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# Review article: Herbal sources as a remedy for rheumatoid arthritis

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## Introduction

Herbal sources of medicinal plants are in great demand for curing various diseases. Medicinal knowledge gained over trial and error over thousands of years in many regions around the world. Knowing that plants have a large number of phyto-constituents with different pharmacological activities, guide us towards the safe use of these plants in future for treatments of many diseases.

**RA** is the most common systemic inflammatory disorder that affects 1% of the population worldwide, it is more common among women than men(3:1), it may be mild self-limiting or may rapidly progress into a multisystem inflammation with irreversible joint destruction[1].

Rheumatoid arthritis (**RA**) is an autoimmune disease that occurs when the body's own immune system mistakenly attacks the synovium which is the cell membrane lining inside the joint leading to joint pain, swelling , stiffness and loss of joint function. **RA** mostly affect elderly people but nowadays it appear in younger age 20-40. Fortunately there are many herbs in nature which act as a remedy for this condition and reduce chronic joint inflammation in RA[2]. Major pharmaceutical companies are currently paying attention on the research on plant materials for their potential medicinal value [3]

**RA** is an inflammation of synovial joint due to immune mediated response. Synovial inflammation, cartilage destruction, and bone erosions characterize the different stages of the disease in which several pro-inflammatory pathways are involved[1].

B cells and T cells lymphocytes are the main two components of the immune system that play an important role in inflammation associated with **RA**[4]. Herbal medicinal products (HMPs) that interact with the mediators of inflammation are used in the treatment of RA

### 1.The immune system

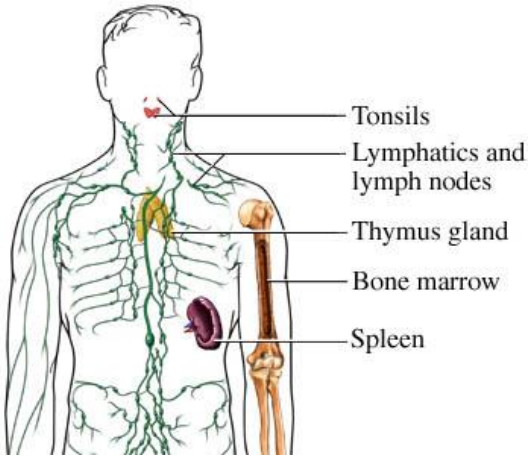
It is a defense system of the body that provides protection against foreign invaders, which are disease causing microbes (bacteria, parasite and fungi). Immune system works in two ways: identifying and killing pathogens. Detection of invaders is difficult because pathogen can modify rapidly according to environment effects and producing adaptation which is hard for the immune system to detect and allow the pathogens to successfully infects their host[5], so there are multiple mechanisms involved in recognition and killing of pathogens[6].

The immune system is a complex set-up of cells, tissues and organs that work together to provide protection against the threat of microorganisms and infections. White blood cells (Leukocytes) are the main components of the immune system as it can eliminate the germs or any other substances responsible for occurrence of diseases. Leukocytes are also called lymphoid organs as they are accumulated in thymus, spleen and bone marrow[5]. Leukocytes move throughout the body between organs and nodes by means of lymphatic vessels and blood vessels. So the defense system works in synchronized method to protect the body against disease causing agents.

**1.1. Organs of the Immune System** [7, 8,9]

**1.1.1.Bone Marrow**:

The bone marrow are responsible for creating all types of cells of the immune systems. It produces : B cells, immature T cells, natural killer cells (NKC), granulocytes and, it also generate red blood cells and platelets.




**1.1.2.Thymus**:

It produce mature T cells which are then migrate into the bloodstream.

1**.1.3**. **Spleen**:

It is an immunologic filter of the blood, capturing foreign materials (antigens) from the blood that passes through the spleen.

**1.1.4**. **Lymph nodes**: The lymph nodes has the same function of spleen it is responsible for filtering bodily fluid known as lymph. They are distributed throughout the body, it is composed mostly of T cells, B cells, dendritic cells and macrophages, antigens are filtered out of the lymph in the lymph node before returning the lymph to the circulation.

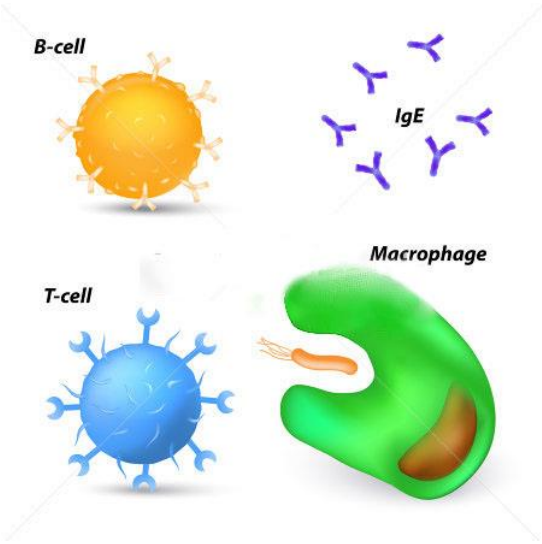
**1.2.Disorders of immune system**.

1.2.1 Acquired immune deficiency disorder: it is caused by virus which reduces efficiency of the immune system

1.2.2. Autoimmune disorders: the body's own immune system cannot distinguish between foreign invader and its own tissues

1.2.3. An allergic disorder: the immune system over reacts is response to an antigen.

1.2.4. Cancers of the immune system




**1.2.2.Autoimmune disease**

The immune system in the body means protection against foreign substances. It has the ability to recognize tissues and cells that are its own (self) and differentiate them from those that are not (non-self). In autoimmune diseases, the body mistakenly attack its own tissues and consider it as foreign invader, the reason for this attack may be due to genetic, environmental factors or of unknown reasons

**2.Pathophysiology of rheumatoid arthritis**

RA starts in synovium which is the membrane lining sac which surround the joint. This sac containing synovial fluid which act as lubricant and cushioning the joints( Fig 1), the synovial fluid which coats the end of bones supplies cartilage with oxygen and nutrients [4]

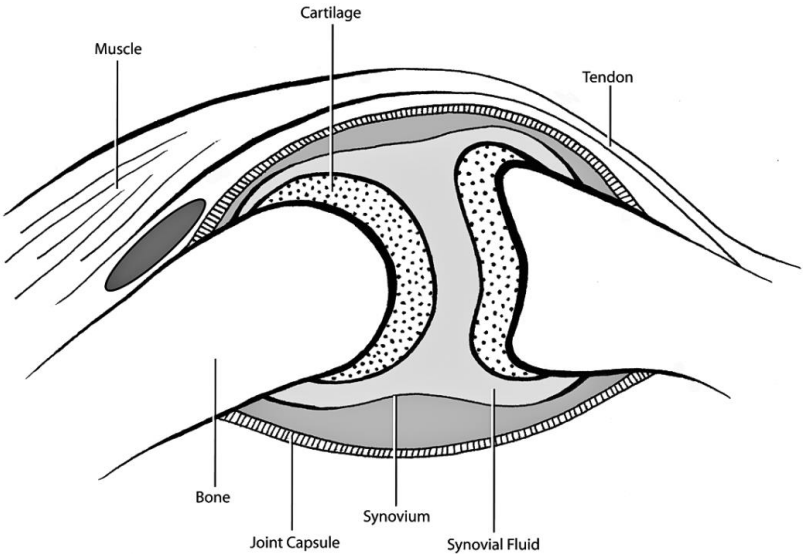



**Fig 1**

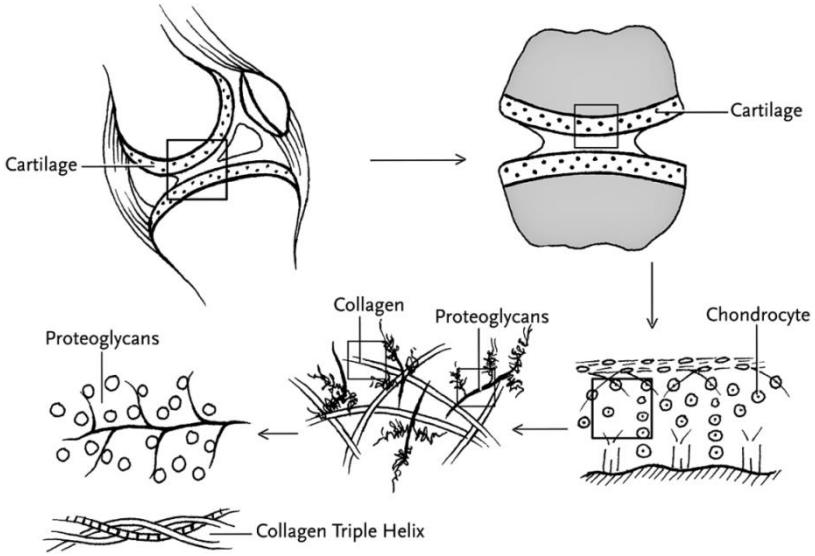



**Fig 2**

Cartilage is made of collagen which gives the joint support and flexibility. In RA harmful molecules produced by an abnormal immune system response cause inflammation of the synovium in turn collagen begin to destroy leading to narrowing the joint space and finally damaging bone. In a progressive rheumatoid arthritis, destruction of the cartilage accelerates(**Fig 3**).

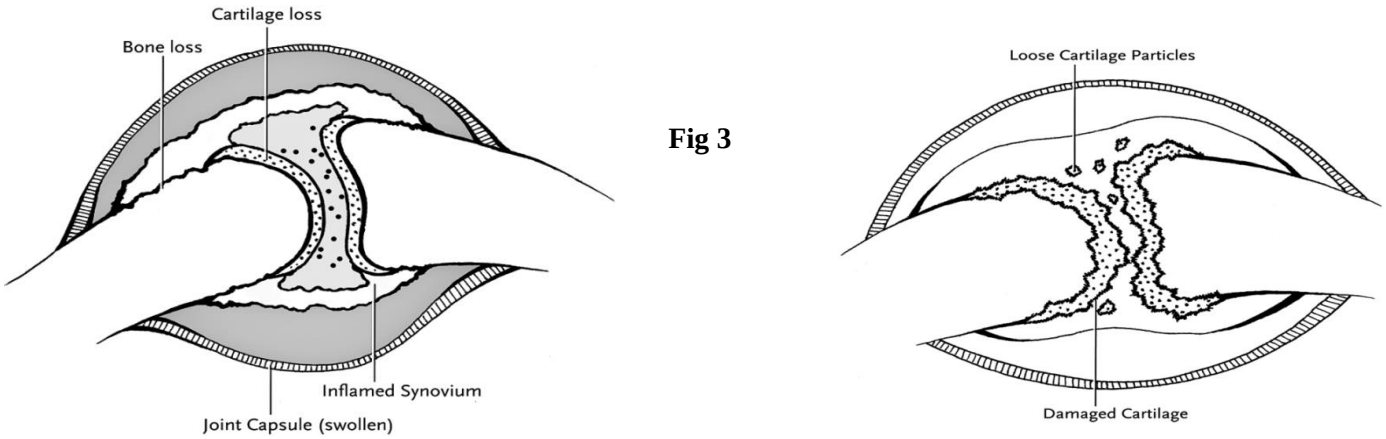
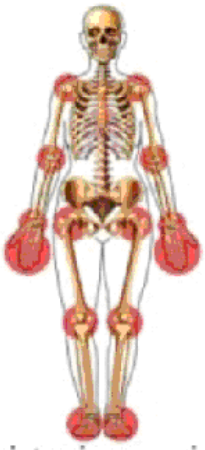



**Fig 3**



Joint pain occurring in various joints

**Which joints are affected**

RA affects any joints of the body but the most affected joint are those of hands wrists and feet

**Symptoms of RA** [10]

Small joints in the body are early affected and symptoms are often felt in:

fingers and toes, shoulders and knees can also be affected

1. Morning stiffness that last for at least 1 hr.
2. Pain, swelling, tenderness and stiffness of the joint after resting
3. Low-grade fever.
4. Appearance of painless small nodules under the skin which results from inflammation of small blood vessels


**3.Diagnosing rheumatoid arthritis**

It is hard to diagnose RA in its early stages, diagnosis is based on clinical assessment, lab. tests and X-rays.

**Lab test**:

1. Rheumatoid factor (RF) is an antibody in the blood it is linked with RA, 80% of people having RA give positive test.

2. Anti-CCP (anti-cyclic citrullinated peptide antibody) test may be also done to give better confirmation when combined with RF test [11]. Other way of diagnosis include X-rays and magnetic resonance imaging (MRI) scans [12].

**4.Etiology:**

The etiology of RA is still unknown, a genetic susceptibility in combination with environmental factors may be the reasons for the onset of RA.

**Factors which are responsible for the disease**

**4.1. Genetic factors:**

RA has a genetic link, and the disease can run in families. Human leukocyte antigen (HLA) genes is linked with people have the chance of developing RA than people who do not have the HLA genes. Still, not everyone with the HLA genes develops RA People with specific.

**4.2. Environmental factors:**

Smoking may be linked to with the development of RF positive, RA has been associated with exposure to mineral oils, silica exposure, diet factors, and blood transfusion

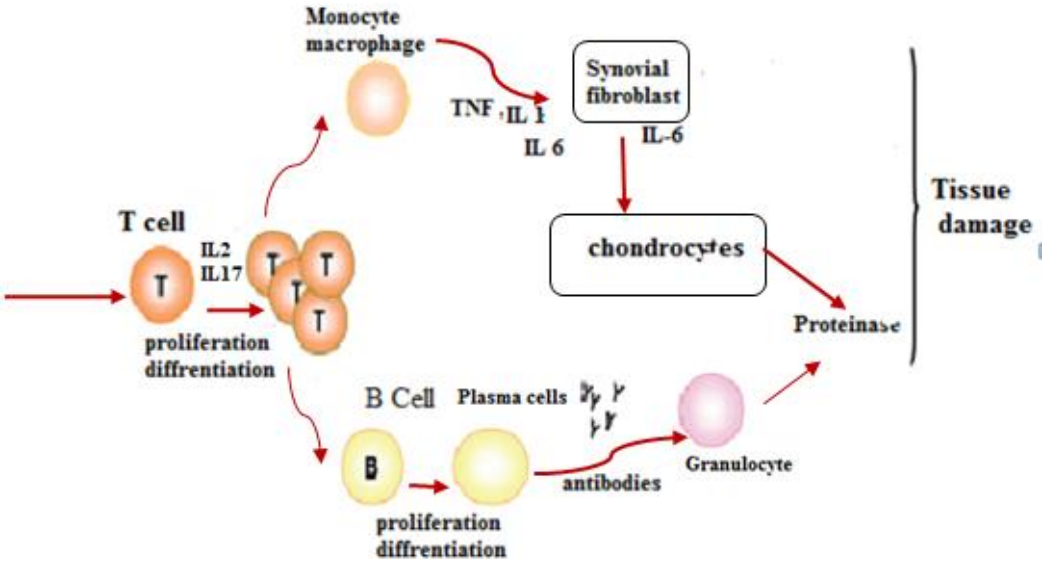
**4.3. Effect of hormones :**

Women were found to be more affected by RA than men , particularly at younger ages. In women, peak incidence is observed in the pri-menopausal, postpartum period and pregnancy.

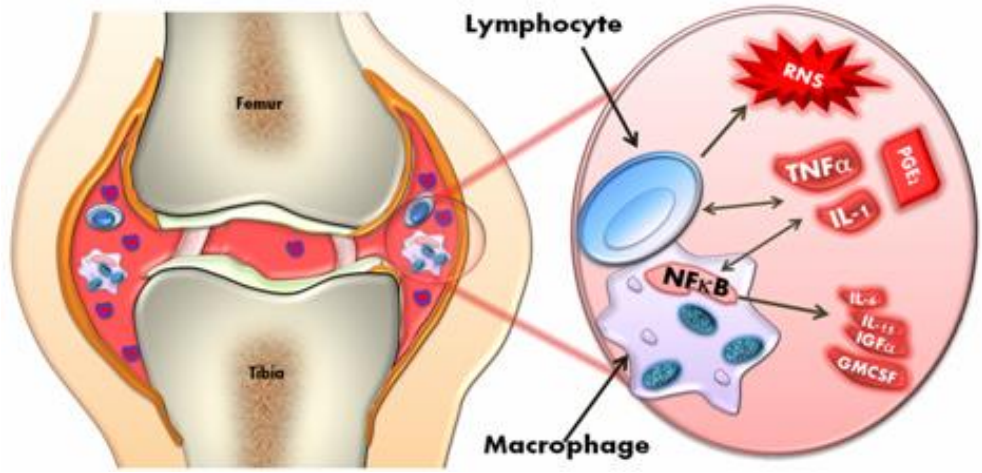
**5.Mechanism of action of the immune system in RA**

The T cell is activated when it recognize an antigen (non-self) it produces chemicals known as cytokines which cause B cells to multiply and release antibodies which circulate in the blood stream, recognizing the foreign particles(Fig 4,5) and causing inflammation to protect the body from invasion [13].

Proinflammatory cytokines: interleukin-1(IL-1)[14] and tumor necrosis factor (TNF-α), are central mediators in RA, the regulation of these mediators and modulation of arachidonic acid metabolism by inhibiting enzymes like COX (cyclooxgenase) and LOX (lipooxygenase) are the potential target for chronic inflammation [15] (Fig 6). There is a relationship between the concentration of IL-1 in and disease activity, it is noticed that patients with erosive RA have higher synovial and circulating levels of IL-1 than patients without erosions.




**(Fig 4)**




**(Fig 5 ) In RA of joints the immune cells lymphocytes produces inflammatory cytokinins reactive oxygen and reactive nitrogen species (ROS/RNS)**

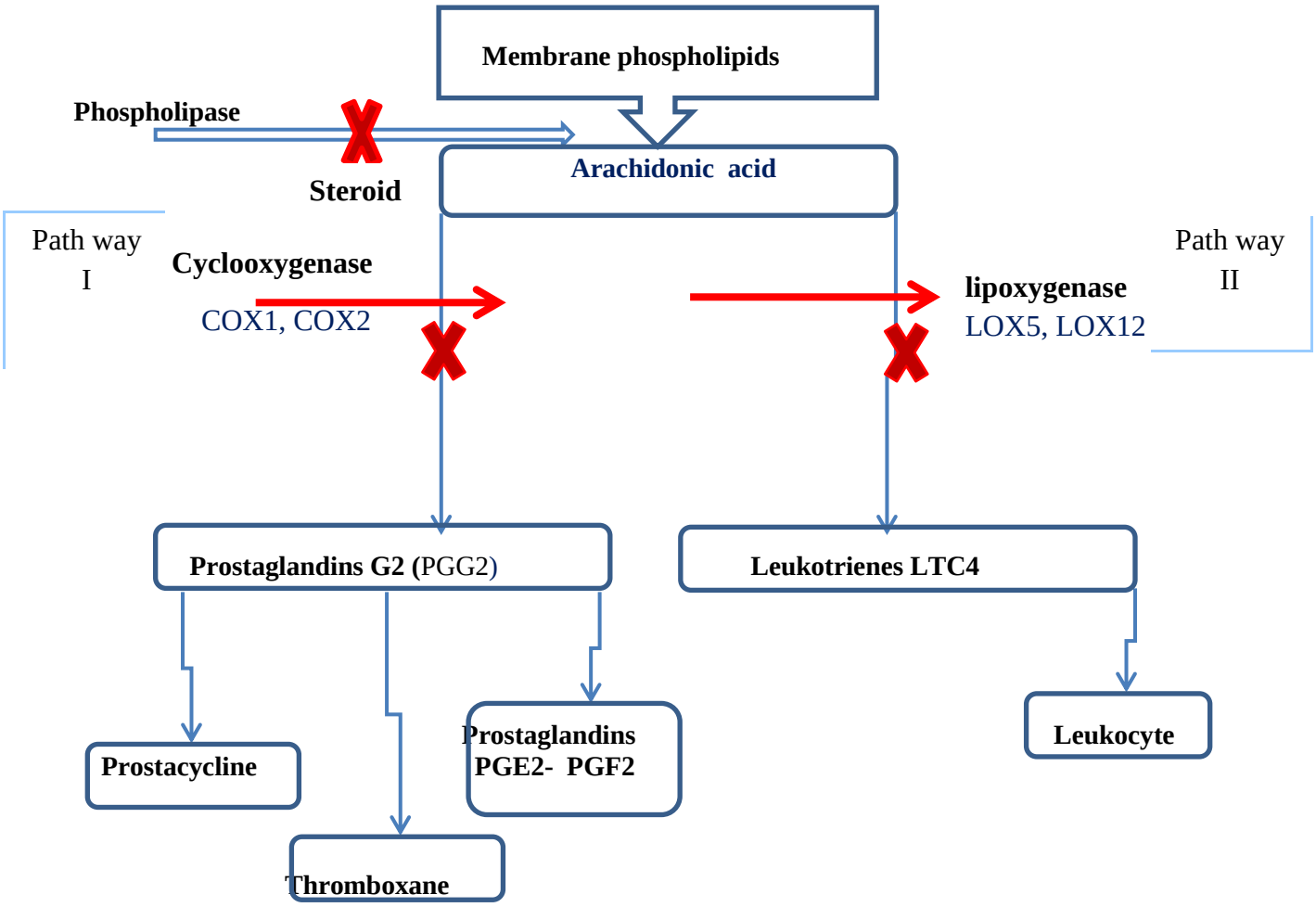



**Fig 6 :Arachidonic acid path way**

## 6. Methodology

### Animal model

### Induction of arthritis in animal models

### 6.1. Complete Freunds Adjuvant Induced arthritis (CFA)[16]

Freund's complete adjuvant induced arthritis in rat model is the best and most widely used experimental model for arthritis. This model is sensitive to anti- inflammatory and immune inhibiting medicines and best for the study of phathophysiological and pharmacological control of inflammation process.

### Design of experiments

Animals are randomly divided into five groups each of six animals.

1. Group I served as controlled received normal saline.
2. Standard and test groups are further divide into two sections of treatment i.e.

3. Group II (Prophylactic P group, before induction of disease)and Group III (Therapeutic T group, after induction of disease). were standard groups received Indomethacin (10 mg/kg body weight).
4. Group IV(P) and V (T) were test groups that received the test drug[17]

On day zero animals are injected into the sub plantar region of the left hind paw with 0.1 ml of complete Freund's adjuvant (FA)Which consists of 6mg Mycobacterium butyric suspended in heavy paraffin oil by through grinding with mortar and pestle to give a concentration of 6 mg/ml. Drug treatment is started from the 14th day i.e. from the day of adjuvant injection and continued till 28th day. The paw oedema and joint thickness is measured on 7th, 14th, 21stand 28th day by using digital vernier callipers or plethys mometer. The mean changes in injected paw edema and joint thickness with respect to initial paw volume and joint thickness, are calculated on respective days and % inhibition of paw edema and joint thickness with respect to untreated group are calculated using following formula.

Inhibition in paw edema / joint thickness = 100 x (1-Vt/VC)

VC = Mean paw edema volume/ joint thickness in control group

VT = Mean paw edema volume/ joint thickness in the drug treated group

**Radiological analysis**: radiographs are taken by using X-ray apparatus. X-rays are taken at the joint of hind paw of the animal for evaluating the bone damage before sacrificing the animal.

**Histopathological analysis**: the ankle joint of rats are removed and separated from the surrounding tissues. To examine the histopathological changes during the experimental period in all the groups under the light microscope, the joints are fixed in 10% formalin and decalcified, sectioned and finally stained with eosin and hematoxyline[18]

Other method were used:

**6.2. Carrageenan induced paw edema in rats[19, 20]**

**6.3.Formaldehyde Induced Arthritis[19, 21].**

**6.4. Collagen Type II Induced Arthritis (CIA) In Rats[16 , 22]**

**6.5. Pristane induced arthritis (PIA) [23]**

**6.6. Oil-induced arthritis (OIA)[24]**

**6.7. Streptococcal cell wall-induced arthritis[25]**

**7.Treatment of RA**

The main idea of treatment is focused on decreasing the disease activity along with minimizing joint destruction which will lead to improvement of the physical activity and quality of life.

**7.1.NSAIDs: Parcetamol, Asprin , Indomethacin**

**7.2.Corticosteroids: Prednisone, Prednisolone, Methyl prednisolone**

**7.3. Disease Modifying Anti-rheumatic Drugs (DMARDs):** Methotrexate, cyclosporine, Leflunomide, Hydroxychloroquine, chloroquine, , sulfasalazine, gold salts.

DMARDs: These are collection of various heterogeneous agents collected together according to their use, they reduce joint swelling, pain, decrease acute phase markers, limit progressive of joint damage, and improve function

### 7.4.Biological therapy

TNF-inhibitor, T- cell blockers, B- cell depletion molecules, IL-1 receptor antagonist were used. TNFα inhibitors : these medication lessen the signs and symptoms of RA, reduce progression of structural damage, and improves physical function , the clinical response can be observed within 2 weeks of treatment BUT:

1. There is a risk of getting microbial infection with the use of TNF inhibitors medication (tuberculosis and sepsis fungal infections)

2.A risk of development of cancer has been observed with the use of TNF- α. (incidence is very low), these compounds are usually administered in combination with other treatments [26]

Most of drugs which are used as anti –arthritic and anti- inflammatory did not suppress T-cell and B-cell mediated response [27].

### 7.5. Herbal sources in RA

All the above mentioned therapies, which are used in the treatment of arthritis such as : NSAIDs, corticosteroids, DMARDs and biological therapy are helpful in decreasing the joint stiffness, pain.

But: the main drawbacks while they reduce the symptoms of the disease the progression of the disease continues, they also have a common side effects which includes: gastrointestinal ulcers, osteoporosis, serious infections like sepsis, tuberculosis, development of various lymphomas[28]. So there is a hope to shift towards the use of herbal therapy in the treatment of RA

### 7.5.1.Ginger

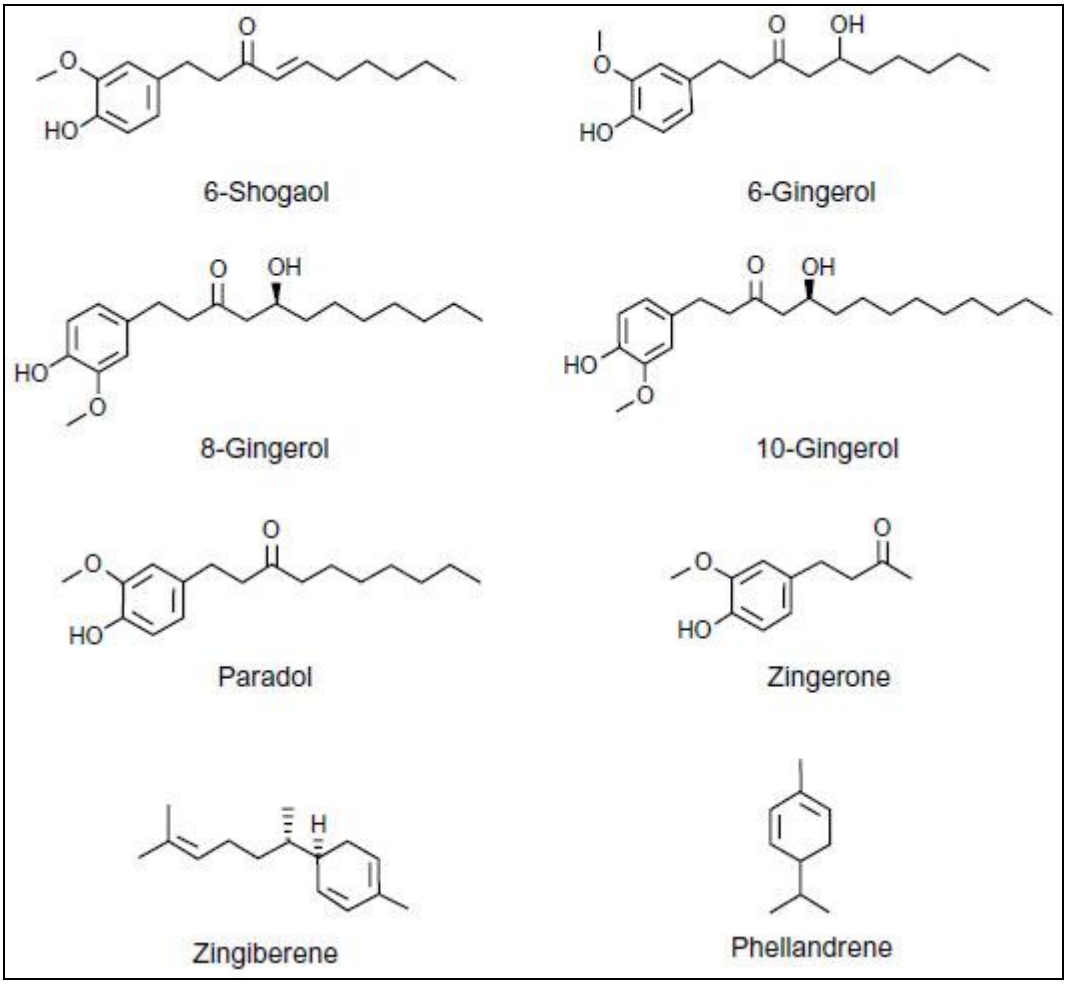
Ginger is obtained from the rhizomes (underground stems) of *Zingiber officinale* (Zingiberaceae), it is well known medicinal herb and spices[29]

**Active constituents**

Ginger contains a large number of phytochemical constituents which were revealed to have valuable effect in RA [30].

Phenolic compounds: Shogaols, paradols, and gingerols [31], Sesquiterpenes: Bisabolene, zingiberene, zingiberol, sesquiphellandrene, and curcurmene [32],

Vitamins: VitaminA, vitamin C, Thiamine, riboflavin, niacin, pyridoxine, and vitaminE [33] and other compounds. [34]




**Mechanism of action on RA**

Ginger showed beneficial effects of reducing the pain associated with RA which is due to inhibition of prostaglandin and leukotriene biosynthesis(block path way I, II), its mechanism of action as anti-inflammatory through blocking the activities of both COX-1 and COX-2, it suppress leukotriene biosynthesis through inhibition of 5-lipoxygenase [35].

Ginger was screened for anti -inflammatory activity using ibuprofen as standard, both showed similar anti-inflammatory activities indicating that ginger as a potential anti-inflammatory agent [36]. The crude extract containing essential oils and more polar compounds exhibited better activities in preventing joint inflammation and bone destruction compared to the essential oils only. It was concluded that gingerol and non-gingerol compounds of ginger had considerable anti-arthritic activity [30]

**7.5.1.1.Ginger therapy**

Ginger was used traditionally by the Chinese in a variety of external application including muscular tension, disorder in metabolism and infection in the chest [37].

**Transdermal delivery**

Topical application of gingerols and/or shogaols to the skin is also tested and proved its efficiency. External application of dry ginger extracts in the form plasters showed promising anti-inflammatory activity indicating that the active constituents of ginger could penetrate through the skin [38].

**Ginger compress**

Ginger compresses to the kidney region warm and reactivate the metabolism of the body. These application have an efficacy in some cases of arthritis ,chest and psychiatric conditions [39].

Ginger compresses provide the body with heat and relaxation[40].

**Ginger footbath**

Ginger footbath is another method of decreasing muscle tension and relaxation of musculoskeletal fatigue

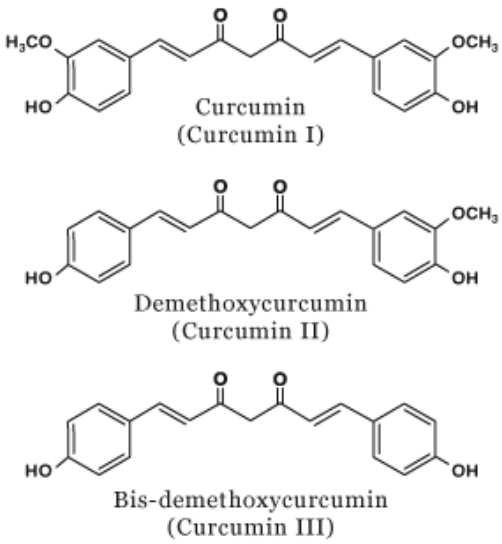
**7.5.2.Tumaric**

It is the rhizome of *Curcuma longa* L

( Zingiberaceae ). It is used in Indian traditional medicine in curing inflammation[41]

**Active constituents**

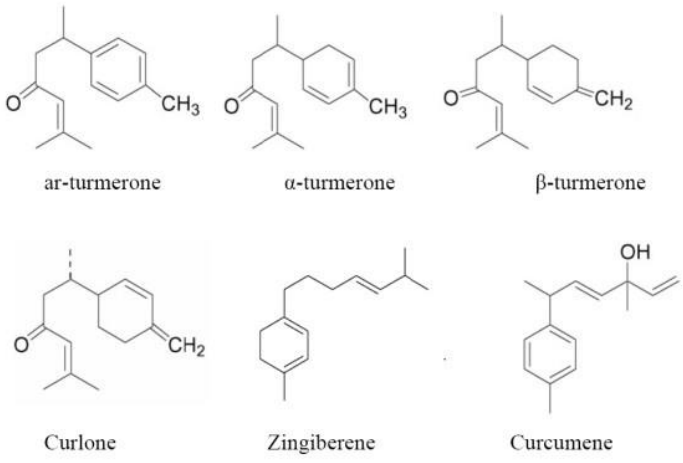
The major active constituents was known to be curcuminoids which comprises into three compounds (curcumin, demethoxy-curcumin, and bisdemethoxy curcumin), it also contain volatile oils constituted about 3-7%, its major compouds were zingiberone tumerone and atlantone [42].




Curcumin is the major curcuminoid in Curcuma longa it constitute 2-6%, it has a strong free radical scavenging activity so it can help in preventing disease result from free radical damage

**Uses**

- Curcuma has been used for centuries as spices , it is usually combined with several other spices for vegetable and meat preparations, it adds a charactestic fragrance and yellow color to foods.
- Curcuma was used traditionally in Asian and Indian medicine in various pharmacological activities : biliary disorders, intestinal disorders, hepatic disorder, diabetic wounds, anorexia, cough, rheumatic pain cancer, and Alzheimer's disease.



- The antioxidant activity of curcumin is important criteria in chronic inflammation[43].

Intraperitoneal injection(IP) of curcuminoids extract before arthritis induction inhibited acute (75%) and chronic (68%) inflammation of joint[44]

**Mechanisms of action**

Curcumin is an alternative TNF-α blocker, it regulates the inflammatory response by inhibiting the activity of COX-2, lipoxygenase, it also decrease the production of cytokines (TNF-α) and Interlukin IL( 1, 2, 6, 8, and 12)[45].

- It also inhibit the metabolism of arachidoic acid in mouse experimental model of skin inflammation through regulation of COX and LOX pathways(I &II)[46].
- 20-80 mg/kg bodyweight of Curcumin was successfully inhibited edema in experimental animals, it is nearly effective as phenylbutazone or cortisone at the same dose,40 mg/kg body weight of Curcumin showed anti-arthritic activity in formaldehyde induced arthritis model in rats .

**7.5.3. Boswellia**

*Boswellia serrata* : Part used is the oleo gum resin obtained by bark injury or natural crack

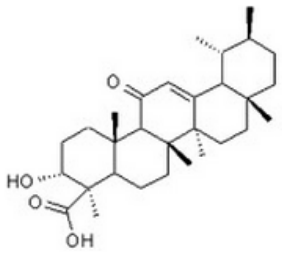
**Active constituents**

It include, oils, terpenoids and gum.

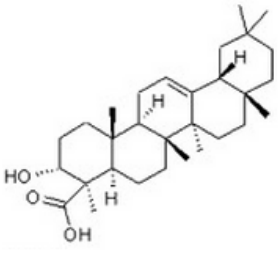
Essential oil is obtained in yield of 16% from oleo-gum-resin by steam distillation.: α-thujene , α-pinene , limonene , p-cymene , cadinene , geraniol and elemol constitute the major compounds in the essential oil [47] boswellic acids was found to be the major terpenoid in the terpenoid part of the oleogum resin in *Boswellia serrata*.

Boswellic acids are series of pentacyclic triterpenes which were used as anti-inflamatory through inhibition of biosynthesis of leukotriene [48]

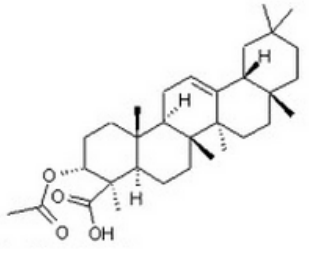
Clinical studies using Boswellia have yielded good results in both osteoarthritis and rheumatoid arthritis [49, 50].



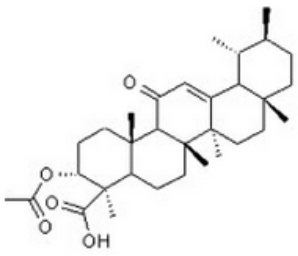

11-keto-β-Boswellic Acid



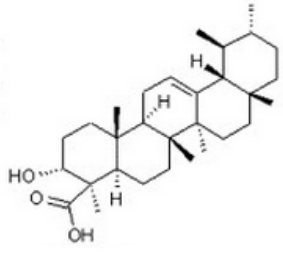

α-Boswellic Acid



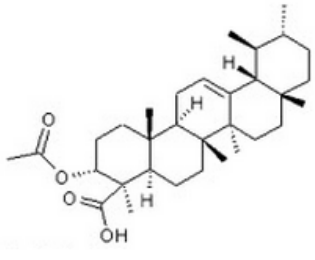

Acetyl-α-Boswellic Acid




3-O-Acetyl-11-keto-β-Boswellic Acid




β-Boswellic Acid




Acetyl-β-Boswellic Acid

**Mechanism of action**

Boswellic acids inhibit the leukotriene synthesis through its action on 5-LOX enzyme but it has no effect on 12-LOX and the COX activities [51, 52] . 11-keto-boswellic acid and acetyl-11-keto-boswellic were found to be the most potent triterpenoids in the series of pentacyclic triterpene, They inhibit HLE (human leukocyte elastase) which is associated with rheumatoid arthritis and respiratory illnesses all of which are linked by inflammation .

- These two triterpenoid acids are potent elastase inhibitor compared with ursolic acid, which did not affect 5-LOX [53, 54, 55, 56].

**7.5.4. Rosemary**

*Rosmarinus officinalis* (Lamiaceae )

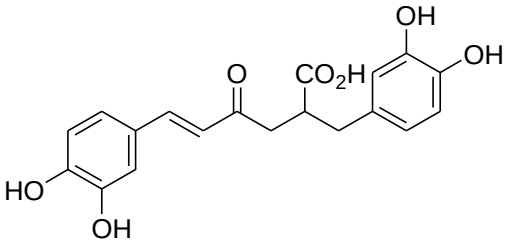
Part used whole plant and essential oils

**Active constituents**

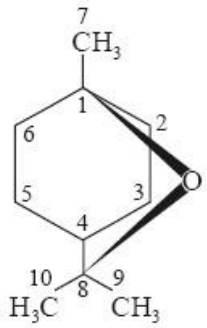
Carnosic acid, methylated carnosic acid, carnosol and rosmanol were the major compounds.

Water-soluble extract from rosemary leaves was rich in rosemarinic acid and flavonoids, oxygenated monoterpenes were also found : l,8 cineole, borneol and terpineol.

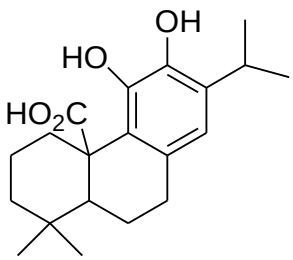
The main constituents in the essential oil of *Rosemary* dried leaves was 1,8 cineole (monoterpene oxide), monoterpene and sesquiterpene hydrocarbons (32.2%) á pinene, â-pinene, â –caryophylene, camphene, limonene, myrcene p-cymene monoterpene ketonec amphor (12.8%) and monoterpene alcohols, borneol .All these compounds amounted to 93.4% of essential oil constituents [57].



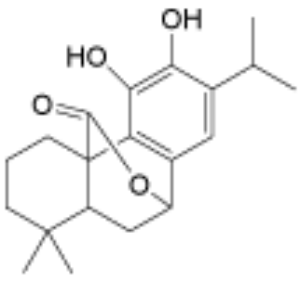

Rosmarinic acid




1,8 cineole




Carnosic acid




Carnosol

**Uses**

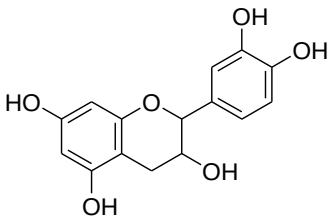
*Rosemary* essential oil is well known in aromatherapy due to its various reported health benefits, from stimulating hair growth to clearing the respiratory tract

- The essential oil of *Rosemary* exert strong antioxidant activity in *in vitro* free-radical scavenging test, this activity is related to their phenolic compounds present in the essential oil, including rosmarinic acid, chlorogenic acid, caffeic acid, rosmanol, carnosolic acid, and carnosol.
- The antioxidant activity are useful for preventing tissue damage from the produced free radicals during inflammation, this explain the usefulness use of the antioxidant in treating musculo-skeletal problems, joints affected by rheumatoid arthritis.
- The high level of free radicals due to the immune system attacking the collagen and other proteins in the joint and as a result, the antioxidant constituents in *Rosemary* oil may scavenge free radicals, reducing tissue damage [58].
- Treatment with *rosemary* decrease the flow of white blood cells and mediators of inflammation[59].
- *Rosemary* essential oil is a pure herbal spray was used extensively for rheumatoid arthritis, joint and muscle pain without any side effects.
- It can be used in treating joint inflammations of rheumatic characteristic[60].Rosmary oil inhibit bone resorption in ovary ectomized rats[61]

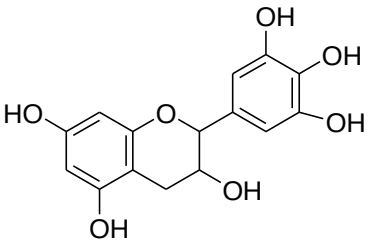

**7.5.*5.Camellia sinensis*** Linn

**The part used : leaves**

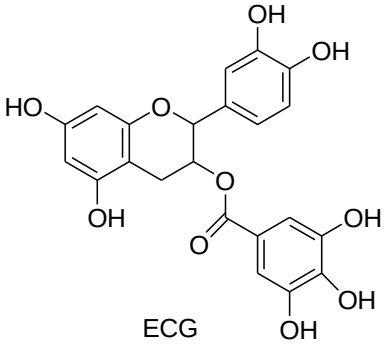
The active constituents are polyphenols catechins, which is the major constituents : epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC), epigallocatechin gallate (EGCG), catechin (C), and gallocatechin (GC) and flavonols[62].



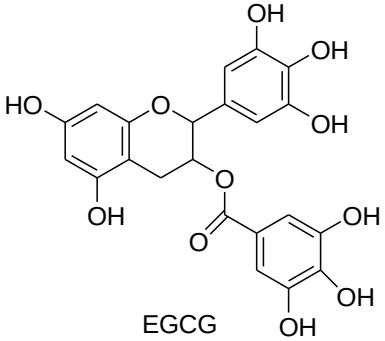

catechin




EGC




ECG




EGCG

**Uses**

- ✓ It has potent antioxidant activity due to high polyphenol contents, it reduces the risk of getting CVD and cancer[63].
- ✓ Black tea contain theophylline which is used as a therapy for respiratory tract diseases[64].

**Mechanism of action**

- ✓ The methanol extract of the leaves reduces inflammation and edema produced by inflammatory mediators. It improves the movement ability experimentally in induced arthritis in rats.
- Green tea reduced inflammation in the collagen-induced arthritic rats model, it reduces the inflammatory cytokines TNF-α & γ-interferon and COX-2[63, 65].
- EGCG found in green tea has a powerful scavenging activity to reactive oxygen species (ROS) which has a pathogenic role in rheumatoid arthritis and excessive quantities of oxygen free radicals have been identified in synovial fluid of 90% of patients with RA[66, 67].
- EGCG was found to have anti-arthritis activity which was first discovered from the finding that consumption of EGCG-containing green tea decrease collagen-induced arthritis in mice, inhibit the inflammatory mediators COX-2, Interferon gamma (IFNγ), and tumor necrosis factor alpha (TNFα) in arthritic joints
- *In vitro* and *in vivo* study supported the use of EGCG as anti- inflammatory and anti-arthritic effects indicating that EGCG or EGCG containing green tea can regulate the expression of cytokines, chemokines and other inflammatory mediator[68]
- EGCG has been reported to have bone-preserving and synovial fibroblast regulatory effect .

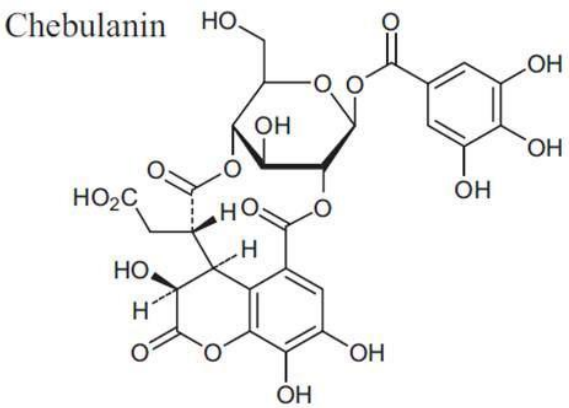
Water extract of black tea lessens in the serum levels of PGE2, TNFα, IL- 1β and IL- 6 as shown in anti-arthritic model of Freund's adjuvant induced arthritic in rats.[69]

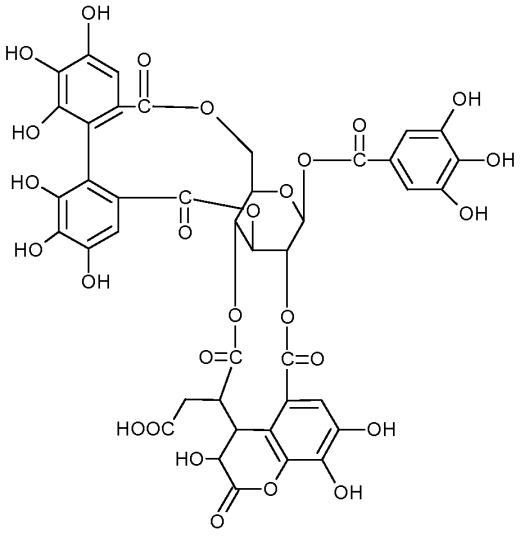
**7.5.6.*Terminalia chebula*** Retz (Combretaceae)

Part used is the herb, fruit

**Active constituents**

*T. chebula* contain hydrolysable tannins 32%, flavonoids, sterols, amino acids, fructose, resin, fixed oils. hydrolysable tannins: Chebulic, chebulinic, chebulagic, gallic, were the main components which are responsible for anti - arthritic effect[70]




Chebulagic acid

**Uses**

- ✓ It has antifungal activity, used in leucorrhoea, It has antioxidant activity which is useful in protecting the neurons from the effect of free radicals
- ✓ Aqueous ethanol extract of *Terminalia chebula*, showed anti-arthritic in CFA induced arthritis activity and formaldehyde model.

**Mechanism of action**

- ✓ The plant perform its action as anti-arthritic activity through its modulatory effect on pro- inflammatory cytokine released in the synovium[71]

The hydroalcoholic extract of *T. chebula* produced a significant inhibition of joint swelling in both formaldehyde induced and CFA-induced arthritis.

- ✓ *T. chebula* could be used as a modulatory agent in treatment of rheumatoid arthritis[72].

That acetone extract of *T. chebula* fruits showed anti-arthritic activity on CFA induced arthritis model through reduction of the inflammatory components[73]higher dose of 320mg/kg of *Terminalia chebula* showed promising activity as antiarthritic and anti-inflammatory activities in contrast to the traditional NSAIDs which causes ulceration of the stomach and GIT bleeding[74].

**7.5.7. Aloe vera**

***Aloe barbadensis* Mill** (Alliaceae**)** part used: leaves

Active constituents : anthraquinones, anthraquinone *C*-glycosides and anthrones [75]which constitute about 30% from the constituents of the latex [76]-, polysaccharides which is a linear polymer of glucose and mannose , amino acids, lipids, sterols and vitamins and enzymes[77]

**Uses**

*Aloe vera* is used in **topical preparation** for skin ailments

It has many medicinal values, anthraquinone and anthranilic acid are quite efficacious against arthritis and articular Rheumatism[77]

**Mechanism of action**

*Aloe vera* inhibits the COX pathway so decrease prostaglandin E2 production from arachidonic acid. *Aloe vera* extract (5.0% leaf homogenate) decreased inflammation by 48% in a rat adjuvant-induced arthritic inflammatory model [78, 79].

Science has not stopped yet, and the need for discovery of many herbal sources having the activity to be used in many disease continue.

Nature provides us with different herbs which possess the activity to be used in treating rheumatoid arthritis (Table 1)

**Table 1: List of plants used in rheumatoid arthritis**

| No | **Name of the plant** | **Family** | **Part used** | **References** |
|---|---|---|---|---|
| 1 | *Aristolochia braceata* | Aristolochiaceae | Whole plant | **80** |
| 2 | *Ammania bacifera* | Lytraceae | Whole plant | **81** |
| 3 | *Calotropis gigantea* (L.) R. Br. | Asclepiadaceae | Latex extract<br>Root extract | **82**<br>**83** |
| 4 | *Capparis spinosa* | Capparidaceae | Fruit | **84** |
| 5 | *Cassia uniflora* | Caesalpiniaceous | Stem | **85** |
| 6 | *Centella asiatica* | Mackinlayaceae | Leaves | **86** |

| | | | | |
|---|---|---|---|---|
| 7 | *Cleome rutidosperma* | Capparidaceae | Aerial parts | **87** |
| 8 | *Commiphora incisa* | Burseraceae | Resin Mansumbinoic acid | **88** |
| 9 | *Commiphora mukul* | Burseraceae | Gum-guggul | **89** |
| 10 | *Cocculus hirsutus* | Menispermaceae | Roots | **90** |
| 11 | *Cyperus rotundus* | Cyperaceae | Essential oil | **91** |
| 12 | *Cyperus esculentus* L. | Cyperaceae | Essential oil | **91** |
| 13 | *Dalbergia volubilis* | Fabaceae | Stem bark | **92** |
| 14 | *Daucus carota* L. | Apiaceae | Ethanol extract | **93** |
| 15 | *Delonix elata* | Fabaceae | Bark | **94** |
| 16 | *Elaeocarpus* sphaericus | Elaeocarpaceae | Fruit | **95** |
| 17 | *Euphorbia atiquorum* | Euphorbiaceae | Whole plant | **96** |
| 18 | *Ficus bengalensis* | Moraceae | Stem bark | **97** |
| 19 | *Glycirrhiza glabra* | Fabaceae | Rhizomes | **98** |
| 20 | *Glycosmis pentaphylla* | Rutaceae | Stem bark | **99** |
| 21 | *Hemidesmus indicus (L)* | Asclepiadaceae | Ethanol extract of root | **100 101** |
| 22 | *Justicia gendarussa* Burn f. | Acanthaceae | leaves | **102** |
| 23 | *Lawsonia Innermis* | Lythraceae | Leaves | **14** |
| 24 | *Leucas aspera* (Willd) Spreng. | Lamiaceae | Aerial parts | **103** |
| 25 | *Machalis macrantha* | Lauraceae | Bark | **104** |
| 26 | *Merremia tridentata* (L.) Hall | Convolvulaceae | Aerial parts , root | **105** |
| 27 | *Ncytanthes arbortristis* Linn | *Oleaceae* | Leaves | **106, 107** |
| 28 | *Paederia foetida L* | Rubiaceae | Leaves | **108, 109** |
| 29 | *Phyllanthus amarus* | Euphorbiaceae | Herbs | **110** |
| 30 | *Pistiostratios* Araceae | Araceae | Leaves | **111** |
| 31 | *Pongammia pinnata* | Fabaceae | Leaves | **112** |
| 32 | *Premna serratifolia* L | Verbenaceae | Wood | **113** |
| 33 | *Punica grantum* | Punicaceae | Seeds | **114** |
| 34 | *Randiadum etorum* | Rubiaceae | Fruit | **115** |
| 35 | *Ricinus communis* | Euphorbiaceae | Leaves | **116** |
| 36 | *Saraca asoka* (Roxb.) wilde | Leguminosae | Flower , leaves | **117** |
| 37 | *Strychnos potatorum Linn* | Loganiaceae | Seeds | **118** |
| 38 | *Saussaurea lappa* | Asteraceae | Roots | **119** |
| 39 | *Sidarhom bifolia* | Malvaceae | Aerial parts | **120** |
| 40 | *Tinospora cardifolia* | Menispermaceae | Leaves | **121** |
| 41 | *Urtica pilulifera* | Urticaceae | Leaves | **122** |
| 42 | *Urgenia indica* | Liliaceae | Bulb | **123** |
| 43 | *Vernonia anthelmintica* | Asteraceae | Seeds | **124** |
| 44 | *Wedeli acalendulaceae* | Asteraceae | Leaves | **125** |
| 45 | *Withania somnifera* (L) Dunal | | Root | **126, 127** |

**7.5.8.Plant constituents and RA**

- **Gallic**: [128, 129] **Ferulic:** [130, 131] **Apigenins:** [132, 133 , 134 , 135,] **Kaempferol:** [128, 136]
- **Quercetin :**[137, 138, 139] **Resveratrol :**[140,141, 142_143] **Genistein:** [144, 145] **Arctigenin:** [146, 147]

**8.Some important relation in RA**

- ✓ **8.1.Vitamin D** is an essential supplement for the immune system**,** it is produced normally by the body when the skin is exposed to sunlight. Deficiency of vitamin D may be one of the leading cause of autoimmune diseases especially RA 148 Vitamin D and its derivatives have been shown to suppress T-cell proliferation and inhibit the expression of pro-inflammatory cytokines involved in RA pathogenesis
- ✓ **8.2.Omega-3 polyunsaturated** fatty acids, found mainly in cold water fish e.g., salmon and the oil produced, can be useful for inflammatory arthritis like rheumatoid arthritis

**BUT**.

- ✓ Omega-3 fatty contraindicated with some medication of high blood pressure. Also patient taking aspirin must take care of omega-3 fatty as it can causes bleeding

**8.3.Calcium**

Calcium is very important for healthy bones and it is needed for the prevention of osteoporosis (brittle bones). Low-fat, milk, cheese, yogurt and the types of fish that are eaten with the bones ( canned salmon or sardines) were the best sources of calcium

**8.4.Protein**

It is important for repairing cells of muscles and healthy immune system, select lean protein sources(chicken), seafood , beans, peas, nuts and seeds.

**8.5.Folic acid**

Folic acid is needed to prevent medication related side effects (liver abnormalities and gastrointestinal intolerances) especially for people taking methotrexate.

**8.6.Glucosamine sulphate and chondroitin**

Glucosamine sulphate and chondroitin supplements were used as supplement, they may help in improving the health of damaged cartilage , these compound were found to decrease inflammation

**9.What to avoid in RA**

**9.1.Weight and Arthritis**

Excess weight puts an extra pressure on your load-bearing joints : feet , ankles , knees, hips and back. When you walk the pressure in your knee joints increase, losing weight will help you and will make a difference than any food or supplement.

There are two measuring parameters of weight which is helpful in health problems average age taken was 18-65 but pregnant and lactating women were not included

- ✓ BMI : body mass index
- ✓ WC : waist circumference adults age 18 to 65 years with the exception of pregnant and lactating women.

**9.2.Trans or saturated fats**

Trans or saturated fats, increase the risk of getting CVD. These two harmful fats were found in processed and fried foods , they also come from animal sources of food. It is preferable to use Polyunsaturated and monounsaturated as the main source of fat it can be found in naturally in olive and canola oil, avocadoes and nuts.

**9.3.Gout and diet**

Gout is a type of inflammatory arthritis caused by the deposition of uric acid crystal in the joints, causing inflammation and severe pain. Uric acid is produced from purines based food, increase in the concentration of uric acid may be due to the kidney problems( excreting too little uric acid) or the body consume too many dietary purines. Decrease the amount of intake of food high in purines such as meat and seafood also organ meats ( liver, kidney and sweetbreads). Vegetables, legumes , cereal , dairy products, soybean products and eggs are low in purine include.

**Finally**

*Before the discovery of synthetic drugs man was completely dependent on the medicinal plants for the treatment of many disease. The medicinal value of plants has been recognized by every person of this society. There are many synthetic drugs that are being used as standard treatment for rheumatoid arthritis but they have adverse effect that can compromise the therapeutic treatment so these adverse effects increase the chances for the use of herbal plants for the treatment rheumatoid arthritis.*

*Rheumatoid arthritis is an inflammatory disease affecting the joint and can lead to improper movement or loss of function. RA is an autoimmune disease that can occur at any age but women are more likely to develop disease that men(3:1), it is more common in persons over the age of 30 years. RA is a systemic disease this means that it can affects the whole body, including internal organs : lungs, heart and blood . RA is a disease that affect vital part of the body which is the musculo-skeletal system and any neglection or delay in treatment may lead to dangerous health problems*.

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