PHCOG REV. : Review Article Natural Compounds as Anti-Arthritic Agents-A Review.

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Abstract:-

The last few years of arthritis researches in India have seen marked advances in our understanding of the basic treatments involved in the connective tissue disease and give a data of certain unexplored anti-arthritic herbs of Indian origin. These discoveries carried in the search for the paramount therapy which will prove to be inexpensive with minimal side effects. In more recent years, herbal treatment has risen to the forefront with the discovery of few Indian natural products which can generate better way for the treatment one of the major concerns of society, rheumatoid and the osteoarthritis. Various treatment modalities has been prescribed, along with the conventional and non-conventional medicine but due to their one or more adverse effects and dissatisfaction amongst users, these treatments are not satisfactory enough to give relief to the arthritic patients. So there has been rise in the use of CAM (complementary and alternative medicine) as compared to the allopathic system of medicine. Now a days, people from all parts of society have started to rely on the herbal therapy and formulations for arthritis. So, this review sparks some important Indian medicinal plants and herbs which benefit in any form of conditions associated with arthritis with special emphasis on rheumatoid arthritis and osteoarthritis.

Key words: - Rheumatoid arthritis (RA), Osteoarthritis (OA), Anti-Arthritic (AA), Complementary and Alternative Medicine (CAM), Anti-Inflammatory (AI), Gouty Arthritis (GA)

Introduction:-

Rheumatoid arthritis (RA) is an autoimmune disease in which a person's immune system starts mistakenly attacking the person's own body. It is a systemic inflammatory disease, characterized by pain, swelling, stiffness in a person's joints. However, RA affects different people in different ways, in terms of the symptoms they have, how serious the symptoms are and how long the symptoms last. It has societal effect in terms of cost, disability and lost productivity. There are 150 varieties of arthritis affecting almost 150 million people in India. The second most affecting type of arthritis is Osteoarthiritis (OA). A major distinction between OA and RA is that the former strikes the larger joints (knees, hips) first whereas latter first strikes the smaller joints (1). OA is the breakdown of the joint articular cartilage which results in release of matrix components into the synovial fluid where they may become exposed to immune systems of the patients. (2). Close to 15 per cent of the general population could have one or other form of arthritis. RA is known to affect 1-2% of population and does not have any racial predilections. Every third person above the age of 70 years suffers from arthritisinduced knee pain (3). In people aged 15 to 45 years, women predominate by a ratio of 6:1, which is equal among patients in the first decade of life and in those more than 60 years old (4). The causes behind this are complex and the exact pathology of disease is still to be understood. However, efforts are been made to understand the molecular mechanism for pathogenesis of RA (5).

Since ancient times our ancestors have used phytochemicals found in plants to curtail the inflammatory process. The emergence of today's pharmaceutical industry, in large part, has been based on natural products. It has been reported that proinflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , and IL-6 are important mediators of the disease perpetuation. Immune cells such as T cells also impart their role in the progress of the disease. Apart from the conventional treatment strategies using non steroidal anti-inflammatory drugs (NSAIDs), disease modifying antirheumatic drugs (DMARDs) and glucocorticoids newer and safer drugs are continuously being searched. Alternative medicine is another therapeutic approach for treatment of the disease, which include herbal and folklore medicines. Many plants and plant products are under scientific exploration to develop a novel therapeutic agent. Here we have tried to review various Indian ancient Ayurvedic medicinal plants for their potential to treat RA.

Pathogenesis of rheumatoid arthritis and possible role of natural compounds:-

In order to explore role of natural compounds, one should know the pathogenesis of the disease. In the pathogenesis of arthritis, natural compounds are acting on most of the stages in treatment of arthritis. Most of these compounds are antioxidants, immunomodulators, chondroprotective, inhibition of T-Lymphocyte proliferation and many of them have anti-inflammatory activity. Exact pathology of the disease is still to be understood. RA represents inflammatory disease of unknown etiology and synovial hyperplasia with local invasion of bone and cartilage. In RA, migration of leukocytes into the synovial tissues occurs. These leukocytes and other cells produce several mediators of inflammation, including chemokines-chemotactic cytokines that recruit leukocytes to the inflammed joint and also play a role in angiogenesis (6-7). Moreover there are also reports that free-radicals worsen the disease and contribute towards damage to bone and cartilage . Following mentioned are the various mediators of RA.

(1) Role of inflammatory Cytokines:-

In RA there is an over production of pro -inflammatory cytokines and henceforth there is an imbalance in the body's immune system e.g., TNF-alpha, IL-1 and a deficiency of antiinflammatory cytokines e.g.IL-10, IL-1. Moreover there are also reports that free-radicals worsen the disease and contribute towards damage to bone and cartilage. RA pathogenesis is regulated by pro-inflammatory cytokines such as IL-1 and TNF-alpha that activate a broad array of intracellular signal transduction mechanisms (8). Recent data are presented illustrating the importance of IL-18 in the induction and perpetuation of chronic inflammation during experimental and clinical rheumatoid synovitis. Also according to the latest studies light has been thrown on the role of IL-17 in RA. It has been studied that there exists a relationship between Immune and skeletal systems as it is a well known fact that RA is one of the conditions associated with musculoskeletal system. RANKL (receptor activator nuclear factor K-B ligand) or TNF-related activation induced cytokine (TRANCE) is a type-1 a transmembrane protein which similar to other members of TNF receptor family, assembles into a functional trimer. RANKL stimulates osteoclastogenesis through nuclear factor of activated T cells (NFAT) c1, which is also a crucial regulator of immunity. In RA, the degradation of bones occur due to the enhanced activity of osteoclasts, which mainly depends upon IL-17 producing Helper T-cells (Th17).Recent data suggests that IL-17 producing Th -cell subset has osteoclastogenic activity whereas Th1 and Th2 cells have anti -osteoclastogenic effects. IL-17 is well known to induce local inflammation in autoimmune diseases through inflammatory cytokine production. Also it has been shown that Th-17 cells express higher levels of RANKL than Th1 and Th2 cells. It was recently shown that tumor necrosis factor and interleukin-1 are master cytokines in the process of human rheumatoid arthritis (9). Studies in experimental models revealed that tumor necrosis factor is indeed a pivotal cytokine in joint swelling and that interleukin-1 is the dominant collagen destructive cytokine. The production of interleukin-1 may occur independently of tumor necrosis factor.

(2) Genetic factors:-

Natural products have been optimized over long time periods against their gene product. They may exert their therapeutic effect by suppressing the genes which are disease causing and activation of those genes that are involved in providing therapeutic relief to the patients. So, it is necessary to know the genetic basis of RA epidemiology, so that more and more natural compounds can be used to benefit in RA.

Studies have shown that the genetic predisposition may be responsible for the pathogenesis of RA. There is epidemiological evidence that genetic factors are related to RA. During the last years, substantial evidence has been accumulated on the relationship of HLA-DRB1 alleles (called the shared epitope [SE] alleles) with susceptibility to RA, as well as with disease expression and severity (10). The recent studies proved the lack of an association of 627 IL- 10 gene polymorphism with RA and the clinical findings implies that the IL-10 gene polymorphism cannot serve as a candidate gene marker for screening RA patients (11). The major histocompatibility complex (MHC) molecules, located on T-Lymphocytes play an important role in most patients with rheumatoid arthritis. These molecules can be characterized using human lymphocyte antigen (HLA) typing. Majority of patients with RA have HLA-DR4, HLA-DR1, or both antigens found in MHC region. Patients with HLA-DR4 antigen are 3.5 times more likely to develop RA than those who have other HLA-DR antigens .Although MHC region being important, it is not the sole determinant, because patients can have the disease without these HLA types .(12)

(3) Role of Proteases:-

Mostly the tissues of synovial joints are composed of extracellular matrix and key pathological roles in degeneration of this matrix is performed by metalloproteinases such as matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs(ADAMTS). However other proteases such as Cathepsin K are likely to play an important role, especially in bone turnover.

Proteases combine to form complex regulatory networks, the correct functioning of which is necessary for tissue homeostasis and the imbalance of which may be the feature of synovial pathology. So it becomes important to precisely understand these proteases involved in these networks which will help to know about the associated pathology. There are various proteases which are involved in the pathology of RA. (13)

Synovium derived proteases, i.e. metalloproteinase with thrombospondin motifs (ADAMTS), Matrix Metalloproeinases (MMPs) and Cathepsin K lead to the degradation of cartilage and bone by proteolysis of cartilage aggrecan . (14) Cathepsin K is known to cause the angiogenesis into synovium which lead to loosening of matrix by proteolysis .MMP-9 is found to play a pivotal role in cleavage of matrix components. Some proteases play an important role in activation of other proteases such as Tryptase and Chymase cause activation of pro-MMP-3 and Chymase cause processing of Pro-MMP-1. Current studies have revealed that ADAMTS-5 is the key protease in aggreecan breakdown in animal models of Arthritis. (15)

So, in view of RA epidemiology we conclude that the natural agents, that have potential to suppress TNF-alfa, IL-1 beta, cycloxygenase-2, lipoxygenase, matrix metalloproteinases or adhesin molecules,or suppression of NF-kB acivation are worth for the treatment of arthritis. Hence, this information may be utilised to produce a lead molecule that may act on suitable targets ultimately leading to the discovery of a suitable compound that may be used in arthritis. Most of the natural compounds that we have listed at the end table act on multiple targets to get benefit in arthritic condition (16).

Current treatment aspects:-

Apart from the herbal therapy, allopathic medicines are used for arthritis treatment in spite of the various side-effects of drugs. Current treatment modalities for both RA and OA are mostly symptomatic although recently it has been suggested that use of disease -modifying anti-rheumatic drugs (DMARDs) has led to important gains in overall ability to treat RA patients, resulting in a better health status for patients with RA (17). The value of (DMARDs) for treating OA or RA is also limited by their side effects and the fact that they are more expensive to use than traditional NSAIDs. In the fifties and early sixties, the treatment of RA revolved around the use of high-dose aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. These drugs provided symptomatic relief but did not have any significant effect on the underlying disease process. In addition, they caused a fair degree of side-effects. Subsequently, diseases modifying antirheumatic drugs (DMARDs) were added to the existing armamentarium. These included gold, d-penicillamine, chloroquine and hydroxychloroquine. These drugs had their limitations. Sulphasalazine was designed for the treatment of RA but failed in its initial trials to produce benefit. The drug was rediscovered about 30 years later and became an important addition to the other DMARDs. Methotrexate, sulfasalazine, hydroxychloroquine and cyclosporine, either alone or in combination have been the principal therapies for RA in the last decade. It is now well established that early therapy with DMARDs is critical for better long term outcome in RA. Also, combinations of DMARDs are well tolerated and result in better outcome than monotherapy. It is well recognized that erosive changes occur early in the disease, often in the first year. In addition, mortality among RA patients who present early is lower than those who present later in the course of the disease. Early and aggressive therapy is the current standard of care for RA . Recently efforts have been focused on using the class of drugs called biologics (antibodies or soluble receptors for IL-1, IL-6 and TNF-alpha) for the treatment of OA and RA. Although these agents reduce inflammation and joint destruction their long term risks and benefits are yet not clear. Additionally higher costs and the findings that they are not effective universally and severe side effects such as life threatening infections and increased risk of malignancies limit the use of such agents in many populations. Thus a final assessment on the use of biologics for the treatment of RA or OA, particularly with regard to risk of infections, malignancies and autoantibody production has to be carefully monitored (18-20). Besides all the above therapies, arthroplasty, synovial fluid replacement and cloned monoclonal antibodies as well as the nanoparticle therapy has been used for RA treatment.

Current Scenario of CAM utilization:-

Nowadays use of Botanicals and natural supplements in various diseased conditions is on rise. Natural compounds in the treatment of arthritis may also be regarded as a part of CAM (Complementary and Alternative Medicine) and these are now widely accepted worldwide as well as in India. There are a wide set of CAM therapies that are used, viz. diet modification, ayurveda, homoeopathy, chiropractic, acupuncture, wearing of copper bracelets, magnetotherapy, use of botanical herbs, and vitamins and mineral supplements because of the belief that modern medicine had no cure for RA and adverse reactions are rare with CAM. Because of these and other limitations the use of CAM therapies such as acupuncture and extracts of medicinal herbals is on the rise and according to reports ~60-90% of dissatisfied arthritis patients are likely to seek the option of CAM therapy. (21) BVA (Bee- Venom Acupuncture) has been considered as a promising therapeutic method for various diseases in Korean medicine. Jae-Dong Lee reported that BVA simultaneously exerts pharmacological actions from the bioactive compounds isolated from bee venom and studies have further revealed the efficacy of BVA for rheumatoid arthritis and osteoarthritis (22). Y.-K. Yim et al reported that Electro-acupuncture at acupoint ST36 reduces inflammation and regulates immune activity in Collagen-Induced Arthritic Mice. Kwon et al. and Seo et al. conducted a comparative study of acupoint versus non-acupoint stimulation on an adjuvant induced RA animal model with BVAand found that Direct injection of bee venom into acupoint ST36 produced a potent anti-nociceptive effect. Kim et al. and Choi et al. conducted an experiment to show effectiveness of BVA at acupoint ST36 by inducing arthritis in rats by a mixture of type II collagen (23). It is highly likely that the effectiveness of BVA for arthritis is a promising area of future research. However, there is limited evidence demonstrating the efficacy of BVA in arthritis.

Huayue Chen et al reported the efficacy of Tibetan medicatedbath therapy on adjuvant arthritis (AA) of rats in comparison water-bath dexamethasone administration. with and Furthermore there have been reports on the use of Indo-Tibetian bath therapy in rheumatoid arthritis. (24) Because of these and other limitations the use of CAM (Complementary and alternative medicines therapies such as acupuncture and extracts of medicinal herbals is on the rise and according to reports ~60-90% of dissatisfied arthritis patients are likely to seek the option of CAM therapy (25-26). Patients who use CAM appear to be very much satisfied with the self care approach. Herbal medicines are the root of various traditional medicines systems around the world. Botanicals are a chemical source that directly provides $\sim 25\%$ of currently used crude drugs, with another $\sim 25\%$ derived from chemically altered natural products. Arthritis is one of the foremost disease for which patient seeks the CAM option (27). An increasing number of people in US as many as 42% use CAM approaches to help meet their personal health problems (28). Many plants and plant products are under scientific exploration novel therapeutic agent. Arthritis is one of the foremost disease for which patient seeks the CAM option worldwide. In Australia the figure is 20-48%.Canada has a figure of CAM utilization which is around 11-32%. Then comes India, amongst next CAM users. i.e. somewhere around 33%. Israel is reported to bear the least figure of CAM users i.e. 6% only. Netherlands comparatively has a good CAM utilization figure of 16%.UK shows the CAM utilization about 25-73%. Then France has 36% CAM utilization and South Africa shows 38% CAM utilization figure. In India 43-72% people use CAM and in US 18-94% people are using CAM. Australian rheumatic patients use 40-82% CAM. In Germany

CAM users are 72% and in Canada 62%. (29) Harvesting of natural godowns

Nowadays, the trend is the discovery and applications of bioactive agents from natural sources. Natural products account for 30% of international drug sales (30). Although most medicines are derived from terrestrial plants and animals, ecologists estimate the number of species in the marine environment to be 0.5 -10 million. Most of these are still on the verge to be discovered (31). Thats the reason why the therapeutic effects of natural product derived drugs are predominantly achieved in antibiotic therapies, oncology and immune regulation. As the natural products are generally not related to the biological environment of the producing organism, henceforth it is less likely to identify potent natural products against molecular targets. Furthermore, higher hit rates are generally obtained for natural product libraries in HTS (High Therapeutic Screening campaigns) compared to medchem or combichem libraries. Certainly, natural products are a valuable source of unsurpassed structural diversity and functional density to identify screening hits. Only a tiny fraction of the microbial world has been explored and new synthetic methodologies are only gradually applied in natural product small library synthesis, one can expect many more

molecules derived from nature with surprising biological activities. After a long neglection for years natural products drug discovery has again claimed attention and is on the verge of a comeback (32). Also WHO has been promoting traditional medicines as a source of less expensive, comprehensive medical care, especially in developing countries as it has been found that eighty percent of the world's population relies on medicinal plants for their primary health care. Such herbal medicines are easily available, cheaper, time tested and considered safer than some of modern synthetic drugs (33). Of the 20 best selling non-protein drugs in 2001, seven were either derived from natural products or developed as a result of leads generated by natural products. No doubt, there has been a long history of achieving success in discovering drugs from natural sources, despite of that natural products have fallen out of favour in current high throughput screening. In 2002, spending on medicines exceeded \$ 400 worldwide. (34). Natural compounds that can modulate the expression of pro-inflammatory signals can be used in the arthritis treatment. So, in view of the use of natural products in arthritis, the table below enlists few Indian medicinal plants with their mechanism of action with reference to their role in arthritis.

Name of Plant	Family	Active Chemical Constituent	Mode Of Action	Type of Arthritis	Ref
Vitex negundo	Verbenaceae	Flavone Glycosides	AI	AA	35-36
Phyllanthus embllica	Rubiaceae	Phyllanthin	Chondroprotective potential	OA	37
Camellia sinensis	Theaceae	Polphenols and Catechins	AI, Coll. Type II inhibition, Cartilage Proteoglycan & Matrix Metalloproteinase.	RA	38-39
Zingiber Officinalis	Zingiberaceae	-	AI	RA	40-41
<i>Curcuma longa</i> Linn	Zingiberaceae	-	AI	RA	42
Commiphora mukul	Burseraceae	Guggulosterones	Inhibition of Collagenase and Hyaluronidase, AI	OA & RA	43-44
Terminalia chebula	Combretaceae	-	Inhibition of collagenase and Hyaluronidase	AA	45
Głycyrrhiza glabra	Leguminosae	-	Inhibition of growth of Rheumatoid Arthritis Cells	RA	46
Tribulus terrestris	Zygophyllaceae	Steroidal Saponins- Terrestrosins	AI	RA	47-48
Boswellia serratia	Burseraceae	Gum Resins	AI	RA	49
Withania somnifera	Solanaceae	Withanolides	Chondroprotective, AI, Immunomodulator	OA & RA	50-51
Semecarpus anacardium	Anacardiaceae	Flavonoids	AI	AA & OA	52-53
Dioscorea deltoidea	Dioscoreaceae	Steroidal Saponins	AI	MA & RA	54-55
Tinospora cordifolia	Menispermaceae	-	AI	RA	56-57
Ocimum sanctum	Labiatae	Eugenol	AI	RA	58-59

List of anti-arthritic drugs with chemical constituents and mode of action.

Allium sativum	Liliaceae	Allicin	AI	AA	60-61
Tylophora indica	Tylophoraceae	Tylophorine	AI	AA	62
Asparagus	Liliaceae	-	Immunomodulator	АА	63
Cinnamomum camphora	Lauraceae	-	AI	RA	64
Garcinia cambogia	Guttiferae	-	AI	АА	65
Momordica	Cucurbitaceae	Charantin	AI, Apalgesic	GA & RA	66
Morinda citrifolia	Rubiaceae	_	Apalgesic	AA	67
Panax Ginseng	Araliaceae	-	AI	AA	68
Myristica fragrans	Myristaceae	Anthocyanins	AI	AA	69
Ricinus communis	Euphorbiaceae	-	Aberrant lectin binding of IgG from Rheumatoid Arthritic Serum	RA	70
Plumbago zeylanica	Plumbaginaceae	-	AI	AA	71
Pluchea lanceolate	Compositae	Sterols	AI	AA	72
Sida cordifolia	Malvaceae	Alkaloid(5-	AI & Analgesic		73-74
·		hydroxymethyl-1)- (1,2,3,9-tetrahydro- Pyrrolo)2,1-b) Quinazoline -1-yl)heptane-1-one)		АА	
Azadirachta indica	Meliaceae	Nimbidin	AI	AA	75-76
Centella asiatica	Umbelliferae	Madecassoside	AI		77
				RA	
Ananas comosus	Bromeliaceae	Bromelain(standardized Complex of proteolytic enzymes –cysteine proteases)	Reduced muscle and tissue inflammation	RA & OA	78-79
Desmodium	Fabaceae	Phenolics and a	AI	RA & OA	80
gangeticum		Pteroterpenoid – Gangetin.			
Linum	Linaceae	Essential fatty acids, α -	AI, suppression of T-lymphocyte	RA	81
usitatissimum		linolenic acid, PUFA's & y-linolenic acid	proliferation		
Tanacetum	Compositae	Parthenolide	AI, Inhibition of proliferation of		82
parthenium	1		fibroblast like sinoviocytes in	RA	
((Feverfew)			vitro		
Crocus sativus	Compositae	Crocetin	AI	АА	83

Role of some essential minerals in arthritis

Science is increasingly finding therapeutic potential in minerals and natural source compounds. Many of these compounds have an esteemed therapeutic lineage, having been used in native medicine for thousands of years to treat arthritis pain and other ailments. Many unique mineral compounds, though ancient, is supported by modern research. Minerals may be nature's gift to ease arthritis pain. An increasing number of diseases today may be associated with mineral deficiency. Though mineral deficiencies are associated with several arthritic conditions, minerals are often overlooked as a needed supplement in the treatment of arthritis. Ancient cultures have used minerals for their health benefits and healing properties for hundreds of generations. By studying the use of minerals in ancient cultures, valuable insight has been gained as to which minerals are the most effective in treating arthritis and joint pain. Choosing the right minerals is a great first step in combating arthritis pain. Here is a quick look at which minerals are recommended. Copper is needed to activate lysyl oxisidase, the enzyme responsible for cross linking collagen and elastin, creating connective tissue. Manganese is needed to build cartilage. We can have substantial levels of Glucosamine but without adequate manganese the production of cartilage grinds to a stop. In a clinical trial studying glucosamine, chondroitin and manganese, 72 people with mild to moderate osteoarthritis of the knee showed significant improvement in symptoms after taking these supplements. An estimated 37% of people have low levels of manganese in their diets. Rheumatoid arthritis sufferers often have a selenium deficiency. It is speculated that selenium, an antioxidant, can help to relieve arthritis symptoms by regulating free radical production and preventing damage to healthy tissues. In addition selenium regulates immune function, which may account for selenium's beneficial effect in rheumatoid arthritis, and autoimmune condition. Now a day's several mineral complexes an also be use in the treatment of arthritis e.g. Lumanite (84).

Conclusion:-

Indian soil germinates thousands of medicinal drugs which are cultivated for the purpose to obtain a novel drug. This review throws light on the current demands of anti-arithritic drugs obtained from Indian natural sources including common therapies used for rheumatoid arthritis at world level. The increasing faith of the population on herbal treatment has given birth to the urge to explore natural wealth so that potent therapeutic natural compounds may be utilized for RA treatment. This review is not only intended to represent picture of the role of herbs in the development of antiarthritic therapies but address attention towards enormous cultivated anti-arthritic drugs in India. Nevertheless, significant challenges remain: RA is still a disease of unknown etiology and none of the therapies described represents a cure. It will be interesting to see whether progress in Indian herbs will eventually provide the profound insights required to conquer this condition. However, it appears highly likely that new drug will continue to generate novel formulation for intervention in RA for the next 25 years.

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