Review on Anti-Rheumatoid Arthritis Potential of Medicinal Plants

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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 ethnotherapeutic 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 etiology 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
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 dosa: 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 dosa 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-κβ mediated by adapter molecules like myeloid differentiation primary-response gene 88 (MyD88) at the onset of disease. The process of phosphorylation of cytoplasmic IκBs is carried by TLR2/6, TLR4, or TLR5 agonist which in turn stimulate target cells and macrophages. After degradation of this complex, NF-κβ translocated into the nucleus where the promoter regions of inflammatory genes like iNOS, COX-2, IL-6 bind to NF-κβ 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-E2 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-κβ 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-1β 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. Many herbal drugs have shown to down-regulate these pro-inflammatory 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. 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. 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. Similar activity of suppression of NF-kB 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. Similar activities have been noted in Zingiber officinale which seen to possess a bioactive constituent 6-gingerol, that blocks the NF-kB and PKC (protein kinase C) pathway and induce anti-inflammatory activity. 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.

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. 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-1β-induced decrease in type II collagen synthesis which is a contributing factor in RA progression. 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-1, Nyctanthes arbor-tristis which lowers down the inflammatory cytokines IL-1, TNF-α in blood serum in experimental set up, Swertia chirayita, works in similar style and lowers down the pro-inflammatory cytokines IL-1β, TNF-α and IL-6 in experimental arthritis 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 phytomedical plants have been observed by experimental methods and are under scientific observations to develop as a natural way for healing. 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. 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-arthritic 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-arthritic 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 |
|-------------------------------|----------------------|---------------------------|--------------------------------------------------------------------------|------------|
| *Alpinia galangal*             | Rhizomes             | The paste of rhizome taken orally | Gives relief in pain                                                    | 29         |
| *Anacyclus pyrethrum*          | Roots                | Infusion drink is taken like tea of roots | Anti-rheumatic & Anti-arthritic                                          | 30         |
| *Aphanamixis polystachya*      | Bark                 | Oil applied on joints to help in pain | Act as analgesic                                                        | 31         |
| *Aquilaria agallocha*          | Wood                 | Decoction taken of wood and oil applied to help in pain | Relieve pain and inflammation.                                          | 32         |
| *Argemone mexicana*            | The whole plant, Latex | The oil used to help in pain | Cure rheumatologic.                                                      | 33         |
| *Callicarpa macrophylla*        | Flowers and fruits   | Decoction taken            | Anti-inflammatory, analgesic and antipyretic effects                     | 34         |
| *Capparis deciduas*            | Roots                | Powder of infusion taken   | Treats rheumatism and fever.                                            | 35         |
| *Cardiospermum halicacabum*     | Roots                | The oil used to relieve pain and powder taken orally | Treats infection in joints by trophic organisms.                       | 36,37      |
| *Carthamus tinctorium*         | Seed                 | Infusion took orally       | Anti-inflammatory and Analgesic.                                         | 38,39      |
| *Cassia fistula*               | Fruits               | Infusion or paste of fruit taken orally | Analgesic                                                                | 40         |
| *Catunaregum Spinosa*          | Bark                 | Paste or oil used          | It is useful in rheumatism.                                             | 41         |
| *Citrlullus colocynthis*        | Roots                | Powder of fruits taken orally | Anti-inflammatory.                                                      | 42         |
| *Commiphora myrrha*            | Gum                  | Oil used for helping in pain and taken gum taken orally | Relive in pain and anti-inflammatory.                                   | 43         |
| *Commiphora wightii*           | Leaves               | Taken orally or infusion   | Relive in pain and Anti-inflammatory.                                    | 44         |
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Table 1: (Continued)

| Name of plant            | Part used                | Mode of use                | Function                          | References |
|--------------------------|--------------------------|----------------------------|-----------------------------------|------------|
| **Cordia dichotoma**     | Fruits                   | Taken orally or in form of powder | Anti-rheumatic.                   | 45         |
| **Coriandrum sativum**   | Fruits and leaves        | Taken orally               | Relive in pain and Anti-inflammatory | 46         |
| **Euphorbia neriifolia** | Leaf                     | Taken in form of juice orally | Relieve pain in rheumatism        | 47         |
| **Euphorbia ligularia**  | Whole plant              | Taken in the form of juice or infusion | Used in the treatment of rheumatism. | 48,4       |
| **Ficus bengalensis**    | Latex                    | Taken as juice             | Used in the treatment of rheumatism. | 50         |
| **Fritillaria roylei**   | Bulbs                    | Taken in form of powder or juice | Used in the treatment of rheumatism. | 51         |
| **Glycosmis Arborea**    | Roots                    | Taken in powder form       | Useful in the treatment of arthritis. | 52         |
| **Gossypium herbaceum**  | Leaves                   | Taken in powder form, juice or infusion | Relive in pain and Anti-inflammatory. | 53         |
| **Heliotropium Indicum** | 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         |
| **Hiptage bengalensis**  | Barks, Leaves and Flowers | Taken in powder form       | Treatment of chronic rheumatism   | 55         |
| **Holarrhena pubescens** | Barks, Seeds and Leaves  | Taken in powder form       | Relive in pain and Anti-inflammatory. | 56         |
| **Hygrophiila auriculata** | Roots, Leaves and Seeds | Taken in powder form       | Relive in pain and Anti-inflammatory. | 57         |
| **Hyoscyamus niger**     | Leaves and Seeds         | Taken in powder form       | Relive in pain and Anti-inflammatory. | 58         |
| **Illicium verum**       | Fruits                   | Taken in powder form, juice | Relive in pain and Anti-inflammatory. | 59         |
| **Inula racemosa**       | Roots                    | Taken orally in powder form | Relive in pain and Anti-inflammatory. | 60         |
| **Ipomoea cairica**      | Seeds                    | The oil used for pain      | Relive in pain and Anti-inflammatory. | 61         |
| **Jasminum lanceolarium** | Leaves and Flowers       | Taken in powder form, juice | Shows effective results against rheumatism and fever. On the other hand, the leaves have anti-inflammatory properties and relieve pain. | 62         |
| **Jatropha curcas**      | Oil                      | The oil used for joint pain externally | Relive in pain and Anti-inflammatory. | 63         |
| **Juglans regia**        | Fruits                   | Taken in powder form, juice | Relive in pain and Anti-inflammatory. | 64,65      |
| **Justicia gendarussa**  | Roots and Leaves         | Taken in powder form, juice | Relive in pain and Anti-inflammatory. | 66         |
Table 1: (Continued)

| Name of plant            | Part used         | Mode of use                          | Function                          | References |
|--------------------------|-------------------|--------------------------------------|-----------------------------------|------------|
| *Kaempferia galangal*    | Rhizomes and Leaves | Taken orally in powder form or juice | Relieve in pain and Anti-inflammatory. | 67         |
| *Lantana Camara*         | Fruits            | Taken orally                         | Used traditionally for the treatment of RA | 68         |
| *Lawsonia inermis*       | Leaves            | Taken orally in powder form or infusion | Used in arthritic disorder. | 69         |
| *Lilium polyphyllum*     | Bulb              | Taken orally in powder form or infusion | Relieve in pain and Anti-inflammatory. | 70         |
| *Madhuca longifolia*     | Oil               | The oil used for joint pain externally | Relieve in pain and Anti-inflammatory. | 71         |
| *Mangifera indica*       | Roots and Barks   | Taken in powder form                 | Relieve in pain and Anti-inflammatory. | 72         |
| *Mimosa pudica*          | Whole plant       | Taken orally                         | Helps to deal with the symptoms of rheumatoid arthritis. | 73         |
| *Momordica charantia*    | Fruits            | Taken orally if different forms or as juice | Relieve in pain and Anti-inflammatory. | 74         |
| *Myxopyrum serratum*     | Leaves            | Taken in powdered form               | Relieve in pain and Anti-inflammatory. | 75         |
| *Naravelia zeylanica*    | Whole plant       | Taken in powder form                 | Relieve in pain and Anti-inflammatory. | 76         |
| *Nilgiranthus ciliatus*  | Roots             | Taken in powder form                 | Relieve in pain and Anti-inflammatory. | 77         |
| *Ocimum basilicum*       | Whole plant       | Taken in form of infusion, powder or leaves taken raw orally | Relieve in pain and Anti-inflammatory. | 78         |
| *Oroxylum Indicum*       | Roots             | Taken in powder form                 | The plant possesses anti-inflammatory activity. | 79         |
| *Pandanus odoratissimus* | Oil               | The oil used for joint pain externally | Relieve in pain and Anti-inflammatory. | 80         |
| *Piper betel*            | Whole Plant       | Orally in powdered form              | Shown effective results in inflammation treatment. | 81         |
| *Piper nigrum*           | Fruits            | Raw fruit used in cooking or taken in powdered form | Relieve in pain and Anti-inflammatory. | 82         |
| *Plumeria Rubra*         | Milky juice       | Applied externally to relieve pain   | Shown positive results in inflammation treatment. | 83         |
| *Pongamia pinnata*       | Leaves            | Taken in powder form                 | Helps in painful rheumatic joints. | 84         |
| *Premna corymbosa*       | Leaves            | Taken in powder form                 | Relieve in pain and Anti-inflammatory | 85         |
| *Premna serratifolia*    | Whole plant       | Taken orally                         | Relieve in pain and Anti-inflammatory | 86         |
| *Ricinus communis*       | Leaves            | Taken in powder form                 | Relieve in pain and Anti-inflammatory | 87         |
| *Rubia cordifolia*       | Roots             | Taken in powder form                 | Relieve in pain and Anti-inflammatory | 88         |
## Table 1: (Continued)

| Name of plant             | Part used       | Mode of use                  | Function                                                                 | References |
|---------------------------|-----------------|------------------------------|--------------------------------------------------------------------------|------------|
| *Ruta chalepensis*        | Oil             | The oil used for joint pain  | Analgesic, antipyretic, anti-inflammatory and relieves rheumatic pain.   | 89         |
| *Sida cordifolia*         | Roots and Leaves| Taken in powder form         |Used for treating rheumatism.                                            | 90         |
| *Solanum nigrum*          | Whole Plant     | Taken in powder form         | Relieve in pain and Anti-inflammatory                                   | 91         |
| *Spondias pinnata*        | Roots           | Taken in powder form         | Relieve in pain and Anti-inflammatory and helps in muscular pain in rheumatism | 92         |
| *Stereospermum colais*    | Leaves          | Taken in powder form         | Relieve in pain and Anti-inflammatory                                   | 93         |
| *Tectona grandis*         | Wood            | Taken in powder form, the    | Used in treating inflammatory swelling.                                 | 94         |
| *Trachyspermum Ammi*      | Fruits          | Taken in powder or juice     | Relieve in pain and Anti-inflammatory                                   | 95         |
| *Tribulus Terrestris*     | Whole Plant     | used for joint pain externally | Used for external application in rheumatic-arthritis.                   | 96         |
| *Vatteria indica*         | Oil             | The oil used for joint pain  | Relieve in pain and Anti-inflammatory                                   | 97         |
| *Vitex negundo*           | Roots           | Taken in powder form         | Relieve in pain and Anti-inflammatory                                   | 98         |
| *Vitis vinifera*          | Stem            | Taken in powder form or      | Relieve 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 |
|---------------------------|--------------------|-----------------------------|----------------------------------------------------------------------------------|-----------|
| *Achyranthes Aspera*      | Apamaraga          | Ethanol                     | Prevented the recruitment of leukocytes                                         | 100,101   |
| *Aconitum vilmorinianum*  | Wolf’s-bane,       | Ethanol                     | Improvement of joint swelling and vascular permeability                            | 102       |
| *Ajuga bracteosa*         | Ground pine        | Ethanol                     | COX-1 and COX-2 inhibition                                                        | 103       |
| *Ajuga decumbens*         | Bugle weed         | Ethanol                     | Regulates the balance between bone formation and bone resorption                 | 104       |
| *Alstonia boonei*         | Cheese wood        | Methanol                    | Relief in early and late phase of pain                                            | 105       |
| *Alstonia scholaris*      | devil tree         | Ethanol                     | Shown activity in Reduction of total leukocyte, lymphocytes and monocytes/       | 106       |
|                           |                    |                             | macrophages migration                                                            |           |
| *Ammania bracifera*       | tooth cup          | Aqueous Alcoholic Petroleum | Decrease the ESR and WBC count                                                   | 107       |
|                           |                    | Ether, Chloroform, Methanol  |                                                                                  |           |
| *Aristolochia bracteata*  | Kidamari           | Petroleum Ether, Chloroform | 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 |
|---------------------------------|-------------|----------------------|-----------------------------------------------------------------------------------|-----------|
| Argyreia speciosa               | Elephant    | Methanol, Ethanol    | Prevented the recruitment of leukocytes                                           | 100, 109  |
| Arisaema rhizomatum             | Jack in the pulp it | Ethanol         | Have shown result against pro-inflammatory cytokines and RA factor secretion    | 110       |
| Arnebia euchroma                 | Pink arnebia | Ethanol (95%)        | Suppression of IL-1β and TNF-α levels                                             | 111       |
| Artocarpus tonkinensis           | Chay        | Ethyl acetate        | Apoptosis induction in activated T-cells                                           | 112       |
| Asystasia dalzelliana            | Violet asystasia | Ethanol           | Decreasing synthesis/release of T-cell mediators                                 | 113       |
| Baccharis genistelloides         | Carqueja    | Aqueous              | Suppresses synovial fibroblast proliferation and induced production of progelatinase B and PGE2 | 114       |
| Bacopa monniera                  | Herpestis monniera | Methanol      | Stabilizing action on lysosomal membranes                                          | 115       |
| Barleria lupulina                | Hophead     | Methanol             | Assisting cell mediated immune responses                                           | 116       |
| Barleria prionitis               | Katsareya   | Hydro-ethanolic      | Lowers the ESR level and have an immuno-modulatory activity                        | 117       |
| Bauhinia variegata               | Kachnar     | Ethanol              | Alteration in antioxidant enzymes such as catalase, superoxide dismutase and glutathione peroxidase | 118,119   |
| Bergenia stracheyi              | Paashaanbhed | Petroleum Ether, Chloroform | Potential Th1/Th2 cytokine balancing activity                                      | 120       |
| Boerhaavia diffusa              | Punarnava    | Petroleum Ether      | Inhibition of inflammatory 7 inhibitor                                             | 121       |
| Boswellia carterii              | Olibanum     | n-Hexane             | Formation of LTB4 leukotriene is reduced                                           | 122       |
|                                  |             |                      | As well as infiltration of leukocytes altered                                       |           |
| Butea monosperma                 | Palash      | Petroleum Ether      | Hemoglobin and RBC level was increased while; WBC, ESR level were suppressed      | 123,124   |
| Caesalpinia sappan               | Sapanwood   | Ethanol              | Showed Inhibitory the expression of TNF-α and pro-inflammatory cytokines IL-1ß      | 125       |
| Calotropis gigantean             | Milkweed    | Petroleum Ether      | Pro-inflammatory cytokines are reduced                                             | 126       |
| Calotropis procera               | Sodom apple | Methanol             | Inhibit cellular influx and vascular permeability                                  | 127       |
| Caltha palustris                 | Kingcup     | Methanol             | Absolute count and percentage of splenic T-regulatory cells CD4+CD25+FOXP3 was reduced | 128       |
| Cannabis sativum                 | Ganja       | Alcoholic            | Diminished IFN-γ production                                                        | 129       |
Table 2: (Continued)

| Name of the plant       | Common name       | Type of Extract used | Activity observed                                                                                                                                  | Reference |
|-------------------------|-------------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| *Capparis erythrocarpus* | Flamingo          | Ethanol              | Inhibit the release of pro-inflammatory cytokines                                                                                                   | 130       |
| *Capparis spinosa*      | Flinders rose     | Hydro-alcoholic      | Counteract the effects of IL-1                                                                                                                     | 131       |
| *Cardiospermum halicacabum* | Ballon plant     | Ethanol              | CFA Histamine and prostaglandin synthesis inhibition                                                                                             | 132       |
| *Cayaponia tayuya*      | Tayuya            | Hydro-alcoholic      | Modify the expression of both COX-2 and nitric oxide synthase-2. Decreases production of IL-1β & TNF-α in lymphocytes                               | 133       |
| *Cassia uniflora*       | One leaf senna    | Methanol, Petroleum Ether, Ethyl Acetate | Reduction of CRP and RF levels in the serum                                                                                                      | 134       |
| *Celastrus aculeatus*   | Gua shan fena     | Ethanol              | CFA down regulate the biochemical and immunological mediator                                                                                      | 135       |
| *Centella asiatica*     | Brahmi            | Methanol             | Have inhibitory activity against protein denaturation and membrane stabilization                                                                    | 136       |
| *Cinnamomomum zeylcanium* | Dalchini         | Aqueous              | Inhibition of leukocyte emigration                                                                                                                  | 137       |
| *Cissampelos pareira*   | Butua             | 50% aqueous:ethanol  | Acid phosphatase and N-acetyl glucosaminidase were reduced while hexose and sialic acid increased.                                                    | 138       |
| *Chelidonium majus*     | 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       |
| *Cleome gyandra*        | Shone cabbage     | Ethanol              | CFA modifying the lysosomal membrane thus Inhibiting lysosomal enzymes release                                                                | 140       |
| *Coriandrum sativum*    | Cilantro           | Hydro-alcoholic      | Inhibit the secretion of pro-inflammatory cytokines including TNF-α                                                                               | 141       |
| *Costus speciosus*      | Keukand           | Methanol             | Suppression of inflammatory mediators                                                                                                            | 142       |
| *Curcuma longa*         | Turmeric           | n-Hexane             | Activation of genes critical to articular inflammation                                                                                           | 143       |
| *Curcuma zeodaria*      | White turmeric    | Chloroform, Petroleum Ether | Decrease the latency time to explore                                                                                                             | 144       |
| *Delonix elata*         | Gulmohar           | Petroleum Ether, Chloroform, Hydroalcoholic | Blocking the action of COX, LO and AT and thus preventing the generation of mediators                                                           | 145       |
| *Dipsacus asperoides*   | Japanese teasel    | Aqueous              | Reduced the levels of anti-CII IgG2a antibody, PGE2, TNF-α and IL-1β                                                                            | 146       |
| *Drynaria quercifolia*  | Oak                | Aqueous              | Inhibition of ROS release                                                                                                                        | 147       |
| *Elaeacarpus sphaericus*| Blue marble       | Ethanol              | Inhibition of leukocytes migration at the site of inflammation                                                                                   | 148       |
| Name of the plant          | Common name    | Type of Extract used | Activity observed                                                                                                                                                                                                 | Reference |
|---------------------------|----------------|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Ephedra sinica            | Ma Haung       | Aqueous              | Expressions of TNF-α and IL-6 genes restored to normal levels in experimental arthritis                                                                                                                         | 149       |
| Euphorbia antiquorum      | Antique spurge | Methanol             | Arachidonic metabolites and cell-mediated immunity was suppressed                                                                                                                                                | 150       |
| Ficus bengalensis         | Banyan tree    | Methanol             | Inhibition of the early phase of inflammation                                                                                                                                                                    | 151       |
| Ginkgo biloba             | Maiden hair tree | Methanol             | Macrophages infiltrated to the inflamed site was inhibited for NO production                                                                                                                                   | 152       |
| Glycosmis pentaphylla     | Orange berry   | Ethanol              | Increased in haematological parameters like RBC count, Hb level and the ESR                                                                                                                                     | 153       |
| Glycyrrhiza glabra        | Liquorice      | Methanol             | Lysosomal membrane stability increased and inhibiting leukocyte migration                                                                                                                                   | 154       |
| Hedera helix              | European ivy   | Ethanol, hydro-ethanolic | Reduction in arthritic symptoms                                                                                                                                                                             | 155       |
| Hemidesmus indicus        | Indian Sarsaparilla | Hydro-ethanolic | Inhibition of bradykinin, caragenin and serotonin concentration in inflammation                                                                                                                  | 156       |
| Hippocratea excels        | Mata piojo     | Ethanol              | Shows activity against both the proliferative phase and exudative phase of inflammation                                                                                                                          | 157       |
| Hybanthus enneaspermus    | Humpback flower | Aqueous, Ethanol    | Inhibits the release of proinflammatory cytokines (IL-1β and TNF-α) and decrease GM-CSF, PDGF and IFN-γ production                                                                                           | 158       |
| Justicia gendarussa       | Willow leaved justice | Ethanol               | Inhibition of migration of leukocytes                                                                                                                                                                        | 159       |
| Lantana camara            | Ethanol        | Ethanol              | Lipoxygenase and/or cyclooxygenase Inhibition                                                                                                                                                                   | 160       |
| Laportea bulbifera        | Mukago-irakusa | Ethanol              | Decreased production of IFN-γ and IL-2, and increased production of IL-10 and TGF-β                                                                                                                               | 161       |
| Lawsonia inermis          | Henna          | 70% aqueous ethyl alcohol | Decrease in inflammatory mediators to suppress both acute and chronic phase of inflammation                                                                                                                     | 162       |
| Leucas aspera             | Thumbai        | n-hexane, Chloroform, Ethyl Acetate, Ethanol | Decreased levels of CRP, TNF-α and IL-2 And the complete formation of cartilage                                                                                                                                      | 163       |
| Linum usitatissimum       | Flax           | Petroleum Ether      | FIA Inhibitory effect on arachidonate metabolism                                                                                                                                                                | 164       |
| Lonicera japonica         | Japanese honey Suckle | Methanol               | Suppress T-cell proliferation                                                                                                                                                                                      | 165       |
| Merremia emarginata       | Kupit-kupit    | Ethanol              | Restores body weight and Improves ESR, hemoglobin values                                                                                                                                                    | 166       |
| Name of the plant          | Common name | Type of Extract used | Activity observed                                                                 | Reference |
|---------------------------|-------------|----------------------|------------------------------------------------------------------------------------|-----------|
| *Operculina turpethum*    | Turpeth     | Ethanol              | Inhibit the denaturation of proteins                                                | 167       |
| *Panax ginseng*           | Ginseng     | Ethanol              | Suppressed TPA-induced acute inflammation                                           | 168       |
| *Phyllanthus amarus*       | Chanca      | Aqueous              | ALT and iT levels were reduced                                                      | 169       |
| *Physalis angulate*       | Fisalia     | Aqueous, Ethanol, Methanol | Inhibit the denaturation of proteins                                                | 170       |
| *Pinus maritime*          | Maritime pine | Hydro-ethanolic     | Inhibits acute and chronic inflammatory lesions                                      | 171       |
| *Piper betle*             | Tambula     | Hydro-ethanolic      | Reduced levels of CD4+T cell specific IFN-γ in splenocytes.                         | 82, 172   |
| *Piper longum*            | 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-κB | 173       |
| *Pisonia grandis*         | Devil's-claws | Ethanol            | IFN, GM-CSF and PGDF cytokines are suppressed in CFA induced mediators              | 174       |
| *Pistia stratiotes*       | Water lettuce | Aqueous, Ethanol   | Low levels of C-reactive proteins and ESR                                           | 175       |
| *Premna serratifolia*     | Agnimantha  | Ethanol              | Suppression of migration of leukocytes                                              | 176       |
| *Pseudocdrea kotschyi*    | Hard cedar  | Aqueous              | Reduction in inflammation due to mediators suppression                              | 177       |
| *Punica granatum*         | Pomegranate | Aqueous              | Inhibition of the spectrum of the signal transduction pathway                       | 178       |
| *Rhus verniciflua*        | Chinese lacquer Tree | n-hexane| In IL-1β-stimulated RA, inflammatory cytokines/chemokines and angiogenic factor were suppressed | 179       |
| *Ruta graveolens*         | Rue         | Aqueous              | Reduces cell influx, the release of mediators, lipid peroxidation and oxidative stress | 180       |
| *Salacia reticulate*      | Khothala himbutu | Ethanol          | Inhibitory affect against regulation of mRNA expression and IL-1β - activated cell proliferation | 181       |
| *Salix nigra*             | Black willow | Methanol            | Inhibition of pro inflammatory inhibitor                                             | 182       |
| *Saraca asoca*            | Ashoka      | Methanol            | Stabilizing effect on lysosomal membrane, this reduced acid hydrolase release. Have Antagonistic action to the pro-inflammatory cytokines | 183       |
| *Saussurea lappa*         | 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 |
|----------------------------|---------------------|----------------------|-----------------------------------------------------------------------------------|-----------|
| *Semecarpus Anacardium*    | Bhallatak           | Aqueous, Ethanol     | Inhibition of cytokine production                                                  | 185       |
| *Sida rhombifolia*         | Cuban jute          | Methanol, Petroleum Ether | Generation of reactive oxygen species was suppressed                               | 186       |
| *Sinomenium acutum*        | Tudurafuji          | Alcoholic            | Inhibition of lymphocyte proliferation and macrophage                               | 187       |
| *Torilis japonica*         | Upright hedge Parsley | Methanol             | Inhibitory effects on CD4 T-cells immune cell trafficking.                          | 188       |
| *Toxicodendron pubescens*  | Atlantic poison     | Aqueous              | Immunosuppressant activity                                                         | 189       |
| *Trigonella foenum*        | Fenugreek           | Aqueous              | Reduces cell influx, mediators release and oxidative stress                        | 190       |
| *Urtica pilulifera*        | Roman nettle        | Methanol             | Suppress the activation of NF-kB                                                  | 191       |
| *Vernonia cinerea*         | Bitter leaf ndole   | Ethanol              | Membrane stability-modulating effect                                               | 192       |
| *Withania somnifera*       | Indian winter Cherry | Hydro-alcoholic      | Inhibiting the release of inflammatory mediators                                  | 193       |
| *Xanthium srtuarium*       | Datura              | Ethanol              | Inflammatory mediators were inhibited, NO level decreased and infiltration of urinary hydroxyproline and neutrophil | 194       |
| *Yucca schidigera*         | Spanish dagger      | Hydro-alcoholic      | Inhibition of NFkB activation                                                      | 195       |

**Graphical Abstract**