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Review on Anti-Rheumatoid Arthritis Potential of Medicinal Plants

Anjana Goel¹, Sunanda Kulshrestha²

¹Associate Professor, Department of Biotechnology, GLA University, Mathura, U.P., India; ²PhD Scholar, Department of Biotechnology, GLA University, Mathura, U.P., India.

ABSTRACT

Autoimmunity is an immunological disorder in which immune response against self-antigens is provoked. Rheumatoid arthritis (RA) is one of its kinds of chronic autoimmune disorder causing inflammation and infiltration of immune cells around the synovial membrane, which leads to destruction and degradation of cartilages. Steroidal and non-steroidal allopathic therapies available so far cannot cure or prevent the disease. Besides their severe side effects, they can only provide temporary relief by suppressing and reducing the pain in the joints. Detailed search for the related literature has been carried out using multiple searches with words 'rheumatoid arthritis'; 'plants for rheumatoid arthritis' etc. with the help of search engines. Pubmed, Research Gate, Google Scholar have been used for more authentic information support. Alternative medicinal approaches for the treatment of Rheumatoid arthritis, as a holistic approach, can be used in a better way for making life much better for the sufferer and restricting the progression of the disease. Some of the approaches carrying ethanotraditional and ethnobotanical importance have been discussed in the review article and tried to assemble all possible plants that show Anti-Rheumatoid Arthritis activity. These approaches are giving some hope for the treatment of RA. The experimental model for investigating the effects of drugs on RA has also been discussed. This could draw a new pathway for future researches as well.

Key Words: Arthritis, Autoimmunity, Ayurveda, Immunological disorder

INTRODUCTION

Rheumatoid arthritis affects almost 0.5-1% of the population worldwide¹ and in case of the Indian population, more than 20 % of the population suffers from any of the forms of arthritis.² It is a multifunctional immune disorder with a known cause. Some factors which may influence RA are a genetic factor, age, hormones, environmental factors, smoking etc. Different strategies for the study of RA have been used. Experimental animal model, which elucidate the onset and progression of the disease as well as evaluate the drugs that can reduce or prevent the disease, can be studied. An ideal model should have close similarities with human disease pathogenesis and symptoms. The use of an ideal animal model contributes significantly to the evaluation of therapeutic molecules against RA.³

Causes

RA is believed to be an autoimmune disorder, although the real cause and aetiology of the disease are still unknown. The

frequency of appearance is three times more in the females rather than the males.⁴ RA sometimes also leads to diffused inflammations in the lungs, pleura and sclera, nodular lesions, and most commonly in the subcutaneous tissue, this is the most severe type of RA. Autoimmunity is known to be the major prognostic factor behind RA and plays important role in its progression towards severity. Inflammations in synovial joints are caused by many kinds of immune-mediated compounds.⁵ The cause is still not clear but the destruction of articular cartilage due to inflammatory responses is the major cause of RA.⁶

Symptoms

Symptoms for the same includes, joint pain and swelling, stiffness in joints, sleeplessness, fatigue, loss of weight and having flu kind of symptoms. Abnormal antibodies IgG have been found in the blood of a person suffering from rheumatoid arthritis. They react to antigens leading to the formation of antigen-antibody complex that leads to inflammation and pain of the synovial membrane.⁷

Corresponding Author:

Anjana Goel, Associate Professor, Department of Biotechnology, GLA University, Mathura, U.P., India
Contact: 91 9897006326; Email: anjana.goel@gla.ac.in; anjanagoel2000@yahoo.com

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Diagnosis

Diagnosis for RA involves the use of clinical methods of imaging and laboratory tests. Laboratory testing methods include anaemia, presence of rheumatoid factor, antibodies against the cyclic citrullinated peptides and elevation in erythrocyte sedimentation rate. While symptomatic detection of stiffness and pain for a long time in the morning gives some clue about the disease. X-rays also help in detecting the RA but at times they can't differentiate in early arthritis too. MRI and ultrasounds are also done to look at the progress of the RA in the patients. No such highly specified test has been developed for validation of the disease.^{8,9}

GENERAL TREATMENT FOR RHEUMATOID ARTHRITIS AND ITS LIMITATION

Management of pain, prevention of long-term damage to the joints and reduction in inflammation are major problematic area to deal with while treating RA. For these, disease-modifying anti-rheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs) have been used as the major approaches to deal with the symptoms and after-effects of the disease. Other steroidal drugs that are used to treat inflammation by RA are corticosteroids, an anti-inflammatory hormone released from adrenal glands. An ideal steroid should meet the requirement of meeting the need at a low dosage and avoid side effects. Both the steroidal and non-steroidal drugs although control the symptoms but in long term, they cannot cure the disease or prevent it. Apart from all this, more severe side effects can be seen in the patients in terms of effects on kidney, liver and heart due to prolonged use to such medicines. Shortness of breath, nausea, infections and allergic reactions have also been noticed as the short-term side effects. This in turns marks the major limitation and issue while dealing with steroidal drugs for curing rheumatoid arthritis.^{4,10} They don't work effectively progression of the disease and cure it of its roots. They are just meant to deal with the symptoms like pain, inflammation, swelling etc. which are the main symptoms as discussed before.

AYURVEDIC PERSPECTIVE OF RHEUMATOID ARTHRITIS

Ayurveda is one of the forms of alternative treatment of medicine. It is typically based on three dosha: Vata, pitta and Kapha. Amavata, an ayurvedic condition has similarities with RA.^{11,12} Amavata is associated with the production of 'Ama' in the gut. Ama is produced due to the disturbed metabolism.^{13,14} It is pro-inflammatory and creates toxicity in the gut and imbalance of Vata in the body. According to Ayurveda the people with Vata dosha are more prone to develop this disorder.¹¹ Thus it can be cured by taking the diet which is rich

in grains, legumes, green leafy vegetables, buttermilk etc. Spices like ginger, garlic and turmeric aid the digestion process and anti-inflammatory, thus recommended. Lukewarm water is always preferred for the digestion in Ayurveda. Ginger roots, boiled in water, also remove toxins from the body and help in the digestion process. The commonly used plants used to treat and mitigate the symptoms of RA have been summed up in table 1.

NEED OF NATURAL REMEDIES

Since time immemorial, the natural remedies used by the population has been helpful to meet the symptoms of any diseases or even used till date by many folks, tribal and traditional medicinal practitioners for treatment. According to WHO, 80% of the population still rely on herbal treatments. Plants and herbs have been taken in form of infusion, raw or juice form and have worked efficiently as per observation in the patients. Just with the inclusion of such plants with medicinal properties in daily diet made a tremendous change in the disease while benefiting the sufferer. This directly indicates that there is a world to explore in the field of phytoconstituents of plants that have been used traditionally for curing RA.

POSSIBLE MECHANISM OF ACTION OF HERBAL DRUGS

Many researchers have tried to elaborate a particular pathway of mechanism that the herbal drugs follow to hit the causative factors that are responsible for symptoms of RA and cure the disease from inside. As the disease progress via different mechanisms and pathways, therefore multi-pathway effects have been noticed by the herbal remedies by many researchers and some of them have been discussed below.

It has been observed that TLRs (toll-like receptors) play a major role in inflammation in RA and stimulate the cellular activity of NF- κ B mediated by adapter molecules like myeloid differentiation primary-response gene 88 (MyD88) at the onset of disease. The process of phosphorylation of cytoplasmic I κ Bs is carried by TLR2/6, TLR4, or TLR5 agonist which in turn stimulate target cells and macrophages. After degradation of this complex, NF- κ B translocated into the nucleus where the promoter regions of inflammatory genes like iNOS, COX-2, IL-6 bind to NF- κ B for transcriptional activation. Augmentation in COX-2 and other pro-inflammatory cytokines modulate the metabolism of arachidonic acid which results in the formation of prostaglandins-E-2 and turn leads to suppression of leukocytes apoptosis and even stimulate proliferation of leukocyte which leads to the pathological condition of hyperplasia and pannus formation at the site. Therefore, it could be inferred why inhibition of NF- κ B would act as a major target for dealing with RA.¹⁵

Apart from this, cytokines and other pro-inflammatory factors play a protagonist progression of the disease. TNF- α , IL-1 β and IL-6 are the major pro-inflammatory cytokines which activate the collagenase and other proteases to degrade the collagen thus increases the degradation of cartilage. It also leads to an increase in the infiltration of T cell, B cell and macrophages causing synovial inflammation. It implies that the herbal drug should be capable to inhibit and inactivate such pathways and complexes.¹⁶ Many herbal drugs have shown to down-regulate these proinflammatory cytokines and reduce oxidative stress.

In this row plants like *Saraca asoca*, which is a commonly used plant having traditional use in RA has shown major anti-inflammatory activities *in vivo* model showing the reduced level of pro-inflammatory cytokines.¹⁶ *Ocimum*, which already holds many therapeutic potentials to its glory also acts on RA by showing anti-inflammatory activity by inhibition of arachidonate metabolism and anti-histaminic activity. Eugenol (1-hydroxy-2-methoxy-4-allylbenzene), which is one of the most active bioactive molecules of *Ocimum*, is playing a major role.¹⁷ *Cannabis sativum*, a notorious plant is known for its addictive properties is also been tested for RA and gave results in favour of it. The cannabidiol, a major constituent of the plant is shown to act for anti-inflammatory by inhibiting COX-2 in mice model.¹⁸ Similar activity of suppression of NF- κ B pathway and COX-2 has been seen by aerial parts of *Cassia* plant which has also been one of the important traditional medicine for treating RA. The leaves have been found experimentally to show results for swelling, improvement in cartilage degradation and leucocyte infiltration in synovial fluid in the rat model study.¹⁹ Similar activities have been noted in *Zingiber officinale* which seen to possess a bioactive constituent 6-gingerol, that blocks the NF- κ B and PKC (protein kinase C) pathway and induce anti-inflammatory activity.²⁰ Another remedy used *Semecarpus Anacardium* which is a tree from the sub-Himalayan region is seen to be effective in RA and has anti-oxidant potential proved by inhibition of ROS in the body. The flavonoids also induce anti-inflammatory action by inhibition of phospholipase A2 that reduces the production of PGE2 and also reduce the level of TNF- α and NO. This all helps in preventing the rupture and release of lysosomal enzyme and help in synovial erosion.²¹

Artemisia absinthium, a Persian plant is also used as a traditional plant for curing RA and is seen to suppress inflammatory diseases by following multiple pathways. It acts by reducing the release of NO and PGE2 which inhibits the iNOS expression. Also, another pathway followed includes inhibition of COX-2 expression by scoparone, a bioactive compound found in the plant. Similar multi-path action is also exhibited by *A. sylvatica* Maxim aerial parts.²² Experimental studies have also supported the use of *Curcuma longa*, a widely used spice containing curcumin. It inhibits the

arachidonic acid cascade by the mode of inhibition of catalytic activities of phospholipases and blocking the catabolic effect of IL-1 β induced upregulation of MMP-3, and IL-1 β -induced decrease in type II collagen synthesis which is a contributing factor in RA progression.²³ Other plants including *Moringa oleifera* which shows anti-inflammatory effect by lowering down serum levels of Rheumatoid Factor (RF) and levels of the cytokines, TNF- α and IL-1²⁴, *Nyctanthes arbor-tristis* which lowers down the inflammatory cytokines IL-1, TNF- α in blood serum in experimental set up²⁵, *Swertia chirayita*, works in similar style and lowers down the pro-inflammatory cytokines IL-1 β , TNF- α and IL-6 in experimental arthritis²⁶ have been found to act effectively on RA following multiple pathways.

Minimal or no side effects by these remedies are the best part of the approach. After prolonged use of allopathic drugs, many side effects have been observed in the patients of RA as listed above. Hence, herbal therapies could act as effective approaches towards the treatment of such diseases. Today, uses of many phytomedicinal plants have been observed by experimental methods and are under scientific observations to develop as a natural way for healing.²⁷ Goals of natural therapy includes a reduction in joint pains, prevention of deformity, prevention of erosion, prevention from progression, control on extra-articular manifestations while maintaining the quality of life as well.^{6,7,28} Medicinal plants which have been tested experimentally and proven their efficacy are represented in tabular form in table 2. Using suitable experimental protocols related to *in vitro* and *in vivo* validations of anti-inflammatory effects, positive results has been observed that supports the ethnobotanical importance of herbal remedies for dealing with rheumatoid arthritis and lays an important source for future researches as well.

CONCLUSION

Rheumatoid arthritis is an autoimmune disease and well known for causing deformities and pain due to inflammations in the joints of the sufferer. Conventionally, the allopathic approaches used to treat RA comprise on disease-modifying anti-rheumatic drugs, Non-steroidal anti-inflammatory drugs and corticosteroids, which relieve the pain and inflammation till a limited time when they are in action. They are also accountable for some side effects in the patients and never show or promise to cure the disease from within. Looking at all the perspectives, the herbal approach can be thought of as an alternative approach for the treatment of RA. Our folk and indigenous treasure of knowledge hold many secrets to cure any diseases without causing any side effects. At present herbal remedies carrying anti-arthritis activities have been developed and potentials of their phytochemicals continuously have been validated. More than 450 species of plants have been listed that promise anti-arthritis activity

in humans ranging from various plant families. The article summarizes data regarding plants that could help and motivate researches in future.

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Table 1: Traditionally used plants for treating Rheumatoid Arthritis

Name of plant	Part used	Mode of use	Function	References
<i>Alpinia galangal</i>	Rhizomes	The paste of rhizome taken orally	Gives relief in pain	29
<i>Anacyclus pyrethrum</i>	Roots	Infusion drink is taken like tea of roots	Anti-rheumatic & Anti-arthritis	30
<i>Aphanamixis polystachya</i>	Bark	Oil applied on joints to help in pain	Act as analgesic	31
<i>Aquilaria agallocha</i>	Wood	Decoction taken of wood and oil applied to help in pain	Relieve pain and inflammation.	32
<i>Argemone mexicana</i>	The whole plant, Latex	The oil used to help in pain	Cure rheumatologic.	33
<i>Callicarpa macrophylla</i>	Flowers and fruits	Decoction taken	Anti-inflammatory, analgesic and antipyretic effects	34
<i>Capparis deciduas</i>	Roots	Powder of infusion taken	Treats rheumatism and fever.	35
<i>Cardiospermum halicacabum</i>	Roots	The oil used to relieve pain and powder taken orally	Treats infection in joints by trophic organisms.	36,37
<i>Carthamus tinctorium</i>	Seed	Infusion took orally	Anti-inflammatory and Analgesic.	38,39
<i>Cassia fistula</i>	Fruits	Infusion or paste of fruit taken orally	Analgesic	40
<i>Catunaregum Spinosa</i>	Bark	Paste or oil used	It is useful in rheumatism.	41
<i>Citrullus colocynthis</i>	Roots	Powder of fruits taken orally	Anti-inflammatory.	42
<i>Commiphora myrrha</i>	Gum	Oil used for helping in pain and taken gum taken orally	Relive in pain and	43
<i>Commiphora wightii</i>	Leaves	Taken orally or infusion	Relive in pain and Anti-inflammatory	44

Table 1: (Continued)

Name of plant	Part used	Mode of use	Function	References
<i>Cordia dichotoma</i>	Fruits	Taken orally or in form of powder	Anti-rheumatic.	45
<i>Coriandrum sativum</i>	Fruits and leaves	Taken orally	Relive in pain and Anti-inflammatory	46
<i>Euphorbia neriifolia</i>	Leaf	Taken in form of juice orally	Relieve pain in rheumatism	47
<i>Euphorbia ligularia</i>	Whole plant	Taken in the form of juice or infusion	Used in the treatment of rheumatism.	48,4
<i>Ficus bengalensis</i>	Latex	Taken as juice	Used in the treatment of rheumatism.	50
<i>Fritillaria roylei</i>	Bulbs	Taken in form of powder or juice	Used in the treatment of rheumatism.	51
<i>Glycosmis Arborea</i>	Roots	Taken in powder form	Useful in the treatment of arthritis.	52
<i>Gossypium herbaceum</i>	Leaves	Taken in powder form, juice or infusion	Relive in pain and Anti-inflammatory.	53
<i>Heliotropium Indicum</i>	Whole plant	The oil used for joint pain externally and other parts are taken in powder form	Gives positive results against use for joint inflammations	54
<i>Hiptage bengalensis</i>	Barks, Leaves and Flowers	Taken in powder form	Treatment of chronic rheumatism	55
<i>Holarrhena pubescens</i>	Barks, Seeds and Leaves	Taken in powder form	Relive in pain and Anti-inflammatory.	56
<i>Hygrophila auriculata</i>	Roots, Leaves and Seeds	Taken in powder form	Relive in pain and Anti-inflammatory.	57
<i>Hyoscyamus niger</i>	Leaves and Seeds	Taken in powder form	Relive in pain and Anti-inflammatory	58
<i>Illicium verum</i>	Fruits	Taken in powder form or juice	Relive in pain and Anti-inflammatory.	59
<i>Inula racemosa</i>	Roots	Taken orally in powder form	Relive in pain and Anti-inflammatory.	60
<i>Ipomoea cairica</i>	Seeds	The oil used for pain	Relive in pain and Anti-inflammatory.	61
<i>Jasminum lanceolarium</i>	Leaves and Flowers	Taken in powder form or juice	Shows effective results against rheumatism and fever. On the other hand, the leaves have anti-inflammatory properties and relieve pain.	62
<i>Jatropha curcas</i>	Oil	The oil used for joint pain externally	Relive in pain and Anti-inflammatory.	63
<i>Juglans regia</i>	Fruits	Taken in powder form or juice	Relive in pain and Anti-inflammatory.	64,65
<i>Justicia gendarussa</i>	Roots and Leaves	Taken in powder form or juice	Relive in pain and Anti-inflammatory.	66

Table 1: (Continued)

Name of plant	Part used	Mode of use	Function	References
<i>Kaempferia galangal</i>	Rhizomes and Leaves	Taken orally in powder form or juice	Relive in pain and Anti-inflammatory.	67
<i>Lantana Camara</i>	Fruits	Taken orally	Used traditionally for the treatment of RA	68
<i>Lawsonia inermis</i>	Leaves	Taken orally in powder form or infusion	Used in arthritic disorder.	69
<i>Lilium polyphyllum</i>	Bulb	Taken orally in powder form or infusion	Relive in pain and Anti-inflammatory.	70
<i>Madhuca longifolia</i>	Oil	The oil used for joint pain externally	Relive in pain and Anti-inflammatory.	71
<i>Mangifera indica</i>	Roots and Barks	Taken in powder form	Relive in pain and Anti-inflammatory.	72
<i>Mimosa pudica</i>	Whole plant	Taken orally	Helps to deal with the symptoms of rheumatoid arthritis.	73
<i>Momordica charantia</i>	Fruits	Taken orally if different forms or as juice	Relive in pain and Anti-inflammatory.	74
<i>Myxopyrum serratum</i>	Leaves	Taken in powdered form	Relive in pain and Anti-inflammatory.	75
<i>Naravelia zeylanica</i>	Whole plant	Taken in powder form	Relive in pain and Anti-inflammatory.	76
<i>Nilgiranthus ciliatus</i>	Roots	Taken in powder form	Relive in pain and Anti-inflammatory.	77
<i>Ocimum basilicum</i>	Whole plant	Taken in form of infusion, powder or leaves taken raw orally	Relive in pain and Anti-inflammatory.	78
<i>Oroxylum Indicum</i>	Roots	Taken in powder form	The plant possesses anti-inflammatory activity.	79
<i>Pandanus odoratissimus</i>	Oil	The oil used for joint pain externally	Relive in pain and Anti-inflammatory.	80
<i>Piper betel</i>	Whole Plant	Orally in powdered form	Shown effective results in inflammation treatment.	81
<i>Piper nigrum</i>	Fruits	Raw fruit used in cooking or taken in powdered form	Relive in pain and Anti-inflammatory.	82
<i>Plumeria Rubra</i>	Milky juice	Applied externally to relieve pain	Shown positive results in inflammation treatment.	83
<i>Pongamia pinnata</i>	Leaves	Taken in powder form	Helps in painful rheumatic joints.	84
<i>Premna corymbosa</i>	Leaves	Taken in powder form	Relive in pain and Anti-inflammatory	85
<i>Premna serratifolia</i>	Whole plant	Taken orally	Relive in pain and Anti-inflammatory	86
<i>Ricinus communis</i>	Leaves	Taken in powder form	Relive in pain and Anti-inflammatory	87
<i>Rubia cordifolia</i>	Roots	Taken in powder form	Relive in pain and Anti-inflammatory	88

Table 1: (Continued)

Name of plant	Part used	Mode of use	Function	References
<i>Ruta chalepensis</i>	Oil	The oil used for joint pain externally	Analgesic, antipyretic, anti-inflammatory and relieves rheumatic pain.	89
<i>Sida cordifolia</i>	Roots and Leaves	Taken in powder form	Used for treating rheumatism.	90
<i>Solanum nigrum</i>	Whole Plant	Taken in powder form Taken in powder form	Relive in pain and Anti-inflammatory	91
<i>Spondias pinnata</i>	Roots		Relive in pain and Anti-inflammatory and helps in muscular pain in rheumatism	92
<i>Stereospermum colais</i>	Leaves	Taken in powder form	Relive in pain and Anti-inflammatory	93
<i>Tectona grandis</i>	Wood	Taken in powder form, the oil used for external use	Used in treating inflammatory swelling.	94
<i>Trachyspermum Ammi</i>	Fruits	Taken in powder or juice form of fresh fruit	Relive in pain and Anti-inflammatory	95
<i>Tribulus Terrestris</i>	Whole Plant	used for joint pain externally	Used for external application in rheumatic-arthritis.	96
<i>Vateria indica</i>	Oil	The oil used for joint pain externally	Relive in pain and Anti-inflammatory	97
<i>Vitex negundo</i>	Roots	Taken in powder form	Relive in pain and Anti-inflammatory	98
<i>Vitis vinifera</i>	Stem	Taken in powder form or infusion	Relive in pain and Anti-inflammatory	99

Table 2: Experimentally proven plants for Rheumatoid Arthritis

Name of the plant	Common name	Type of Extract used	Activity observed	Reference
<i>Achyranthes Aspera</i>	Apamaraga	Ethanol	Prevented the recruitment of leukocytes	100,101
<i>Aconitum vilmorinianum</i>	Wolf's-bane,	Ethanol	Improvement of joint swelling and vascular permeability	102
<i>Ajuga bracteosa</i>	Ground pine	Ethanol	COX-1 and COX-2 inhibition	103
<i>Ajuga decumbens</i>	Bugle weed	Ethanol	Regulates the balance between bone formation and bone resorption	104
<i>Alstonia boonei</i>	Cheese wood	Methanol	Relief in early and late phase of pain	105
<i>Alstonia scholaris</i>	devil tree	Ethanol	Shown activity in Reduction of total leukocyte, lymphocytes and monocytes/macrophages migration	106
<i>Ammania gracifera</i>	tooth cup	Aqueous Alcoholic Petroleum Ether, Chloroform, Methanol	Decrease the ESR and WBC count	107
<i>Aristolochia bracteata</i>	Kidamari	Petroleum Ether, Chloroform, Methanol	It maintains vascular permeability and synovial membrane and with inhibition of cytokines and leukotriene infiltration	108

Table 2: (Continued)

Name of the plant	Common name	Type of Extract used	Activity observed	Reference
<i>Argyreia speciosa</i>	Elephant Creeper	Methanol, Ethanol	Prevented the recruitment of leukocytes	100, 109
<i>Arisaema rhizomatum</i>	Jack in the pulp it	Methanol	Have shown result against pro-inflammatory cytokines and RA factor secretion	110
<i>Arnebia euchroma</i>	Pink arnebia	Ethanol (95%)	Suppression of IL-1 β and TNF- α levels	111
<i>Artocarpus tonkinensis</i>	Chay	Ethyl acetate	Apoptosis induction in activated T-cells	112
<i>Asystasia dalzelliana</i>	Violet asystasia	Ethanol	Decreasing synthesis/release of T-cell mediators	113
<i>Baccharis genistelloides</i>	Carqueja	Aqueous	Suppresses synovial fibroblast proliferation and induced production of progelatinase B and PGE ₂	114
<i>Bacopa monniera</i>	Herpestis monniera	Methanol	Stabilizing action on lysosomal membranes	115
<i>Barleria lupulina</i>	Hophead	Methanol	Assisting cell mediated immune responses	116
<i>Barleria prionitis</i>	Katsareya	Hydro-ethanolic	Lowers the ESR level and have an immuno-modulatory activity	117
<i>Bauhinia variegata</i>	Kachnar	Ethanol	Alteration in antioxidant enzymes such as catalase, superoxide dismutase and glutathione peroxidase	118,119
<i>Bergenia stracheyi</i>	Paashaanbhed	Petroleum Ether, Chloroform	Potential Th1/Th2 cytokine balancing activity	120
<i>Boerhaavia diffusa</i>	Punarnava	Petroleum Ether	Inhibition of inflammatory 7 inhibitor	121
<i>Boswellia carterii</i>	Olibanum	n-Hexane	Formation of LTB ₄ leukotriene is reduced As well as infiltration of leukocytes altered	122
<i>Butea monosperma</i>	Palash	Petroleum Ether	Hemoglobin and RBC level was increased while; WBC, ESR level were suppressed	123,124
<i>Caesalpinia sappan</i>	Sapanwood	Ethanol	Showed Inhibitory the expression of TNF- α and pro-inflammatory cytokines IL-1 β	125
<i>Calotropis gigantea</i>	Milkweed	Petroleum Ether	Pro-inflammatory cytokines are reduced	126
<i>Calatropis procera</i>	Sodom apple	Methanol	Inhibit cellular influx and vascular permeability	127
<i>Caltha palustris</i>	Kingcup	Methanol	Absolute count and percentage of splenic T-regulatory cells CD4+CD25+FOXP ₃ was reduced	128
<i>Cannabis sativum</i>	Ganja	Alcoholic	Diminished IFN- γ production	129

Table 2: (Continued)

Name of the plant	Common name	Type of Extract used	Activity observed	Reference
<i>Capparis erythrocarpus</i>	Flamingo	Ethanol	Inhibit the release of pro-inflammatory cytokines	130
<i>Capparis spinosa</i>	Flinders rose	Hydro-alcoholic	Counteract the effects of IL-1	131
<i>Cardiospermum halicacabum</i>	Ballon plant	Ethanol	CFA Histamine and prostaglandin synthesis inhibition	132
<i>Cayaponia tayuya</i>	Tayuya	Hydro-alcoholic	Modify the expression of both COX-2 and nitric oxide synthase-2. Decreases production of IL-1 β & TNF- α in lymphocytes	133
<i>Cassia uniflora</i>	One leaf senna	Methanol, Petroleum Ether, Ethyl Acetate	Reduction of CRP and RF levels in the serum	134
<i>Celastrus aculeatus</i>	Gua shan fena	Ethanol	CFA down regulate the biochemical and immunological mediator	135
<i>Centella asiatica</i>	Brahmi	Methanol	Have inhibitory activity against protein denaturation and membrane stabilization	136
<i>Cinnammomum zeylanicum</i>	Dalchini	Aqueous	Inhibition of leukocyte emigration	137
<i>Cissampelos pareira</i>	Butua	50% aqueous:ethanol	Acid phosphatase and N-acetyl glucosaminidase were reduced while hexose and sialic acid increased.	138
<i>Chelidonium majus</i>	Tetterwort	Methanol	Decreased number of CD4+T cells in lymph node and spleen, immunosuppression by lowering the CD4+T-cells and enhance CD8+T-cells.	139
<i>Cleome gyandra</i>	Shone cabbage	Ethanol	CFA modifying the lysosomal membrane thus Inhibiting lysosomal enzymes release	140
<i>Coriandrum sativum</i>	Cilantro	Hydro-alcoholic	Inhibit the secretion of pro-inflammatory cytokines including TNF- α .	141
<i>Costus speciosus</i>	Keukand	Methanol	Suppression of inflammatory mediators	142
<i>Curcuma longa</i>	Turmeric	n-Hexane	Activation of genes critical to articular inflammation	143
<i>Curcuma zeodaria</i>	White turmeric	Chloroform, Petroleum Ether	Decrease the latency time to explore	144
<i>Delonix elata</i>	Gulmohar	Petroleum Ether, Chloroform, Hydroalcoholic	Blocking the action of COX, LO and AT and thus preventing the generation of mediators	145
<i>Dipsacus asperoides</i>	Japanese teasel	Aqueous	Reduced the levels of anti-CII IgG2a antibody, PGE ₂ , TNF- α and IL-1 β	146
<i>Drynaria quercifolia</i>	Oak	Aqueous	Inhibition of ROS release	147
<i>Elaeocarpus sphaericus</i>	Blue marble Tree	Ethanol	Inhibition of leukocytes migration at the site of inflammation	148

Table 2: (Continued)

Name of the plant	Common name	Type of Extract used	Activity observed	Reference
<i>Ephedra sinica</i>	Ma Haung	Aqueous	Expressions of TNF- α and IL-6 genes restored to normal levels in experimental arthritis	149
<i>Euphorbia antiquorum</i>	Antique spurge	Methanol	Arachidonic metabolites and cell-mediated immunity was suppressed	150
<i>Ficus bengalensis</i>	Banyan tree	Methanol	Inhibition of the early phase of inflammation	151
<i>Ginkgo biloba</i>	Maiden hair tree	Methanol	Macrophages infiltrated to the the inflamed site was inhibited for NO production	152
<i>Glycosmis pentaphylla</i>	Orange berry	Ethanol	Increased in haematological parameters like RBC count, Hb level and the ESR	153
<i>Glycyrrhiza glabra</i>	Liquorice	Methanol	Lysosomal membrane stability increased and inhibiting leukocyte migration	154
<i>Hedera helix</i>	European ivy	Ethanol, hydro-ethanolic	Reduction in arthritic symptoms	155
<i>Hemidesmus indicus</i>	Indian Sarsaparilla	Hydro-ethanolic	Inhibition of bradykinin, caragenin and serotonin concentration in inflammation	156
<i>Hippocratea excels</i>	Mata piojo	Ethanol	Shows activity against both the proliferative phase and exudative phase of inflammation	157
<i>Hybanthus enneaspermus</i>	Humpback flower	Aqueous, Ethanol	Inhibits the release of proinflammatory cytokines (IL-1 β and TNF- α) and decrease GM-CSF, PDGF and IFN- γ production	158
<i>Justicia gendarussa</i>	Willow leaved justice	Ethanol	Inhibition of migration of leukocytes	159
<i>Lantana camara</i>		Ethanol	Lipoxygenase and/or cyclooxygenase Inhibition	160
<i>Laportea bulbifera</i>	Mukago-irakusa	Ethanol	Decreased production of IFN- γ and IL-2, and increased production of IL-10 and TGF- β	161
<i>Lawsonia inermis</i>	Henna	70% aqueous ethyl alcohol	Decrease in inflammatory mediators to suppress both acute and chronic phase of inflammation	162
<i>Leucas aspera</i>	Thumbai	n-hexane, Chloroform, Ethyl Acetate, Ethanol	Decreased levels of CRP, TNF- α and IL-2 And the complete formation of cartilage	163
<i>Linum usitatissimum</i>	Flax	Petroleum Ether	FIA Inhibitory effect on arachidonate metabolism	164
<i>Lonicera japonica</i>	Japanese honey Suckle	Methanol	Suppress T-cell proliferation	165
<i>Merremia emarginata</i>	Kupit-kupit	Ethanol	Restores body weight and Improves ESR, hemoglobin values	166

Table 2: (Continued)

Name of the plant	Common name	Type of Extract used	Activity observed	Reference
<i>Operculina turpethum</i>	Turpeth	Ethanol	Inhibit the denaturation of proteins	167
<i>Panax ginseng</i>	Ginseng	Ethanol	Suppressed TPA-induced acute inflammation	168
<i>Phyllanthus amarus</i>	Chanca	Aqueous	ALT and iT levels were reduced	169
<i>Physalis angulate</i>	Fisalia	Aqueous, Ethanol, Methanol	Inhibit the denaturation of proteins	170
<i>Pinus maritime</i>	Maritime pine	Hydro-ethanolic	Inhibits acute and chronic inflammatory lesions	171
<i>Piper betle</i>	Tambula	Hydro-ethanolic	Reduced levels of CD4+T cell specific IFN- γ in splenocytes.	82, 172
<i>Piper longum</i>	Pippali	Aqueous	Neutrophils adherence to endothelial monolayer was inhibited due to TNF- α induced ICAM-1, VCAM-1 and E-selectin expression inhibition and also reduced activation of NF-kB	173
<i>Pisonia grandis</i>	Devil's-claws	Ethanol	IFN, GM-CSF and PGDF cytokines are suppressed in CFA induced mediators	[174]
<i>Pistia stratiotes</i>	Water lettuce	Aqueous, Ethanol	Low levels of C-reactive proteins and ESR	175
<i>Premna serratifolia</i>	Agnimantha	Ethanol	Suppression of migration of leukocytes	176
<i>Pseudocedrea kotschy</i>	Hard cedar	Aqueous	Reduction in inflammation due to mediators suppression	177
<i>Punica granatum</i>	Pomegranate	Aqueous	Inhibition of the spectrum of the signal transduction pathway	178
<i>Rhus verniciflua</i>	Chinese lacquer Tree	n-hexane	In IL-1 β -stimulated RA, inflammatory cytokines/chemokines and angiogenic factor were suppressed	179
<i>Ruta graveolens</i>	Rue	Aqueous	Reduces cell influx, the release of mediators, lipid peroxidation and oxidative stress	180
<i>Salacia reticulate</i>	Kothala himbutu	Ethanol	Inhibitory affect against regulation of mRNA expression and IL-1 β - activated cell proliferation	181
<i>Salix nigra</i>	Black willow	Methanol	Inhibition of pro inflammatory inhibitor	182
<i>Saraca asoca</i>	Ashoka	Methanol	Stabilizing effect on lysosomal membrane, this reduced acid hydrolase release. Have Antagonistic action to the pro-inflammatory cytokines	183
<i>Saussurea lappa</i>	Kuth	Ethanol	InLPS-stimulated murine macrophage cell line, TNF- α release was inhibited	184

Table 2: (Continued)

Name of the plant	Common name	Type of Extract used	Activity observed	Reference
<i>Semecarpus Anacardium</i>	Bhallatak	Aqueous, Ethanol	Inhibition of cytokine production	185
<i>Sida rhombifolia</i>	Cuban jute	Methanol, Petroleum Ether	Generation of reactive oxygen species was suppressed	186
<i>Sinomenium acutum</i>	Tudurafuji	Alcoholic	Inhibition of lymphocyte proliferation and macrophage	187
<i>Torilis japonica</i>	Upright hedge Parsley	Methanol	Inhibitory effects on CD4 T-cells immune cell trafficking.	188
<i>Toxicodendron pubescens</i>	Atlantic poison	Aqueous	Immunosuppressant activity	189
<i>Trigonella foenum</i>	Fenugreek	Aqueous	Reduces cell influx, mediators release and oxidative stress	190
<i>Urtica pilulifera</i>	Roman nettle	Methanol	Suppress the activation of NF-kB	191
<i>Vernonia cinerea</i>	Bitter leaf ndole	Ethanol	Membrane stability-modulating effect	192
<i>Withania somnifera</i>	Indian winter Cherry	Hydro-alcoholic	Inhibiting the release of inflammatory mediators	193
<i>Xanthium srtuarium</i>	Datura	Ethanol	Inflammatory mediators were inhibited, NO level decreased and infiltration of urinary hydroxy-proline and neutrophil	194
<i>Yucca schidigera</i>	Spanish dagger	Hydro-alcoholic	Inhibition of NFkB activation	195

Graphical Abstract