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A REVIEW ON ANTI-RHEUMATIC PHYTOMEDICINAL TREATMENT

Dr. Mohd. Wasiullah[1], Piyush Yadav*[2], Devesh Yaduvanshi[3] and Om Prakash Maurya[4]

[1]Principal, Dept. of Pharmacy, Prasad Institute of Technology, Jaunpur (222001) U.P, India.

[2]Principal, Dept. of Pharmacy, Prasad Polytechnic, Jaunpur (222001) U.P, India.

[3]Dept. of Pharmacy, Prasad Institute of Technology, Jaunpur (222001) U.P, India.

[4]Assistant Professor, Dept. of Pharmacy, Prasad Institute of Technology, Jaunpur (222001) U.P, India.

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***Corresponding Author**
Piyush Yadav
Principal, Dept. Of Pharmacy, Prasad Polytechnic Jaunpur 222001 (U.P.), India.

ABSTRACT

Chronic joint inflammatory disorder Rheumatoid Arthritis (RA) and other arthritis forms have common upsurge of inflammation, pain and deformity of the joints resulting in progression of histological alterations and disabling symptoms. The current review discusses the toxic and chronic adverse effects of the conventional RA treatment along with the need for herbal therapy as an effective anti-rheumatic alternative approach. Anti-inflammatory, anti-oxidant and other medicinal properties of some easily available herbal plants are elaborated in this review with scientific evidences collected from various literatures which proceeds towards a natural drug therapy for RA. The reviewed herbs are safe and further research is required to examine their efficacy, safety, and potential drug interactions.

KEYWORDS: Rheumatoid arthritis (RA), herbal therapy, anti-rheumatic, anti-inflammatory, herbal plants.

1. INTRODUCTION

Medicinal plants have always been considered as a healthy source of life for everyone. The therapeutic properties which those medicinal plants hold, are very useful for healing various diseases and the advantage of medicinal plants is that these are 100 percent natural. Phytotherapy (herbal remedies) is the study of the use of extracts of herbal plants as medicines or health-promoting agents.

The popularity of phytotherapy has significantly increased over the last three decades in the U.S, due to the resistance to conventional therapy and its associated side effects. According to World Health Organisation (WHO), about 80 percent of the Asian and African population rely on the traditional medicines which include herbal remedies.

According to the University of Maryland Medical Centre, about 70 percent of the German physicians regularly prescribe between 600-700 phytomedicines to their patients.[1] The failure of conventional therapies in the treatment of chronic conditions has arised the need for use of herbal remedies for the management/treatment of those chronic health conditions. One of such chronic health problem is Arthritis. Arthritis represents one of the most frequent chronic health problem and is a leading cause of disability.[2] Arthritis affected 43 million U.S adults in 2002[3] and is the leading cause of disability in the U.S.[4] In India also, more than 20 percent of total population is suffering from arthritis.

Arthritis is a condition where one or more joints are affected, featuring inflammation of those joints. At the joints, that means in between the two bones, there is cartilage which acts as a shock absorber when pressure is applied on the joint[5] either by walking or lifting weight. In arthritis joints become swollen, tender and warm to touch or red[6] and movement becomes very painful. There are 100 different forms of arthritis; the most common is osteoarthritis,[7] others are misdirected immune system which causes rheumatoid arthritis (RA) and psoriatic arthritis with autoimmunity.[8] Septic arthritis is the result of joint infection.[9] Arthritis can occur at any age,[10] but usual age of onset is in between 25 and 50 with a peak effect in the 40s and 50s.[11]

The common risk factors for arthritis includes age, gender, obesity, infection, congenital factor, lifestyle, environmental factors and lack of physical activities. RA is a chronic systemic disease that is delineated by the inflammation of the joints in mostly elderly people. RA is associated with the production of auto-antibodies such as “rheumatoid factor” (RF) and anti-citrullinated protein antibodies (ACPA) which causes cartilage and bone-damage as well as disability by affecting the synovial joints.[12] Other modulator of the immune system including various signalling pathways, cytokines and chemokines plays an essential role in the progression of the symptoms of the disease and the disease itself.

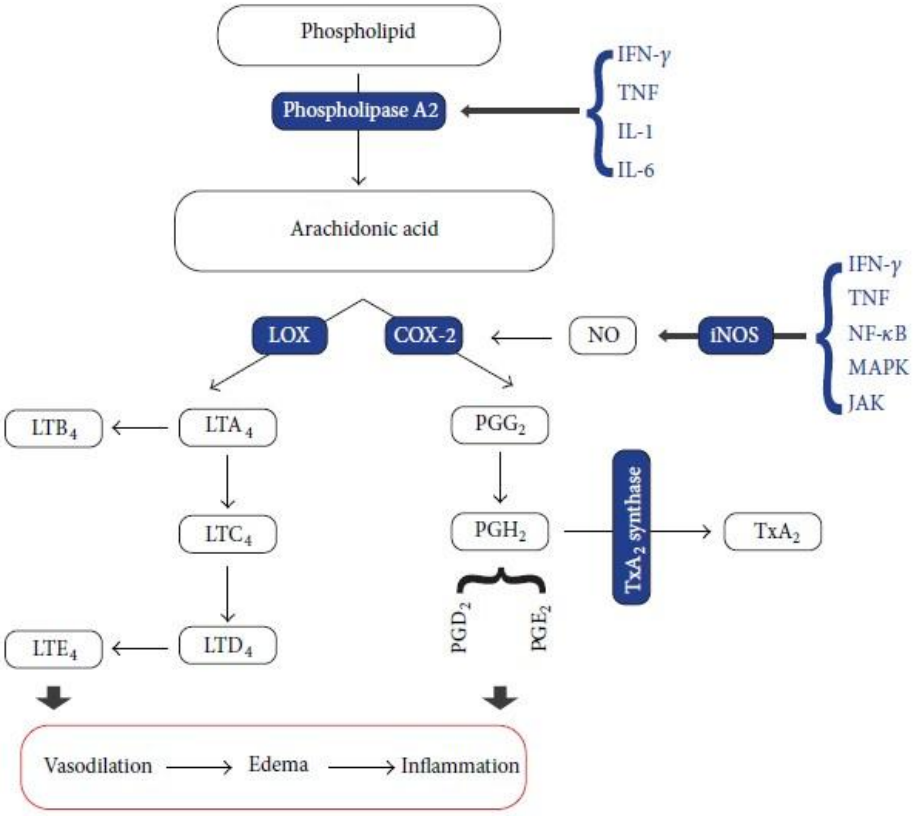

Figure 1.1: Inflammation pathway. COX, cyclooxygenase; LOX, lipoxygenase; PG, prostaglandin; LT, leukotriene; TX, thromboxane; NO, nitric oxide; iNOS, inducible NO synthase; IFN, interferon; TNF, tumor necrosis factor; NF-κB, nuclear factor-κB; MAPK, mitogen activated protein kinase; JAK, janus kinase; IL, interleukin.

Complications which are associated with RA includes pain swelling, stiffness and loss of functions of the joints. The dysregulated immune system resulting in the inflammation, is not only confined to the joints but also affects multiple organs like lungs, heart, eyes, kidney and even the skin.[13] The factors which are responsible for the progression of this disease are mainly genetic, epigenetic and environmental. RA is more prevalent in women than in men, occurring between the ages of 35-50 years as reported in 80 percent of the total cases.[14] For curing this chronic illness, several synthetic drugs including Disease modifying anti-rheumatic drugs (DMARDs) are currently used. These conventional drugs are useful but are also associated with critical and adverse effects. This reason has arised the diversion of the focus towards using phytomedicines as a potential herbal product with no or minimal side effects. The treatment of RA includes physical exercise, medication and surgery. Physical exercise is very beneficial in all chronic health conditions. Medication is useful to reduce the symptoms and other problems but not the root cause of the disease. The disadvantages of

those conventional drugs which are used to treat RA symptoms lie in their toxicity, adverse effects and reappearing of the symptoms after the discontinuation of therapy.[15]

Table 1.1: Adverse effects associated with various drugs.

DRUGS	COMPLICATIONS	REFERENCES
Methotrexate	Pneumonitis, Mouth ulcers, Alopecia	[16]
Hydroxychloroquine	Retinal toxicity, Haemolytic anaemia, skin discolouration Nausea, Diarrhoea, Vomiting, Loss of appetite, Skin rash	[16]
Sulfasalazine	Gastrointestinal disorder, myelosuppression, rashes, Haemolytic anaemia	[16]
Corticosteroids	Adrenal suppression	[17]
Infliximab	Tuberculosis, hepatic reactions, including acute liver failure, jaundice and hepatitis	[17]
Etanercept	Multiple sclerosis, inflammation of spinal cord and optic nerves	[17]
Adalimumab	Hypersensitivity reactions, Anaemia	[18]
Golimumab	Pneumonia, fungal infection, tuberculosis, hepatitis B, malignancies	[18]
Glucocorticoid	Peptic ulcer, cataract, muscle atrophy	[19]

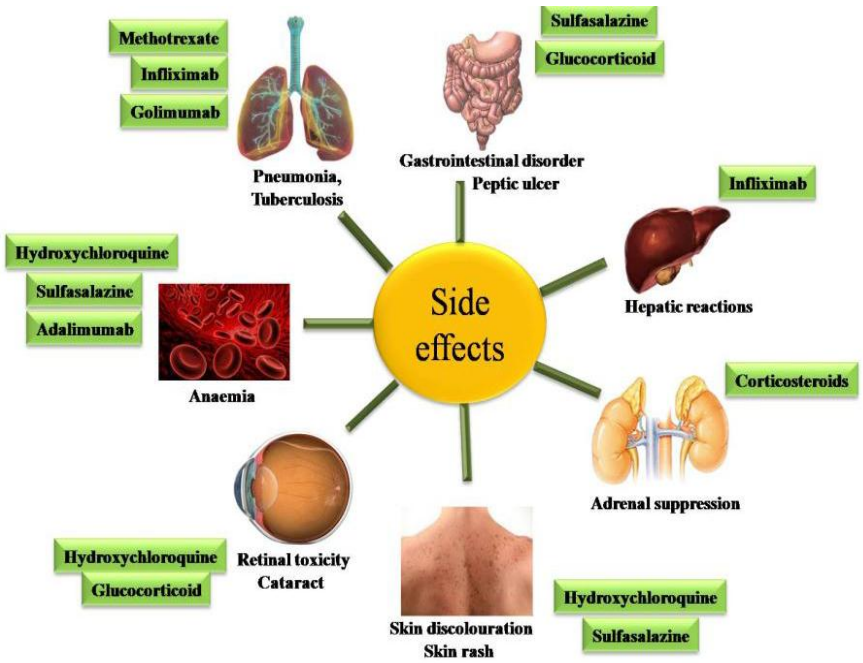

Figure 1.2: Side effects exerted by commonly used synthetic drugs for RA.

Surgery is the last treatment option. Surgeon may perform surgery to re-align the joint, replace the damaged part of joint or to wholly replace the joint.

ADVANTAGE OF PHYTOTHERAPY OVER CONVENTIONAL THERAPY

Ayurveda is the most ancient healing system in India. It was nearly about 5000 years ago introduced in India. The aim of Ayurveda is to firstly find out the root cause of a disease and then eradicated it completely from the patient. It is not the fastest but surely the most effective treatment, and even WHO has accepted this.

Phytomedicines with their various medicinal properties including anti-inflammatory, anti-oxidative, anti-proliferative, immunosuppression has proved to be effective in diminishing RA progression in various experiments. These medicinal plants contain different phytoconstituents which targets different signalling pathways reducing the severity of the disease.

The search strategy of this article is based upon the following databases which were searched for publications dated between 1966 and 2001; MEDLINE, EMBASE, CINAHL, Cochrane Controlled Trials Register (CCTR), Science Citation Index, BIDS ISI and Cochrane Complementary Medicine Field Specialized Registry. Thesaurus and free-text searches were performed across several database to combine the terms ‘arthritis’ and ‘herbal medicine’. This review will discuss some selected potential herbal plant species which are considered as potent phytomedicine in supressing RA pathogenesis.

2. **ANTI-RHEUMATIC MEDICINAL PLANTS:** Following are the most commonly used anti-rheumatic herbs:

2.1 Blackcurrant seed oil (*Ribes Nigrum*): The black currant oil is obtained after crushing the seeds of the black currant plant. It contains high levels of GLA (Gamma-linolenic acid), a beneficial fatty acid that the body converts to prostaglandin E1 (PGE1), and a hormone like substance which acts as an anti-inflammatory agent.

Fig.2.1.1: Blackcurrant plant.

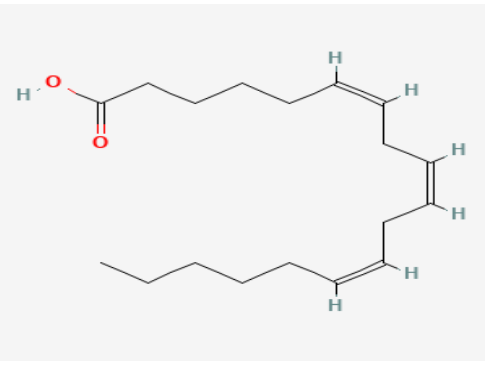

Fig.2.1.2: Gamma linolenic acid.

2.2 Ginger (*Zingiber Officinale*): Ginger is a well known natural spice which has medicinal properties. Recent studies which were conducted in the University of Miami suggests that ginger is effective in the treatment of arthritis as it has anti-inflammatory properties. Chemical constituents of ginger are zingiberon and zingirol which are important anti-oxidant that clears the joint impurities. Some clinical evidences related to ginger in arthritis treatment shares its effect could be related to prostaglandin and leukotriene biosynthesis so it works as a dual inhibitor of eicosanoid biosynthesis.[20]

Fig.2.2.1: Ginger plant.

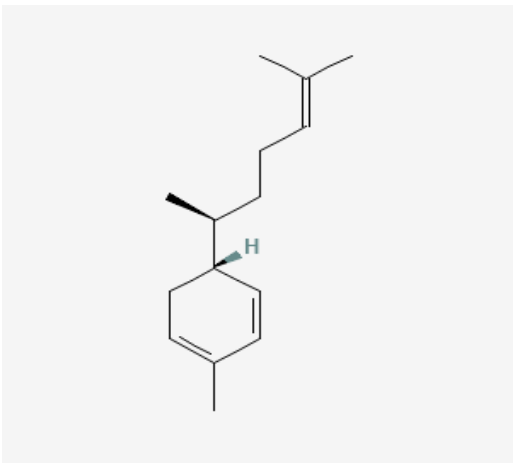

Fig.2.2.2: Zingiberone.

2.3 Turmeric (*Curcuma Longa*): In Indian System of medicine it has been used from ancient time. It is popularly called “Haldi” in India. Its use, range from constipation to skin diseases. Polyphenolic compound curcuminoid gives turmeric its yellow colour. Curcumin is the main curcuminoid found in turmeric. Other curcuminoids found in turmeric are bisdimethoxycurcumin, 5’-methoxycurcumin and dihydrocurcumin. In a clinical trial, efficacy of curcumin was compared with a Non-steroidal Anti-inflammatory Drug (NSAID) known as Phenylbutazone. In the study 18 patients received curcumin 1200 mg/day orally and it was found that improvement in morning stiffness, walking time and joint swelling after 2 weeks, compared to the NSAID therapy Phenylbutazone (300 mg/day). Though larger clinical trials are needed to determine the efficacy of curcumin in the treatment of RA.[21]

Fig.2.3.1: Turmeric plant.

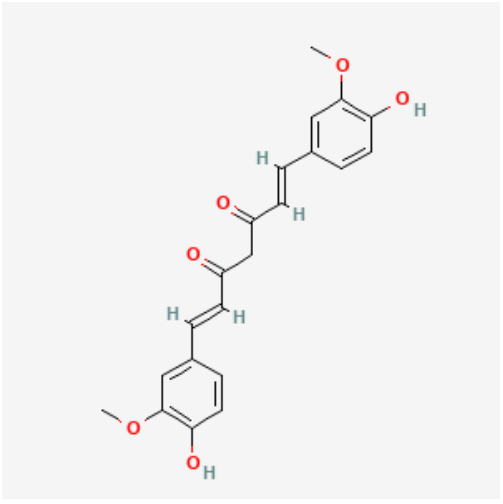

Fig.2.3.2: Curcumin.

2.4 Ashwagandha (*Withania Somnifera*): It constitutes steroidal alkaloid, steroidal lactones such as withanolide like withaferin A, bitter alkaloid 'somniferin' which has hypnotic property and other contents like phytosterol, mixture of saturated and unsaturated acid. It has been used in the disease like rheumatism, asthma, leprosy and arthritis. Many clinical evidences suggests that it has good response in the improvement of pain and swelling.

Fig.2.4.1: Ashwagandha plant.

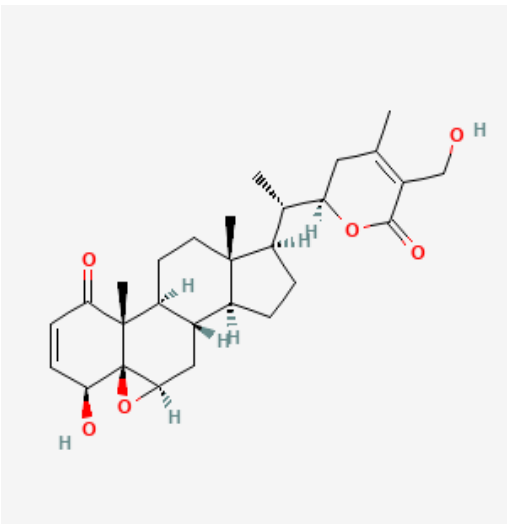

Fig.2.4.2: Withaferin A.

2.5 Boswellia (*Boswellia Serrata*): Historically Boswellia serrata is recommended for osteoarthritis (OA), juvenile RA, etc. It possesses analgesic and anti-inflammatory properties. It also acts as COX-2 inhibitor and reduce pain and inflammation. It soothes the joints and also helps to improve the level of synovial fluid making entire structure lubricated and easy to move. The gum is used as an anti-inflammatory when applied

externally or internally. One of the principle constituent of gum resin is boswellic acid which show anti-inflammatory activities.

Fig.2.5.1: Boswellia plant.

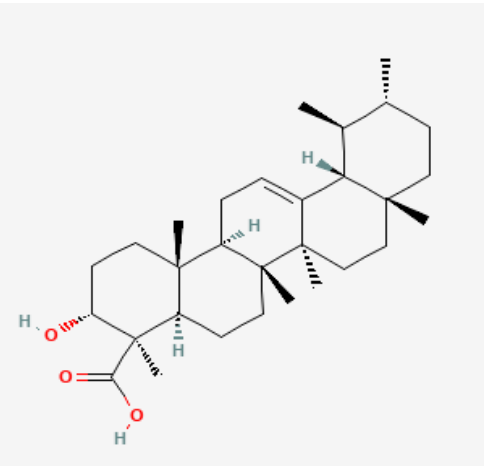

Fig.2.5.2: Boswellic acid.

2.6 Guggul (*Comiphora mukul*): It acts as an anti-inflammatory agent. It reduces joint pain, inflammation, morning stiffness. Guggulsterone is the gum resin of C. mukul, this sterol can inhibit nuclear factor-κB (NF-κB) activation and downregulate the expression of inflammatory gene product such as COX-2 and MAPK which are major player in the development of RA. The anti-arthritic and anti-inflammatory activities of gum guggul were first demonstrated by Gujral et al; in 1960.[22]

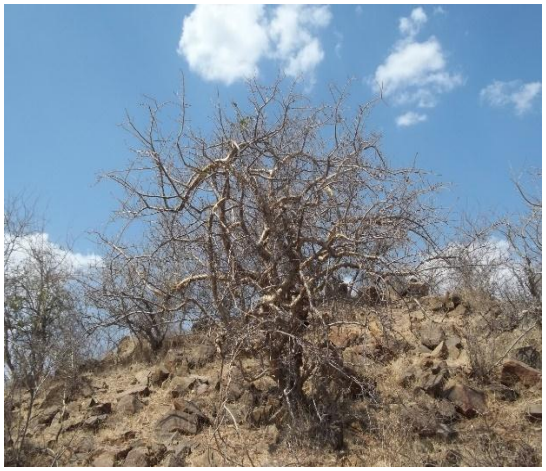

Fig.2.6.1: Guggul plant.

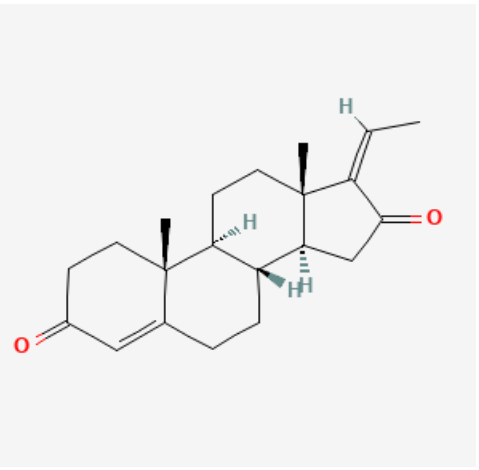

Fig.2.6.2: Guggulosterone.

2.7 Devil's claw (*Harpagophytum Procumbens*): It has been used to treat migraine and RA. Principle constituent of Devil's claw is Iridoid glycosides- harpagoside, harpagide, procumbide, other constituents are flavonoids- kaempferol and luteolin, phenolic acid triterpene etc. It has anti-inflammatory and analgesic properties.

Fig.2.7.1: Devil's claw plant.

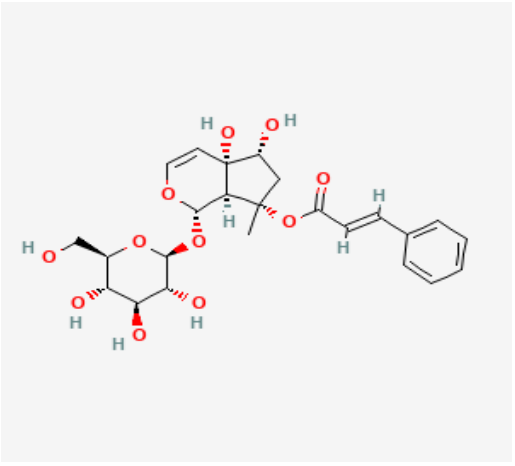

Fig.2.7.2: Harpagoside.

2.8 Guduchi (*Tinospora Cardifolia*): T. cardifolia is most widely used plant in folk and Ayurveda system of medicine, found throughout India. Its principle constituents are alkaloids, diterpenoid lactones, glycosides steroid, sesquiterpenoid, phenolic, aliphatic compounds and polysaccharides. It has anti-pyretic, anti-inflammatory, anti-arthritic, anti-oxidant, immuno-modulator and many other medicinal properties.

Fig.2.8.1: Guduchi (Giloy) plant.

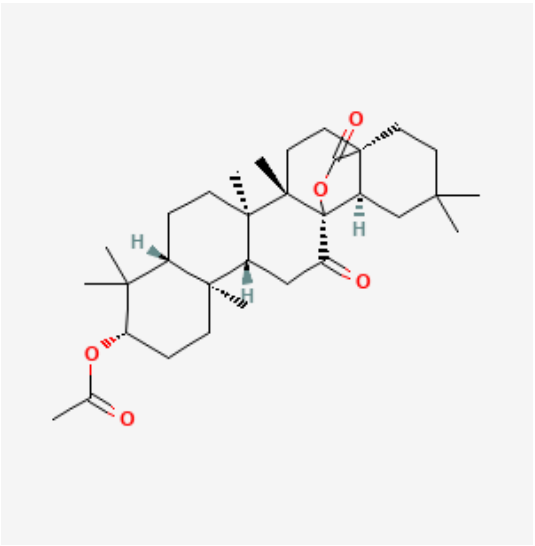

Fig.2.8.2: Terpinoid lactone.

2.9 Nirgundi (*Vitex Nigundo*): It has anti-inflammatory, analgesic, anti-arthritic and anti-oxidant actions. The leaves contain iridoid glycosides, isomeric flavanones and flavonoids and glucosides and its derivatives. Several anti-inflammatory tri-terpenoids and flavonoids have also been isolated from its seeds. Anti-inflammatory and analgesic activities of fresh leaves of nirgundi is responsible for the inhibition of prostaglandin synthesis, anti-histamine membrane stabilizing and anti-oxidant activities.[23]

Fig.2.9.1: Nirgundi plant.

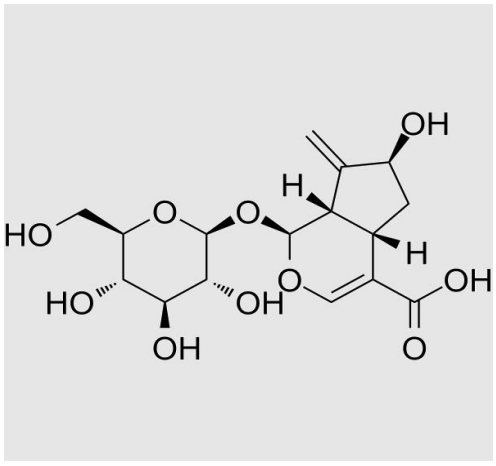

Fig.2.9.2: Gardoside iridoid glycoside.

2.10 Cayenne pepper (*Capsicum Minimum*): It has been used from centuries as a spice but also a natural remedy in reducing inflammation in body and to reduce platelet stickiness. It contains a principle constituent called capsaicin, which reduce inflammation and pain. Thus it makes the cayenne pepper a natural addition to any arthritic person's diet.

Fig.2.10.1: Cayenne pepper plant.

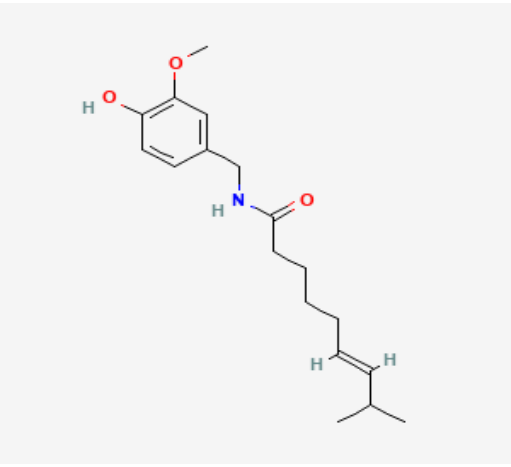

Fig.2.10.2: Capsaicin.

2.11 Cinnamon (*Cinnamomum cassia*): It is of Lauraceae family and is an ancient spice.[24] It exhibit anti-cancer, anti-inflammatory, anti-ulcer and other medicinal properties and it is potent inhibitor of NO and COX. The essential oil of cinnamon bark inhibits the syntheses of pro-inflammatory cytokines such as monocyte chemoattractant protein-1, IFN-γ, interferon inducible T-cell α chemoattractant and monokine induced by gamma interferon [MIG].[25] Some recent studies reported that cinnamaldehyde (CA), an essential component of cinnamon have the potential to impart anti-inflammatory effects against RA.

Fig.2.11.1: Cinnamon plant.

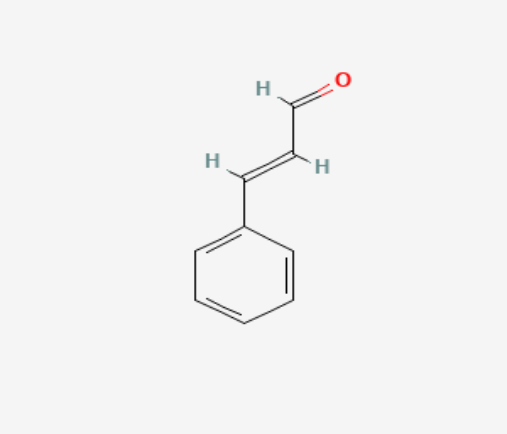

Fig.2.11.2: Cinnamaldehyde.

2.12 Garlic (*Allium Sativum*): It belongs to Liliaceae family, which is native to Asia, but also cultivated in numerous countries. Its chemical constituents are allicin, alliin, diallyl sulfide, ajoene, etc. Leaves and cloves of garlic are used as traditional medicines and are known for its many therapeutic properties which include anti-inflammatory, anti-cancer, cardioprotective, etc. Presence of sulfur compound thiacremonone inhibits inflammation of nervous tissues and amylodogenesis via inhibition of NF-κB activity.[26]

Fig.2.12.1: Garlic plant.

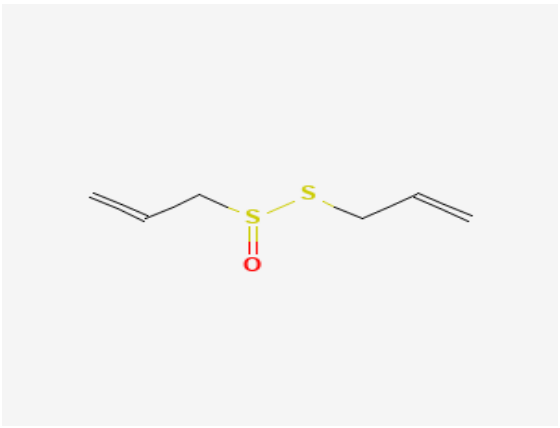

Fig.2.12.2: Allicin.

2.13 Coriander (*Coriandrum Sativum*): It is an annual herb belongs to Apiaceae family. It is used as a herb which possesses anti-oxidant, anti-diabetic, anti-inflammatory, hepatoprotective properties. It significantly lowers the production of NO, PGE2, iNOS, COX-2 and pro-interleukin-1β expression, which indicates its strong anti-inflammatory property. Its chemical components are borneol, coriandrin, dodecanal, undecanal, myristyl aldehyde, geraniol, etc.

Fig.2.13.1: Coriander plant.

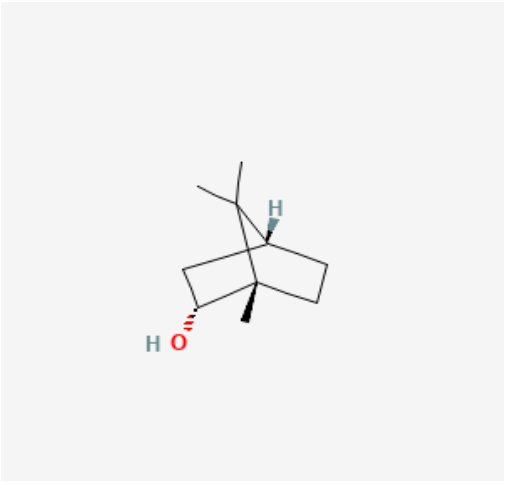

Fig.2.13.2: Borneol.

2.14 Indian Gooseberry (*Emblica Officinalis*): It belongs to the Euphorbeaceae family, and also known as Amla. Its chemical components are ascorbic acid (Vit. C), ellagitannins such as emblicanin A, emblicanin B, punigluconin and pedunculagin. It is native to India. Various Preclinical studies state it has cardioprotective, anti-pyretic, wound healing, analgesic and anti-arthritic properties.[27] It significantly lowers the expression of pro-inflammatory cytokines IL-6, TNF-α and supresses the phosphorylation of NF-κB. Its fruits have the potential to trigger programmed cell death of human primary osteoclasts that are involved in the pathogenesis of RA.[28]

Fig.2.14.1: Indian Gooseberry plant.

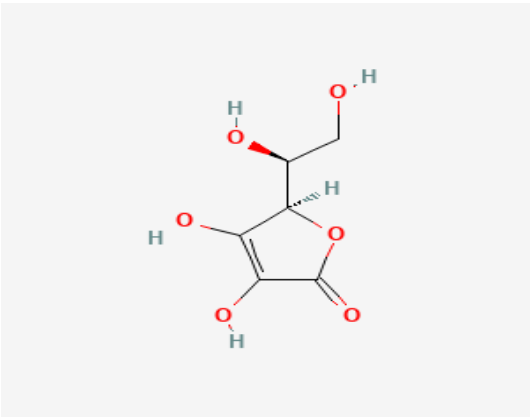

Fig.2.14.2: Ascorbic acid.

2.15 Guava (*Psidium Guajava*): It is a common fruit belonging to Myrtaceae family, majorily found in tropical and temperate regions.Its chemical constituents are quercetin, avicularin, guaijaverin, kaempferol, gallic acid and apigenin etc. It has anti-oxidant, hepatoprotective, anti-allergy, anti-inflammatory properties.[29] It is known to reduce the

levels of iNOS and COX-2 at transcription level, and also suppresses extracellular signal-regulated kinases ERK ½ of MAPK pathway thereby acting as an anti-inflammatory agent.[30]

Fig.2.15.1: Guava plant.

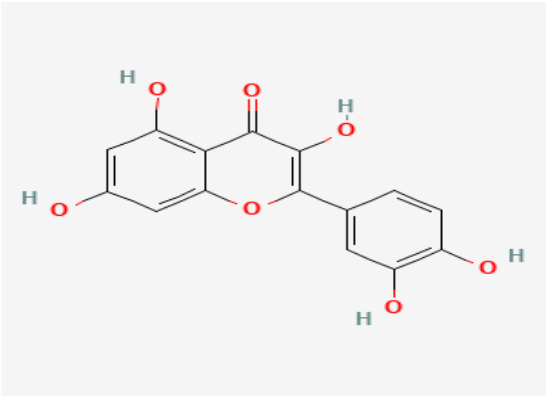

Fig.2.15.2: Quercetin.

PLANT SOURCE	ACTIVE COMPONENT	MECHANISM OF ACTION	REFERENCE
Allium cepa (onion)	Quercetin	NF-kβ, COX-2, TNF-α, 5LOX, TNF-α, IL-1β, AMs, RANKL	[31]
Veratrum grandiflorum	Resveratrol	JNK, NF-kB, TNF-α, 5LOX, AMs, COX2, PGE2, MMP13	[32]
Albizia myriophylla	8-methoxy-7,3′,4′-trihydroxyflavone	Nitric oxide [NO]	[33]
Trachydium roylei	Myristicin	IL-6, IL-1β, TNF-α, NO, PGE2	[34]
Actinidia polygama	Alpha-linolenic acid (ALA)	iNOS, COX-2, TNF-α	[35]
Garcinia mangostana	α-Mangostin	IL-6, TNF-α, MCP-1	[36]
Stephania tetrandra	Tetrandrine	TNF-α, IL-1β, IL-6, COX-2	[37]
Arnica montana	Phenols, flavonoids	(-) NO, TNF- α, IL-1 β, IL-6, IL-12, anti-type II collagen antibodies, (+) antioxidants (AM)	[38]
Equisetum arvense	Kynurenic acid	(-) synoviocyte proliferation (in vitro)	[39][40]
Panax notoginseng	Saponins	(-) TNF-alpha, IL-1, iNOS, MMP-13 (AM)	[41][42]
Salix spp.	Salicin, Polyphenols, Flavonoids	(-) TNF α, COX-2, IL-1, IL-6 (in vitro)	[43][44]
Sesamum indicum	Sesamin, Sesamol, Sesamolin	(-) thiobarbituric acid reactive substances, LOX (in vitro), TNF-α, IL-1 β,IL-6, hyaluronidase, MMP-13, MMP-3, MMP-9, exoglycosidases, cathepsin D,	[45]-[49]

		phosphatases, COX-2, PGE2, ROS, H2O2, MDA (AM), IL-6 (HS) / (+) GSH, GPx (AM)	
Symphitum officinalis	Rosmarinic Acids, Glycopeptides, Amino Acids	(-) PG (in vitro)	[50]

Table 2.1- Other medicinal plants with therapeutic potential in ostheoarthritis and rheumatoid arthritis (Legend: AM, animal model; CAT, catalase; COX, cyclooxygenase; GPx, glutathione peroxidase; GSH, glutathione; GST, glutathione-S-transferase; HS, human study; IL, interleukine; iNOS, inducible nitric oxide synthase; LOX, lipooxygenase; PGE1-S, prostaglandin E2 synthase; ROS, reactive oxygen species; SOD, superoxide dismutase; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MIP-1α, monocyte inflammatory protein-1; MMP, matrix metaloproteinase; NO, nitric oxide; TNF, tumoral necrosis factor; (-), decreased synthesis/decreased activation/inhibition of various mediators, enzymes, transcription factors, and processes; (+), increased synthesis/increased activation of various mediators, enzymes, transcription factors, and processes). Note: References in the table correspond only to the mechanism of action.

CONCLUSION

Rheumatoid arthritis (RA) is associated with the inflammation and pain of multiple joints. Activation of several auto-immune pathways and an imbalance in the cytokine networks which significantly contributes to the pathogenesis and inflammatory response to RA. The available conventional treatment includes NSAIDs and steroids, which only can manage the disease to a certain degree. These conventional treatments have certain drawbacks including the cost, safety and therapeutic efficacy.

Herbal medicines could be an effective treatment for curing diseases like RA. Many herbs has anti-inflammatory, analgesic, anti-oxidant and other medicinal properties which have been evaluated in clinical and experimental studies. This review expressed the evidences which showed the different extracts of medicinal plants are potential enough to be established into certain agents which has good performance in the prevention of RA. The poor-bioavailability of the herbal products imposes a significant obstacle. But to overcome this issue, researchers are looking for nano-particle delivery mechanism of such products. This delivery system improves the pharmacological and therapeutical properties of the medicine and consequently reduce the dose frequency and dosage of the required drug to achieve its

maximum desired response. Numerous herbal medicines along with their phytochemicals and mechanism of action are listed in this review paper.

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