC) in the synovial compartment. The cellular composition of synovitis includes innate immune cells (mast cells, monocytes, dendritic cells) and adaptive immune cells (T-helper1, T-helper17cells, B-cells, plasma cells). This complex network of chemokine and cytokine regulates the inflammatory place in the synovial compartment which is activating the endothelial cells. The complex chemokine and cytokine leads to the introduction and provoke

the inflammatory response and attracts the immune cells to incorporate in the synovial compartment. Osteoclast are cells which is generally triggered by the activated fibroblast cell together with the incorporated activated T and B cells and monocytes via receptor activator of nuclear factor κ-B ligand (RANKL) which is expressed on T-cells, B-cells and fibroblasts [5].

Recent Therapy Used In Rheumatoid Arthritis:



Non-steroidal Anti-inflammatory drugs:

These are drug used for the symptomatic control in rheumatoid arthritis. NSAIDs reduce joint pain and swelling but don't alter the course of disease and should not be used alone. From the past few years the aspirin is the most widely used in the treatment of rheumatoid arthritis. It inhibits the cyclooxygenase, an enzyme that catalyses the conversion of arachidonic acid to prostanoids. Gastric irritation and nephrotoxicity are the common side-effects. The NSAID'sare the drug used in the treatment of RA however, along and serious adverse effects of NSAID's [7-8].

DMARDs Therapy:

These are drugs also used in the therapy of Rheumatoid arthritis known as disease modified anti-rheumatic drugs. In 1980's the term DMARD's was coined. These are used to alter the disease condition. [11, 12] These are classified into the two categories: synthetic DMARDs and biologic DMARDs [6,9].

Synthetic DMARDs used for Rheumatoid arthritis.

Synthetic DMARDs: The synthetic DMARDs are classified in two categories traditional and targeted DMARDs. The traditional synthetic DMARDs are mainly used in the treatment of rheumatoid arthritissuch as azathioprine, cyclophosphamide, cyclosporine, hydroxyl-chloroquine sulphate, leflunomide, methotrexate and sulfasalazine.

Targeted DMARDs are the drugs used for particular target such asapremilast (Otezla), Tofacitinib (Xeljanz).

Biologic DMARD Therapy:this therapy has been used from last decay the following drugs are used such as tocilizumab (actemra), cetrolizumab (cimzia), etanercept (enbrel), adalimumab (humira), anakinra (kineret), abatacept (orencia), infliximab (remicade), rituximab (rituxan), golimumab (simponi) [10].These drugs have following side effects like severe infections, such as lung infections, liver damage, reduced ability to make new blood cells, nauseaand pain or swelling at the injection site.

Gold therapy:

This therapy is generally used for the complete treatment of the poncet's arthritis. Poncet's arthritis is a rare aseptic form of arthritis recognised in the active TB patients. Gold therapy became a first DMARD in the treatment of the rheumatoid arthritis. The currently used gold salts preparation given by intramuscular are gold sodium thiomalate and gold sodium - thioglucose and these preparations have comparable efficacy to methotrexate and the oral preparations of gold salt are also available including auranofin but the oral preparation of gold salt is not much effective. Its mechanism of action is not clear but it has been shown to decrease levels of COX-2, IL-6, MMP-3 thought to be as a result of inhibition of MAP phosphatase-1 [13].

The mechanism of action and side effects of commonly useddrugs are in the treatment of RA are mentioned in table no1.

Table:1

Drugs used in the treatment of rheumatoid arthritis[14]:

Drugs	**Mechanism of action**	**Useful benefits**	**Side effects**
NSAIDs: **Sulfasalazine**	It inhibits the COX and sulfasalazine reduces the production of IL and also	It helps in the improvement of RA activity, reduction of	Nausea, vomiting, loss of appetite, headache, dizziness,

	inhibits TNF-α expression of macrophages.	radiographic progression.	bone marrow depression, hepatotoxicity.
DMARDs: Leflunomide	It inhibits the dihyroorotate dehydrogenase by which pyrimidine synthesis stops.	It helps in the improvement of the rheumatoid arthritis.	Diarrhoea, allergic reactions, hepatotoxicity.
Glucocorticoids	It induces the apoptosis of leukocytes.	It helps in maintaining the joint function and in the improvement of the RA.	Hypertension, glaucoma, different infections, growth retardation, diabetes.
Anti-cancer: Methotrexate	It inhibits the dihydrofolatereductase enzyme by which synthesis of purine and pyrimidines.	It helps in the improvement of the rheumatoid arthritis, physical activity. It also provides the protection against the development of heart diseases.	Hepatotoxity, bone marrow suppression, pulmonary fibrosis.
Immunosuppressants:Cyclosporine A	It inhibits the calcineurin.	It provides the protection against the development of the heart diseases.	Hypertension, renal toxicity, tremor, renal toxicity.
Antimalarials	It raises the pH of intracellular lysosomes and other cytoplasmic vesicles.It alters the protein functioning which	It helps in the improvement of the RA	Skin rashes, ocular toxicity, nausea, vomiting, and epigastric burning.

	may lead to decrease in the autoantibody formation.		
TNF-inhibitor: **Etanercept** **Infliximab** **Adalimumab** **Golimumab** **Certolizumab**	Etanercept-it inhibits the functioning of TNF receptor.	It helps in the reduction of radiographic progression.	Headache, abdominal pain, vomiting, rashes, injection site reaction, bleeding, itching, increased risk of pulmonary fibrosis and malignancies.
Anakinra	It is the IL-1 receptor antagonist.	It helps in the reduction of radiographic progression and improves the quality of life and provides the improvement of RA activity.	Injection site reactions.

Supplements for Rheumatoid Arthritis:

Thefollowing different supplements are used for the treatment of RA:- SAM-e (S-adenosylmethionine), Boswellia serrate (Indian frankincense), Capsaicin , Turmeric / Curcumin (Curcuma longa), Avocado-Soyabeanunsaponifiables, Cat's claw, Fish oil, Gamma linolenic acid (GLA), Cinnamon , Willow bark , Black pepper, Garlic, Ginger.

Role of Food in Rheumatoid Arthritis as Per Ayurveda

Ayurveda has been recognized by the World Health Organization (WHO) as a complete system of natural medicine, but it is not widely known that the every first study of a traditional medical system sponsored by WHO, classical Ayurvedic treatment for rheumatoid arthritis (RA) was conducted in collaboration with the Indian Council for Medical Research (ICMR) and the Ayurvedic Trust, Coimbatore, Tamil Nadu, India, from 1977 to 1984 [15]. The following foods are:

A. *Grains:* Grains like one year old variety of rice (long grain rice), red variety rice (*Raktashali*) or red rice available now in health food stores. Rice are harvested in 60 days or short grain rice (*Shasthika*), barley (Yava) and millets (*kodo* or fox millet) are good as foods for Rheumatoid arthiritis. These foods are light and easy to digest. Barley kernels and other products made from barley lowers inflammatory markers.

B. *Legumes and Pulses:* In particular chickpeas and horsegram are good foods for Rheumatoid arthritis.

C. *Fruits and Green Leafy Vegetables:* Green leafy vegetables and fruits contain a variety of polyphenols, bioflavonoids, catechins, carotenoids, vitamin C, riboflavin, vitamin E, and low molecular weight compounds.

   These constituents have antioxidant, fibrinolytic and anti-inflammatory characteristics. Herbs with a bitter taste like neem (*Azadirachtaindica*), bottle gourd, bitter gourd, pointed gourd, brinjal, drum stick and goose foot (*chenopodium*) are recommended. We can also find the bitter taste in arugula, dandelion greens, radicchio and kale. Fruits like berries (strawberries, tart cherries, and red-raspberries), avocados and watermelon are beneficial foods for Rheumatoid arthritis.

D. *Spices:* Beneficial spices include ginger, turmeric and garlic are helps to prevent the arthritic.Spices add flavour to the food which have antimicrobial, anti-inflammatory and analgesic properties besides their digestion promoting impact.

E. *Ashwagandha:* It is medically known as *Withaniasomnifera.* In the West, Ashwagandha is popularly known as Winter Cherry. Also, it has a therapeutic properties, which include reducing joint pains.

F. *Banyan:* The Banyan tree's medical name is *Ficusbenghalensis*. The Banyan tree's sap is externally applied over the joints and the pain usually disappears after a few regular applications.

G. *Garlic:* The biologically name for garlic is *Allium sativum.* Five to six cloves eaten everyday has proved to reduce knee pain[16].

H. *Ginger:* Ginger is biologically called as *Zingiberofficinale*. These can be easily included in diet and it helps to reduce the knee joint.

Role of Homeopathic Remedies Used In Rheumatoid Arthritis

A. *Arnica:* Arnica is a homeopathic remedy generally used to treat the symptoms of chronic arthritis. The symptoms tend to worsen if you touch the affected area.

B. *Bryonia*: It is recommended when severe pain is in the joints. The symptoms tend to worsen in cold weather.

C. *Calcareafluorica*: This remedy is recommended if the pain tends to improve with the application of heat. The symptoms include swelling of the joints and formation of nodes. It is especially used if the arthritis develops after an injury.

D. *Kali carbonicum*: If the joints are extremely stiff with the pain aggravating during the early morning hours, then this remedy is prescribed. It also helps if the symptoms tends to worsen in damp and cold weather.

E. *Pulsatilla*: This remedy is prescribed in cases where the intensity of the pain keeps on fluctuating and also if the pain is not localized. The symptoms tend to worsen in warm conditions and improve in cold conditions.

F. *Rhododendron:* Rhododendron is recommended if the symptoms of arthritis tend to flare up and aggravate in cold conditions. Generally the pain increases during the early morning hours or if you stay stationary for a long time.

G. *Kali bichromicum**:*** This is useful when arthritic pains alternate with asthma or stomach symptoms. Pains may suddenly come and go, or shift around. Discomfort and inflammation are aggravated by heat and worse when the weather is warm [17].

Conclusion:

Rheumatoid Arthritis is a common disease with a focal joint destruction and complications which is secondary to the systemic inflammation. As from the knowledge of the etiology and pathogenesis of the disease, it is important to adapt and modify the treatment of the disease. On the basis of treatment options it is better understanding of the molecular Pathophysiology of disease have led to produce changes in the management of the disease.

The conventional use of DMARD's has allowed patients to achieve improved function and it helps to decrease joint destruction. These medications also have side effects. Homeopathic medicines are used for the treatment of RA. These drugs protect the disease not cure. The herbal medicines are also used these are effective against RA with less side effect. As per Ayurveda supplements play an important role to treat the

RA. The purpose of this review article is that the supplement is essential with using the drugs in treatment of Rheumatoid arthritis.

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