Alternative Approaches for Rheumatoid Arthritis Management: Future Perspective, Herbal, Dietary, Lifestyle, Psychological, Nutritional Intervention and Healthcare

ABSTRACT

Rheumatoid arthritis is an inflammatory disease autoimmune disorder that develops when our immune system attacks the tissues near joints due to the release of chemicals and enzymes. Although the exact pathogenesis of the disease has yet to be determined, studies indicate that cellular proliferation of synoviocytes results in pannus formation, which damages cartilages and bones. Recent research also supports the role of free radicals in the disease's pathogenesis. For rheumatoid arthritis treatment, a variety of anti-inflammatory and other types of drugs are available. However, long-term use of such types of pharmacological drugs is associated with serious side effects. As a result, herbal remedies, lifestyle, nutritional, probiotics, dietary and psychological interventions provide a rich source of anti-arthritic agents along with management of rheumatoid arthritis. This review focused on pathogenesis, treatments approaches for RA, mechanism of action, patents of marketed products. Tailored made approaches for arthritis management helps the scientists and researchers for finding newer leads, promotes growth and development of herbal industries, significantly improving health.

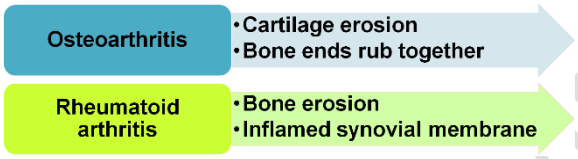
Keywords: Rheumatoid arthritis, patents, lifestyle intervention, psychological intervention, nutritional requirement, herbal remedies, health.

1. INTRODUCTION

Arthritis is a widespread health problem that affects millions of people in the United States. It is a condition characterized by chronic joint pain and inflammation. There are about 200 rheumatic diseases or serious ailments related to tissues, joints, and other connective tissues. Rheumatoid Arthritis (RA) develops when immune system targets the tissues near our joints, resulting in the release of specific chemicals and enzymes that begin to eat away at the cartilage and bone [1,2]. Although the etiology of RA is uncertain and thought to be caused by a dysfunctional immune system [3]. The fundamental aspect of arthritis is a continuous discomfort that gets localized in the damaged joint. The pain worsens with daily wear and tear on the joints, muscle tension from vigorous motions against stiff, painful joints, and exhaustion [4-6]

Patients with arthritis have significant joint pain and approximately half of all people with arthritis experience chronic pain [7]. There are over 100 different forms of arthritis. Osteoarthritis and rheumatoid arthritis are two of the most frequent forms [8]. Rheumatoid arthritis (RA) is an inflammatory illness that mostly disturbs the body's junctions coated with synovium (specific tissue responsible for sustaining the nutrition and lubrication of the joint). The distribution of afflicted joints (synovial joints) is typical [9] According to the WHO, Rheumatoid arthritis affects 0.3-1 % of the global residents, with females three times more than males [10]. RA is a systemic autoimmune disease that results in chronic inflammation. The foremost symptoms of RA include pain, swelling, cartilage, and bone degeneration,

resulting in permanent disability [11]. Although the actual cause is unknown, various studies suggest, that is caused by a combination of hereditary tendencies and exposure to environmental factors such as viruses [12]. Inflammation of the joints causes pain, edema, and joint deterioration, as well as deformity. Other internal organs, such as the eyes, lungs, heart, and nerves, can be affected on rare occasions. The symptoms fluctuate significantly from individual to individual. In various situations, RA begins by infecting a few joints and then spreads to other joints all over the body over the development of a few weethks or months. RA, on the other hand, can proceed exceedingly quickly; non-specific indications of RA include weariness, discomfort in and around the joints, fever, and weight loss/poor appetite. RA can expand to more and more joints on both sides of the body over time, generally in a symmetrical pattern [13].



Pic 1. Symmetrical pattern

The goal of rheumatoid arthritis treatment is to alleviate indications, halt disease development, and improve value of life. Before beginning RA treatment, consider the conditions such as analgesia relief, inflammation reduction, articular structure protection, function maintenance, and systemic involvement control [14].

1.1 Rheumatoid arthritis versus osteo-arthritis

The development of osteoarthritis and rheumatoid arthritis and the differences between them are shown in Fig. 1-3 and Table 1.

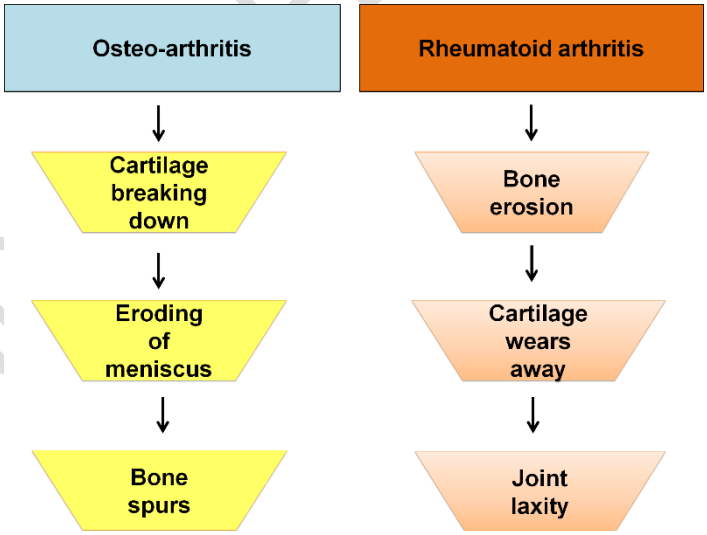


Fig. 1. Difference between formation of osteoarthritis and rheumatoid arthritis.

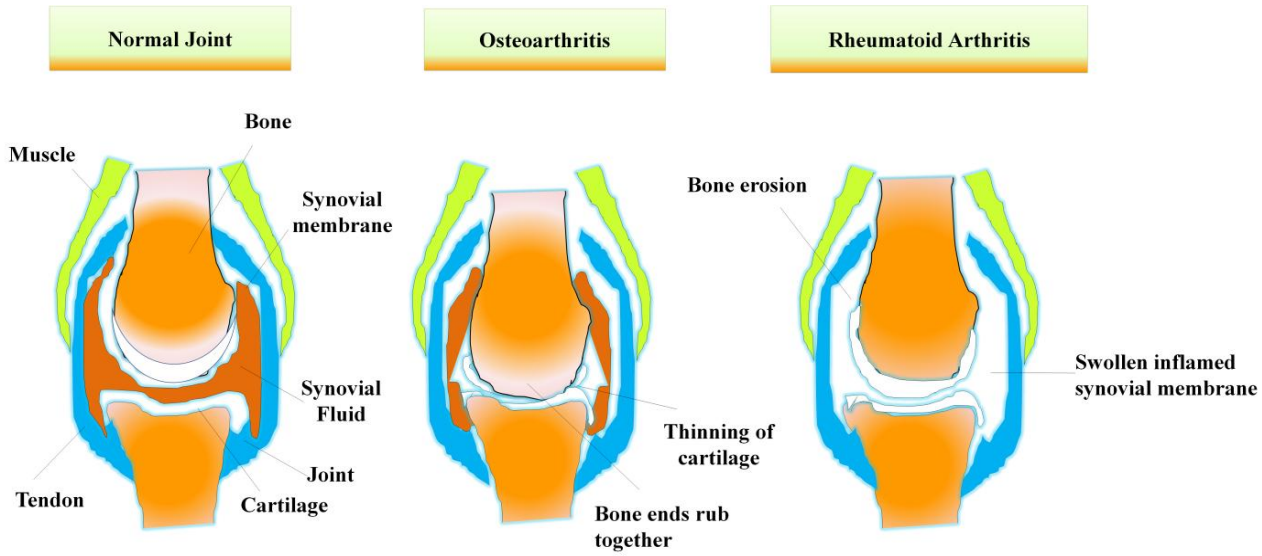


Fig. 2. Comparison between normal joints and joints having osteoarthritis and rheumatoid arthritis.

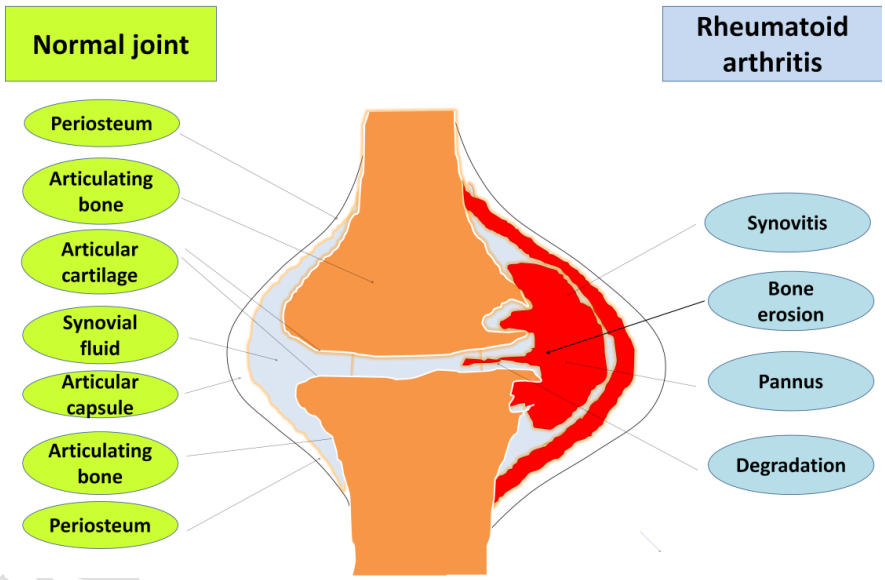


Fig. 3. Difference between normal joint and joint having rheumatoid arthritis.

Table 1: Difference between rheumatoid arthritis and osteoarthritis [15].

Rheumatoid arthritis	Osteoarthritis	Characteristics
Begin at any time in life	Leggings later	Age at which it starts
Rapid, weeks to months	Slow, over years	Onset speed
Swollen and stiff	Ache but no swelling	Symptoms of joints
Longer than 1 hour	Less than 1 hour	Duration of stiffness
Frequent fatigue	Whole-body symptoms are not present	Presence of symptoms
Positive rheumatoid factor	Negative rheumatoid factor	Laboratory findings

2. PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

Immune complexes and the complement system initiate RA, supported by cytokines, and rely on metalloproteinases Antigen-activated CD4 + T cells stimulate monocytes, macrophages, and synovial fibroblasts to produce the cytokines interleukin 1 (IL-1), interleukin 6 (IL-1), and Tumor Necrosis Factor (TNF), as well as matrix metalloproteinases, via cell surface signaling. In the early stages of RA, the synovial fluid contains a high concentration of neutrophils. Protrusions in the joint capsule form as a result of chronic hypertrophy and hyperplasia. Immunoglobulin G (IgG)/antigen-anti-IgG antibody complexes found in synovial fluid. In RA, cartilage dissolved results in erosion caused by osteoclasts and proteolytic enzymes. Immunoglobulins M and A (IgM and IgA) are significant pathogenic markers in RA [16,17]. Molecular mechanism involved in rheumatoid arthritis, is shown in Fig. 4.

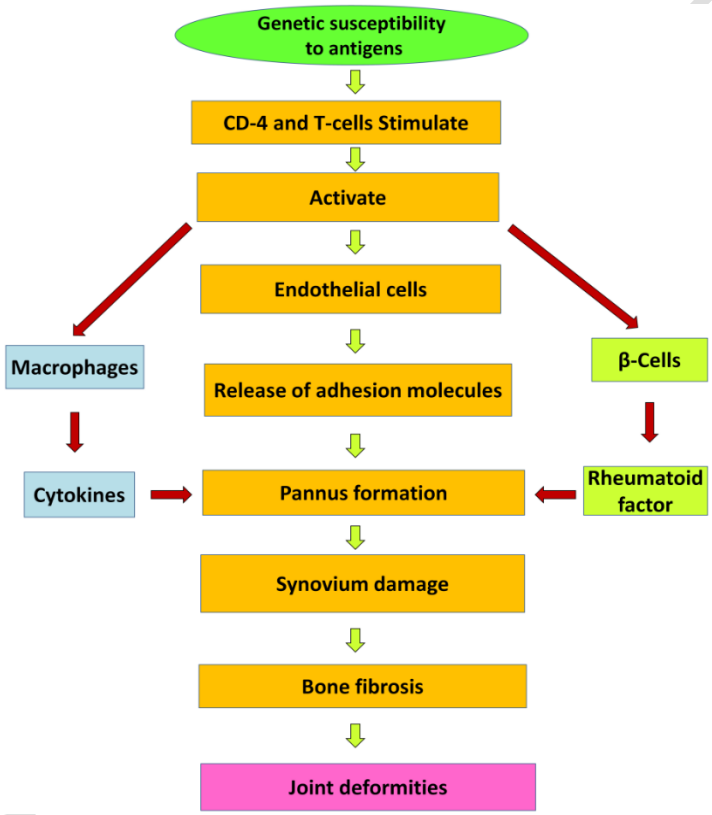


Fig. 4. Molecular mechanism of rheumatoid arthritis.

3. PROCESS OF TARGETING STAGE TO FULMINANT DISEASE

Many cells and their cytokines play vital roles in the development of RA. Leukocytes infiltrate the synovial section and the synovial fluid flood with pro-inflammatory mediators. It starts an inflammatory cascade that involves fibroblasts like synoviocytes interacting with innate immune system cells like monocytes, macrophages, mast cells, dendritic cells, and adaptive immune system cells (T and B cells). Endothelial cells play an essential role in angiogenesis. The hyperplastic synovial membrane, cartilage damage, bone erosion, and systemic consequences are all in the fulminant stage. Bone resorption causes bone erosion, usually found where the synovial membrane is introduced into the periosteum and referred to as an area bare by certain anatomical features. Degeneration of articular cartilage can occur due

to the destruction of subchondral bone, reduction in osteoblasts and an increase in osteoclasts and synovial cells. TNF, matrix metalloproteinase (MMP), transforming growth factor (TGF), platelet growth factor (PGF), interferon (IFN), granulocyte-macrophage colony-stimulating factor (GMCSF), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) are involved in fulminant disease [9,18].

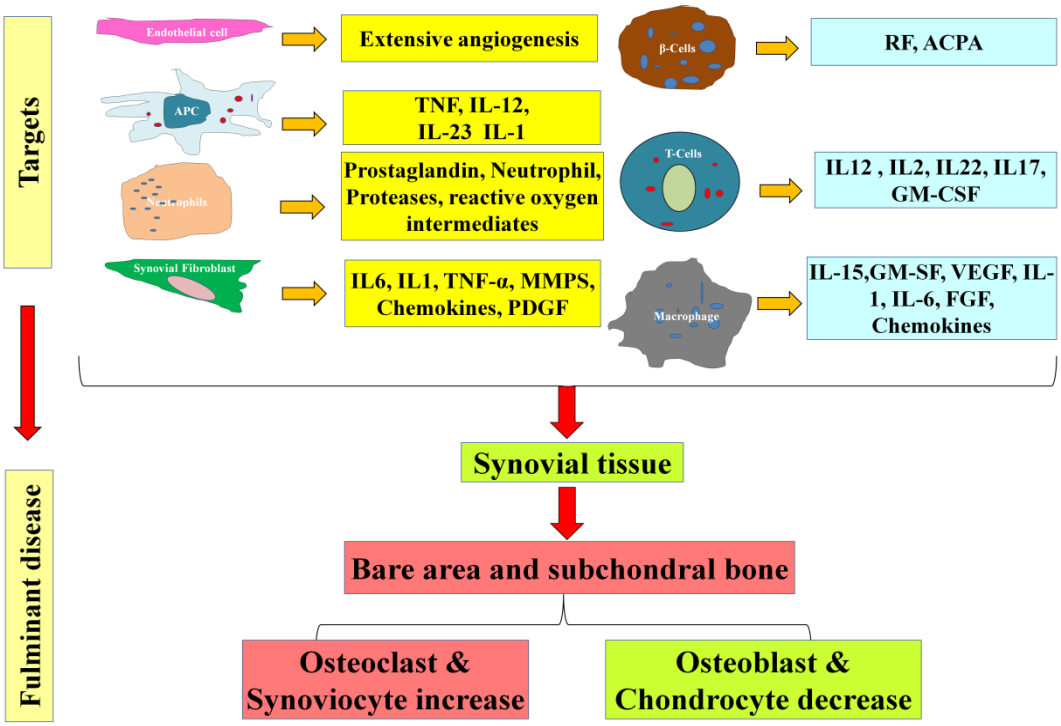


Fig. 5. Process of targeting stage to formation of fulminant disease.

4. STAGES/ CAUSES OF RHEUMATOID ARTHRITIS

RA happens when the immune system attacks the synovial membrane, the lining of the membranes, surrounding the joints; the resulting tenderness thickens the synovial membrane, ultimately abolishing the cartilage and bone inside the joint. The tendons and ligaments holding the joint together, deteriorate and stretch. Gradually, the joint loses the figure and arrangement [19].

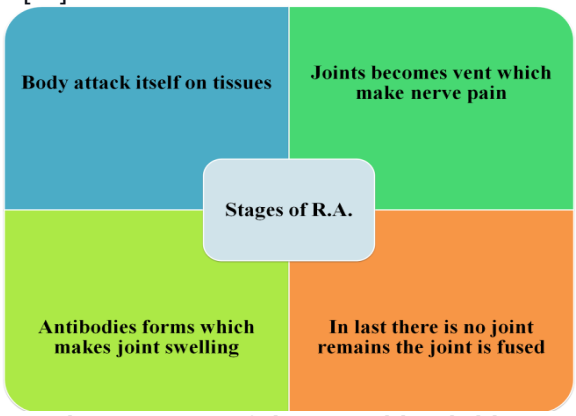


Fig. 6. Stages of rheumatoid arthritis.

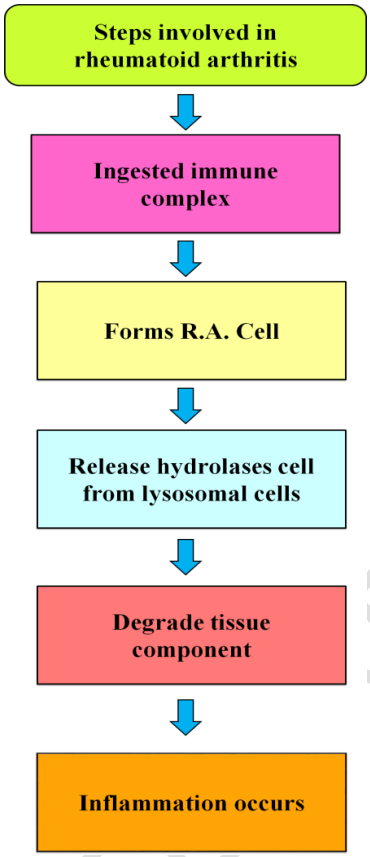


Fig. 7. Steps involved in rheumatoid arthritis

5. SYMPTOMS

Symptoms include joint swelling, discomfort, morning joint stiffness, lack of sleep, exhaustion, weight loss, and the sensation of having flu symptoms. Rheumatoid factors, antibodies (IgG) found in the blood are used to diagnose rheumatoid arthritis. These bind to the antigen and create an antigen-antibody complex, causing discomfort and inflammation of the synovial membrane. The American College of Rheumatology requires at least four out of the seven criteria listed below to confirm the diagnosis [20].

- Morning joint stiffness lasts at least one hour.
- Three or more joints have been arthritic for at least six weeks.
- Hand joints have been arthritic for at least six weeks.
- At least six weeks of arthritis on both sides of the body.
- Under-the-skin rheumatoid nodules.
- Rheumatoid factor detected in blood tests.
- X-rays show evidence of RA [21].

6. DIAGNOSIS

Rheumatoid arthritis is problematic to diagnose in its early phases because the symptoms are parallel to those of other diseases. There are no results from blood tests or physical checkups to back up the analysis. During the physical examination, look for swelling, redness, and hotness in the joints. You can also put your responses and strength to the test [22].

6.1 Blood tests

People with RA have a higher rate of red blood cell sedimentation. Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), signifying an inflammatory process in the body. Other standard blood tests look for rheumatoid factor antibody levels and anti-circulating citrulline peptides (anti-CCP).

6.2 Visual examination

X-rays can aid in tracking the development of rheumatoid joint arthritis over time. In addition, MRI and ultrasound scans help assess the severity of the disease.

7. ALLOPATHIC TREATMENT FOR RHEUMATOID ARTHRITIS AND ITS LIMITATIONS

7.1 Treatment

Treatment aims to reduce the inflammatory state with some relief, minimize joint damage, and ultimately improve physical condition and quality of life. If you change your lifestyle, medications may be prescribed. There are medications available to treat rheumatoid arthritis [22]. Based on the severity of symptoms and the length of time, various drugs are used in the treatment of RA.

7.1.1 Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are medications that are used to treat pain and inflammation. Over-the-counter NSAIDs include ibuprofen (Advil, Motrin IB, and others) and naproxen sodium (Aleve). Possible side effects include stomach upset, heart problems, and kidney damage [23].

7.1.2 Steroids

Prednisone and other corticosteroid drugs relieve inflammation and pain while also reducing joint deterioration. Bone deterioration, weight gain, and diabetes are all possible side effects. Doctors frequently prescribe corticosteroids to relieve symptoms quickly and gradually wean patients off the medication [20].

7.1.3 Traditional Disease-modifying anti-rheumatic medications (DMARDs)

These drugs may reduce the development of rheumatoid arthritis and avoid permanent damage to joints and other tissues. Methotrexate (Trexall, Otrexup, etc.), leflunomide (Arava), hydroxychloroquine (Plaquenil), and sulfasalazine are examples of common DMARDs (Azulfidine). Side effects can range from mild to severe but can include liver damage and severe lung infections [5,16].

7.1.4 Biologic agents

This new class of DMARDs, known as biologic response modifiers, includes abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), sariluma (Actemra) [24].

7.1.5 Surgery for Rheumatoid Arthritis

Some people require joint replacement surgery if joint pain and inflammation become unbearable or significantly injured joints. The hips and knees and the shoulders, on occasion, are the most commonly replaced joints. The pain and mobility are significantly improved with surgery. Most people wait until they are over 50 since prosthetic joints wear out after 15 to 20 years [5,25].

7.2 Limitations of rheumatoid arthritis treatment

The management of pain, avoiding long-term joint damage, and reducing inflammation are critical issues when treating RA. DMARDs and non-steroidal anti-inflammatory medicines (NSAIDs) have been the primary treatments utilized to treat the disease's symptoms and after-effects. [26] Corticosteroids, an anti-inflammatory hormone generated by the adrenal glands, are another steroidal medication used to treat RA inflammation [27]. An optimal steroid should meet the requirements at a low dose while avoiding adverse effects. Both steroidal and non-steroidal medications reduce symptoms but cannot cure or prevent disease in the long run [28].

Aside from that, patients may experience severe side effects, such as impacts on the kidney, liver, and heart, resulting from long-term usage of such medications. Short-term adverse effects include shortness of breath, nausea, infections, and allergic reactions, result in fundamental constraints and issues, dealing with steroidal medicines for the treatment of rheumatoid arthritis [29].

8. MANAGEMENT AND TREATMENT APPROACHES OF RHEUMATOID ARTHRITIS

8.1 Herbal Intervention for Rheumatoid Arthritis

Traditional treatments have been used successfully to treat inflammatory and arthritic disorders. Chronic inflammatory illnesses, such as rheumatoid arthritis, remain one of the world's major health concerns. Although various medications are used to treat it, long-term use results in unfavorable severe side effects, the most prevalent being gastrointestinal bleeding and peptic ulcers. As a result, new anti-inflammatory medicines with negligible side effects. It is worth noting that most of today's analgesic medicines have an extensive variety of adverse properties [30].

Most ethnic people still rely on native medicinal plants to heal various diseases, employing knowledge of herbal treatment passed down from their forefathers as summarized in Table 2. However, due to the accessibility of recent medical facilities and other socioeconomic circumstances, this ethno-therapeutic knowledge and medicinal plants are decreasing at a distressing rate. On the other hand, the command is helpful in the quest for novel medicines to improve human health. Herbal medicines have gained popularity in recent years, both at home and abroad, because of less hazardous than synthetic medicines [30,31]. The Inflammation pathway in RA and mechanism of action of herbs are depicted in Fig. 8.

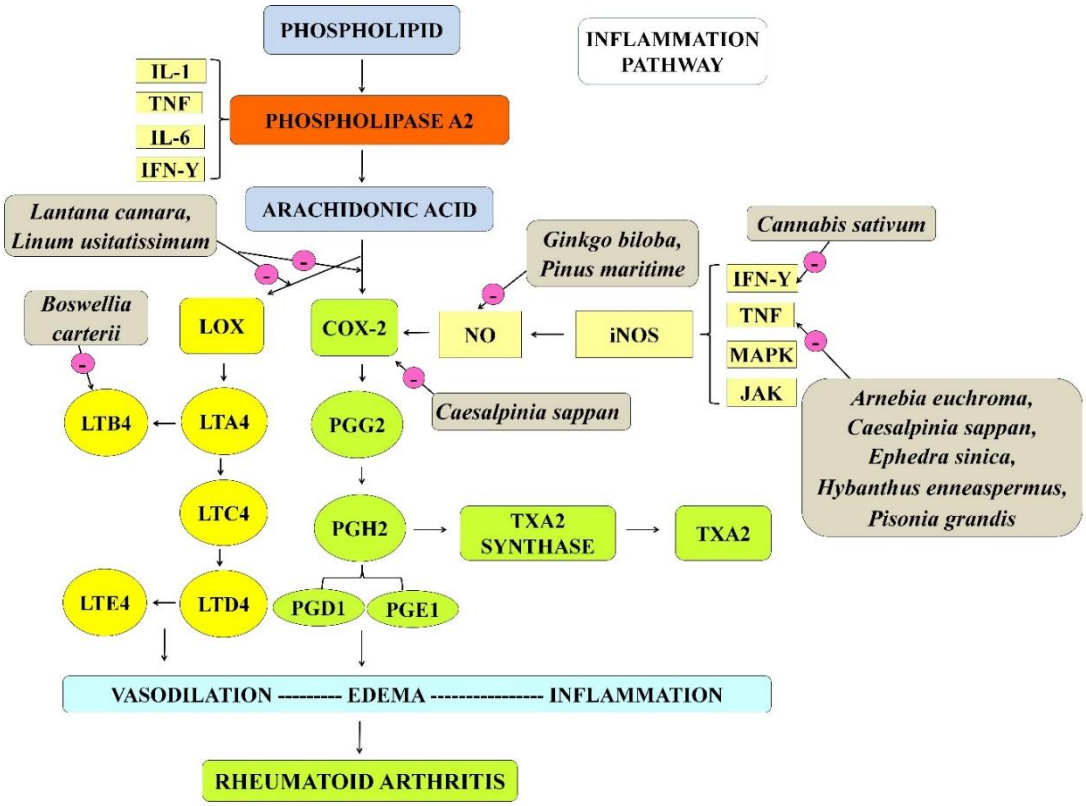


Fig. 8. Inflammation pathway in RA and mechanism of action of herbs.

Table 2. Role of herbs in the managements of rheumatoid arthritis.

Plant name	Family	Part used	Chemical constituents	Extract	Mechanism of action
Acyranthus aspera Linn.	Amaranthaceae	Root, Stem	n-hexacos-14-enoic acid	Alcoholic	Inhibition of secondary lesions [30,32].
Aconitum vilmorinianum Kom	Ranunculaceae	Root	Vilmorrianines E-G	Ethanolic	Improvement of join allodynia, swelling, hyperaemia and vascular permeability [33].
Alstonia scholaris Linn. R.Br.	Apocynaceae	Leaf	Alstonine, Echitamine	Ethanolic	Total leukocyte migration, as well as lymphocytes and monocytes/macrophages migration, are reduced [34].
Ammania bracifera	Lythraceae	Leaf	4-hydroxy-a-tetralone, tetralone-4-O-B-D-glucopyranosid, ellagic acid	Aqueous alcoholic	ESR and WBC count decreases [35].
Argyreia speciosa Sweet	Convulvulaceae	Root	Ergometrine	Ethanolic	Prevents recruitment of erythrocytes]36,37].
Artocarpus tonkinensis A. Cheval	Moraceae	Leaf	Alphitonin-4-O-b-D-glucopyranoside	Ethyl acetate extract	T- cells apoptosis induction [38].
Asystasia dalzelliana	Acanthaceae	Leaf	Aesculetin	Ethanolic	Decrease synthesis if t cells generation [39].

Santapau.					
Arnebia euchroma Johnst.	Boraginaceae	Root	β,β'-dimethylacrylshikoni	95% Ethanolic	Suppress level of TNF-α and lL-1β [40].
Bacopa monniera Penell.	Scrophulariaceae	Whole plant	Jujubogenin or pseudo-jujubogenin	Methanolic	Stabilize the action of lysosomal membrane [41].
Barleria lupulina Lindl.	Acanthaceaea	Leaf	Hexadecanoic acid, ethyl 9,12,15-octadecatrienoate	Methanolic	Assist cell mediate immune response [42].
Barleria prionitis Linn.	Acanthaceae	Whole plant	7-methoxy diderroside, lupulinoside	Hydro - alcoholic	It lowers the ESR level [43].
Bauhinia variegata	Caesalpiniaceae	Stem	5,7-dimethoxy-30, 40-methylene dioxy flavone	Ethanolic	Superoxide dismutase, catalase, glutathione Peroxidase, lipid peroxide [44].
Bergenia stracheyi	Saxifragaceae	Rhizome	β-Sitosterol, Stigmesterol	Pet-ether and Methanol extract	Potential Th1/Th2 cytokine balancing activity [45].
Boerhaavia diffusa	Nyctaginaceae	Root	b-Sitosterol, a-2-sitosterol, palmitic acid	Pet-ether extract	Inhibit inflammatory 7 inhibitor [30].
Boswellia carterii, Birdw.	Burseraceae	Root	β, 11β-dihydroxy boswellic acid	70% aqueous acetone extract	Decrease the formation of leukotriene LTB4 and reduce the infiltration of leucocytes. [46]
Butea monosperma	Fabaceae	Whole plant	Palasonin, d-mecantharidin proteolytic	Pet-ether extract	levels of WBC, ESR were suppressed [47].
Caesalpinia sappan Linn.	Leguminosae	Whole plant	Heamatin	Ethanolic	Inhibited the expression of pro-inflammatory cytokines IL-1ß and TNF-α [48].
Caesalpinia sappan Linn.	Leguminosae	Whole plant	11b-dihydrobenz, Brazilin	Ethanolic	Decreasing the levels of IL-1β, IL-6, TNF-α and PGE2 in serum and the expression of COX-2 and transcription factor NF-Kb [49].
Capparis spinosa Linn.	Capparaceae	Fruit	Bis(5-formyl furfuryl) ether, α-D-fructofuranosides methyl	Hydroalcoholic extract	Counteract the effects of IL-1 [50].
Cardiospermum halicacabum Linn.	Spindaceae	Leaf	Cyclohexane-1, 4, neophytadiene	Ethanolic	Reduction of RF and CRP levels in the serum [51].
Cassia uniflora Mill.	Caesalpiniaceae	Leaf	Alatinone, Aloe-emodin	Methanolic	Inhibit prostaglandin and histamine synthesis [30].
Centella asiatica Urban.	Mackinlayaceae	Leaf	Asiatic acid, asiaticoside	Methanolic	Inhibition of protein denaturation membrane stabilization and proteinase inhibitory [52].
Cissampelos pareira	Menispermaceae	Root	Dihydrodicentrine, cycleanine	Ethanolic	Levels of acid phosphatase and N-acetyl glucosaminidase were

Linn.					reduced and hexose, sialic acid increased [53].
Chelidonium majus Linn.	Papaveraceae	Whole Plant	Sparteine, coptisine	Methanolic	Lower the absolute number of CD4+T cells in spleen and lymph node, induce Immunesuppressive response by lowering the CD4+T-cells & enhancing CD8+T-cells [54].
Cleome gyandra L.	Cleomaceae	Leaf	β-carotene	Ethanolic	Modifying the lysosomal membrane or inhibiting the release of lysosomal enzymes [55].
Curcuma zeodaria Rosc.	Zingiberaceae	Root	α-terpinyl acetate, dehydrocurdione	Pet-ether Chloroform extract	Decrease the latency time to explore [56].
Ephedra sinica Staph.	Ephedreae	Leaf	6-methoxy kynurenic acid, methylephedrine	Aqueous extract	mRNA expressions of TNF-α and IL-6 genes restored to normal levels [57].
Ficus bengalensis Linn.	Moraceae	Stem, Bark	Quercetin-3-galactoside	Methanolic	Inhibition of early phase of inflammation [58].
Ginkgo biloba Linn.	Ginkgoaceae	Leaf	Protocatechuic acid	Methanolic	Inhibition of NO production from the macrophages that infiltrated to the inflamed site [59].
Glycosmis pentaphylla Linn.	Rutaceae	Bark	5,7,4'-trihydroxydihydroflavonol	Ethanolic	significant improvement of the hematological parameters like RBC count, Hb level and the ESR [60].
Glycyrrhiza glabra Linn.	Fabaceae	Rhizome	Glycyrrhetic acid	Methanolic	Lysosomal membrane stability modulating effect, inhibiting leukocyte migration, controlling the production of auto antigens [61].
Hemidesmus indicus R.Br.	Asclepdiaceae	Root	Lupeol, α-amyrin	Hydroalcoholic extract	Inhibition of inflammation induced by carrageenin, bradykinin and serotonin [62].
Hybanthus Enneaspermus Muell.	Violaceae	Whole Plant	Cedarn-diol, D-mannitol	Hydroalcoholic extract	Inhibits the release of mediators like cytokines (IL-1β and TNF-α), GM-CSF, IFN and PGDF [63].
Justica gendarussa	Acanthaceae	Leaf	Friedelin, lupeol	Ethanolic	Inhibition of migration of leukocytes [64].
Lantana camara Linn.	Verbinaceae	Leaf	11-trimethyl-1,6,10-dodecatriene	Ethanolic	Lipoxygenase and/or cyclooxygenase Inhibition [65].
Linum usitatissimum	Linaceae	Seed	Cadmium, linoleic acid	Petroleum ether extract	Inhibitory effect on arachidonate metabolism.[66]
Lonicera japonica Thumb.	Caprifoliaceae	Leaf	Flavoyadorinin-B	Methanolic	Suppress T-cell proliferation [67].
Mallotus oppositifolium Mull.	Euphorbeaceae	Leaf	Coumarins, cardenolides	Methanolic	Anti-proliferative activity [68].
Merremia tridentate	Convulvulaceae	Whole Plant	Luteolin	Ethanolic	Inhibition of second phase of inflammation and release of

Hall.					kinins and PG's [69].
Operculina turpethum	Convolvulaceae	Root	etulinic acid	Ethanolic	Inhibit the denaturation of proteins [70].
Panax ginseng C.A. Meyer.	Araliaceae	Root	Spermine, Choline	Ethanolic	Suppressed TPA-induced acute inflammation [71]
Phyllanthus amarus	Euphorbiaceae	Whole Plant	Quercetin	Aqueous extract	ALT and 1T levels were reduced [72].
Physalis angulate Linn.	Solanaceae	Leaf	Physalins, Carotenoids	Methanolic extract	Inhibit the denaturation of proteins [73].
Pinus maritime Roxb.	Pinaceae	Bark	Catechins, taxifolin,	Hydroalcoholic extract	Inhibiting acute and chronic inflammatory lesions and production of NO [74].
Piper betle Linn.	Piperaceae	Leaf	γ-lactone, allyl catechol	Hydroalcoholic extract	Elevated level of CD4+T cell specific IFN-c in splenocytes is reduced [75].
Pisonia grandis R.Br.	Nyctaginaceae	Leaf	Allantoin	Ethanolic	Release of mediators like cytokines, GM-CSF, interferons and PGDF are suppressed [30].
Pistia stratiotes Linn.	Araceae	Leaf	Stigmasteryl stearate, Palmitic acid.	Hydroalcoholic extract	Low levels of C-reactive proteins and ESR [76].
Ruta graveolens Linn.	Rutaceae	Whole Plant	Undecan-2-one	Aqueous extract	Reduces cell influx, release of mediators, lipid peroxidation and oxidative stress [77,78].
Salix nigra Linn.	Saliaceae	Bark	Salicin	Methanolic	Inhibition of pro inflammatory inhibitors [79].

8.2 Lifestyle Intervention for RA Management

Rheumatoid arthritis is a chronic disease and may be exacerbated in patients due to unhealthy lifestyle, nutrition and exercise. There are certain evidences and facts that are proven beneficial for management of arthritic pain. Regular exercise, along with healthy eating habits reduces stiffness in joint and helps in weight management, thus reduces stress on the hips and knees and lower back. The consumption of omega 3 fatty acids, nuts, vegetables and fruits further helps in weight management, reduces inflammation and promotes well-being [80-83].

Regular exercise reduces pain and swelling of joint and improves endurance capacity and muscle strengthening around joints. Walking and swimming are non-impacted exercises found beneficial for management of arthritic patients. Exercising 30 minutes at moderate intensity for 5 times a week are recommended for arthritic patients [84-85].

Other lifestyle interventions for arthritic pain are education, dietary management, smoking cessation, massaging and psychological intervention. The exercise goals for RA patients are explained in Table 3 [81-85].

Table 3. Lifestyle intervention for management of rheumatoid arthritis.

Exercise	Recommendation and Implementation
General exercise	Active warm up and cooling session before and after exercise. Variation to increase compliance of patients. Use joint protection devices or splints.
Improving range of motion (ROM) of joints	ROM perform after hot bath or shower. Perform 2-3 times, gradually increase.

	Muscles around joints must go under flexibility test.
Muscle strengthening and improving endurance capacity	ROM performed 3-4 times a day, improves muscle strength, increase contraction 6-7 times. Cycling, swimming, aerobic exercise, training session lasts for 30 min, improves breathing and heart rate.
Special consideration for pains	Wear soft footwear and pressure points should be monitored

8.3 Nutritional intervention

Nutrition helps in improvement of arthritic condition where modern medicine fails to provide permanent cure. Dieticians play important role in educating patients about safety and effectiveness of healthy eating. This further controls comorbidities like hypertension, diabetes and obesity. Dietary intervention like grains, omega 3 fatty acids, fruits and leafy vegetables are successful medium for management of arthritic patient through weight control. Healthy nutrition helps in improving joint pain and increases endurance capacity. Nutritional interventions are discussed in Table 4 [83, 85-89].

Table 4: Nutrients used in the management of rheumatoid arthritis.

Nutrition requirement	Recommendation and Implementation
Overall nutrition status	Over all nutrition is affected during pain, must be considered effectively to cope and provide proper counselling
Omega 3 fatty acids	EPA, DHA, ALA rich foods like soya, walnuts, beans, canola, flaxseed, increase inflammatory mediators, reduce pain
Antioxidant, mineral and vitamins consumption	In arthritic patients, bone demineralization occurs, Vitamin D, E, Folic acid and Calcium supplements improve bone strength

8.4 Psychological Intervention

Psychological stress is very common in arthritic patient due to pain discomfort. The chronic pain disturbs the mental psychology and affects patients' behaviour. This results in treatment withdrawal symptoms and avoidance from therapy by patients and causes feeling of fear, anger and stress. Medical intervention for improving mental well-being plays significant role in improving psychological stress through self-regulation and regular follow ups [81-82, 85].

8.5 Educational intervention

Education programmes of right information in appropriate manner should be shared and delivered for management of chronic patients. The following points for educating the patients are discussed below [82-85].

- Understanding disease pharmacology and patient mind-set.
- Make patient aware about of movements of joints.
- Focuses on lifestyle intervention.
- Educating patients how to cope with disease with pain.
- Involvement of family members, positive impact on patient.
- Other intervention are low-laser therapy and electro therapy.

9. FUTURE PERSPECTIVE

Alternative medications are way forward for management of arthritis pain. The drug therapy is complicated and troublesome due to risk of adverse effects, patient withdrawal and cost of medication. The various herbs such as Devil's claw, Boswellia, Rosehip used for management of RA results in side effects like insomnia, stomach upset and some interact with prescribed medicines but are not so significant [86]. Natural remedies patents for management of RA are discussed in Table 5.

Table 5. Patents on herbal drugs used in rheumatoid arthritis.

Patent no. & Date	Plant name	Patent title	inventor
EP2952201A1, 09/12/2015	*Alipinia galangal (A. galangal) linn.*	A. galangal or A. conchigera compositions with a high content of 1'S-1'-acetoxychavicol acetate suitable for pharmaceutical processing	Giversen, Ina 2720 Vanløse (DK)Jakobsen, Henrik Byrial 4320 Lejre (DK) [87]
US6589516B1, 08/07/2003	*Boswellia serrate*	Compositions containing Boswellia extracts	Heather Eyre, Kent (GB); Maxine Jayne Hills, Kent (GB); Stephen David Watkins, Kent (GB) [88]
US8192768B2, 05/06/2012	*Boswellia serrate*	Synergistic anti-inflammatory and antioxidant dietary supplement compositions	Ganga Raju Gokaraju, Rama Raju Gokaraju, Trimurtul Golakoti, Vendateswarlu Somepalli, [89]
US7205011B2, 17/04/2007	*Turmeric*	Anti-inflammatory activity of a specific turmeric extract	Guan Jie Chen, Robert Clark Lantz, Aniko M Solyom, Barbara N. Timmermann, Shivanand D. Jolad [90]
CN102697887A 26/06/2012		Composition of Traditional medicine for treatment of RA	Chang Ruixue, Fan Ming, Hu Xionglin, Tang Meichun [91]
WO2007056811 A1, 24/05/2007	*Zingiber officinale*	Zingiber plant extract	Hawkins, Clifford [92]
US5494668A, 27/2/1996	*Zingiber officinale*	Method of treating musculoskeletal disease and a novel composition therefor	Bhushan 14 aifeng1414n [93]
KR101055172B1 , 02/08/2011	*Black pepper*	Pharmaceutical composition for inhibiting or treating arthritis, containing piperine or a plant extract containing the same as an active ingredient	Kim kyungsoo, Bang junsu, Yang hyung in, Oh dahee yumyeongcheol, Hyunmi choi, Daehyun ham[94]
EP0935964A1, 18/08/1999	*Black pepper*	Pharmaceutical compositions containing NSAIDs and piperine	Rajesh jain,14aifeng singh [95]
US7943184B2, 17/05/2011	*Hedera helix Linn*	Process for preparing an extract from ivy leaves	Frank Runkel, Wolfgang Schneider, Oliver Schmidt, Georg Maximilian Engelhard [96]
CN102091104B, 19/06/2013	*Capparis spinosa Linn.*	Method for obtaining refined extract from 14 aifeng 14 spinosa and application of extract	Wo tong, Li yan, Liu quanhai, Zhog 14aifeng, Huang akira, Tan quiong, Yu meijing, Zhang lele, Liu minyu, Yang fang, Jiang renji, Yan zaofeng. [97]
US20020136784 A1, 26/09/2002	*Paeonia albiflora pall*	Selective COX-2 inhibition from plant extracts	Mark G. Obukowicz, Susan L. Hummert, [98]
CA2744514C, 08/05/2018	*Vitis venifera*	Vinifera plant extract for use as a phytochemical	Francois mairel [99]

US20100173028 A1, 08/07/2010	*Vitis venifera*	Process for preparing vitis vinifera pip extract and pharmaceutical composition for preventing or treating rheumatoid arthritis comprising the same	Jun-Ki Min, Mi-La Cho, Ho-Youn Kim, Seoul Jong-Hyeon Hyun-Gyu Kim, Geun-Hyeog Lee [100]

10. HERBAL MARKETED PRODUCTS FOR ARTHRITIS

The various marketed herbal products used in the management of arthritis shown in the (Table 6).

Table 6. Herbal marketed products used in arthritis.

Brand Name	Manufacturer	Herb	Uses
Boswellia	The Himalaya drug company	*Boswellia serrate*	It supports normal joint fluid function.
Cassia fistula	Dr. Wakde's	*Cassia fistula*	Controls the symptoms of Rheumatoid Arthritis.
Turmeric 95	The Himalayan drug company	*Turmeric/curcumin*	Improves circulation and immune activity in the area around your joints and muscles. Supports cellular health and reduces inflammation caused by strenuous exercise overexertion.
Black pepper essential oil	India essential oils	*Black pepper*	Arthritis and rheumatism
Arniflora arnica gel	Boirockae and tafel	*Arnica montana*	Relieves muscle pain. Topical pain relieving gel. Relieve after effects of injury, and overexcretion.
Yuvika Khurasani Ajwain	DKC agrotech pvt.ltd	*Hyosyamus niger linn.*	Arthritis
RADINEX	Bio resource inc.	*Arctium lappa*	For relief of occasional tiredness due to environmental stresses.
Arthrohills	Isha Agro Developers Pvt. Ltd	*Vitex negundo* *Trigonella foenum-graecum*	Anti-inflammatory, anti-arthritic & analgesic properties.
Dolonil Herbal Pain Relief Oil	Atharva herbals pvt. Ltd.	*Commiphora wightii* *Oroxylum indicum*	Chronic pain in disorders such as rheumatoid arthritis.

CONCLUSION

In today's scenario arthritis affect a large population of the world. The main problem of arthritis is our lifestyle. RA is a chronic inflammatory disease affecting humans and there are many drugs and therapies available in the market for its management. These medications are expensive and have adverse effects, so alternative therapy can be considered as a primitive stone for the management. Nature has bestowed us with very rich botanical treasure. There are many shreds of evidence that tell the use of herbs in various diseases. Appropriate treatment with herbal remedies, life style, dietary and nutritional intervention is the need of hour, help in improving medication response of patients. Tailor made approaches of omega fatty acids, physical activity programme, reduction of sedentary lifestyle, and breathing exercise together improve mental well-being and reduce co-

morbidities in cardiovascular, diabetic and obese patients. Therefore, further findings are necessary for improving the safety and efficacy of herbal approach. This helps in disease management and building confidence among patients.

ABBREVIATIONS

RA: Rheumatoid Arthritis; Ig: Immunoglobulins; IL: Interleukin; TNF: Tumor Necrosis Factor; MMP: Matrix Metalloproteinase; TGF: Transforming Growth Factor; PGF: Platelet Growth Factor; IF: Interferon; GMCSF: Granulocyte-Macrophage Colony-Stimulating Factor; VEGF: Vascular Endothelial Growth Factor; FGF: Fibroblast Growth Factor; ESR: Erythrocyte Sedimentation Rate: CRP: C-Reactive Protein; Anti-CCP: Anti-Circulating Citrulline Peptides; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; DMRADS: Disease-Modifying Anti-Rheumatic Medications; RBC: Red Blood Cells; WBC: White Blood Cells; LTB4: Leukotrienes B4; PG: Prostaglandins; COX: Cyclo-Oxygenase; NO: Nitric oxide; TPA: Type Plasminogen Activator, ALT: Alanine Aminotransferase; ROM: Range of Motion; ALA: Alpha-Linolenic Acid; DHA: Docosahexaenoic Acid; EPA: Eicosapentaenoic Acid.

COMPETING INTERESTS DISCLAIMER

There is no conflict and competing interests among the authors.

REFERENCES

1. Senthelal S, Li J, Goyal A, Bansal P, Thomas MA. Arthritis. [Updated 2021 Aug 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. *(In press)*
2. Yap H-Y, Tee SZ-Y, Wong MM-T, Chow S-K, Peh S-C, Teow S-Y. Pathogenic Role of Immune Cells in Rheumatoid Arthritis Implications in Clinical Treatment and Biomarker Development. Cells. 2018;7(10):161. doi:10.3390/CELLS7100161
3. Chauhan K, Jandu JS, Goyal A, Bansal P, Al-Dhahir MA. Rheumatoid Arthritis: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. *(In press)* PMID: 28723028.
4. Salaffi F, Di Carlo M, Carotti M, Farah S, Ciapetti A, Gutierrez M. The impact of different rheumatic diseases on health-related quality of life: A comparison with a selected sample of healthy individuals using SF-36 questionnaire, EQ-5D and SF-6D utility values. Acta Biomed. 2018;89(4):541-557. doi:10.23750/abm.v89i4.7298
5. Bullock J, Rizvi SAA, Saleh AM, *et al.* Rheumatoid Arthritis: A brief overview of the treatment. Med Princ Pract. 2019;27(6):501. doi:10.1159/000493390
6. Hunter DJ, McDougall JJ, Keefe FJ. The Symptoms of Osteoarthritis and the Genesis of Pain. Rheum Dis Clin North Am. 2008;34(3):623-643. doi:10.1016/j.rdc.2008.05.004
7. Lawrence RC, Felson DT, Helmick CG, *et al*. Estimates of the Prevalence of Arthritis and Other Rheumatic Conditions in the United States, Part II. Arthritis Rheum. 2008;58(1):26. doi:10.1002/ART.23176
8. Mohammed A, Alshamarri T, Adeyeye T, Lazariu V, McNutt L-A, Carpenter DO. A comparison of risk factors for osteo- and rheumatoid arthritis using NHANES data. Prev Med Reports. 2020;20. doi:10.1016/J.PMEDR.2020.101242
9. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res. 2018;6(1). doi:10.1038/S41413-018-0016-9
10. Vollenhoven RF van. Sex differences in rheumatoid arthritis: more than meets the eye... BMC Med. 2009;7:12. doi:10.1186/1741-7015-7-12
11. Rheumatoid arthritis - Symptoms and causes - Mayo Clinic. Accessed 29 October 2021. Available:https://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/symptoms-causes/syc-20353648

12. Deane KD, Demoruelle MK, Kelmenson LB, Kuhn KA, Norris JM, Holers VM. Genetic and environmental risk factors for rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2017;31(1):3. doi:10.1016/J.BERH.2017.08.003
13. Basisht GK, Singh RH, Chandola H. Management of rheumatoid arthritis (Aamavata) using symbiohealth healthcare system. Ayu. 2012;33(4):466. doi:10.4103/0974-8520.110513
14. Heidari B. Rheumatoid arthritis: Early diagnosis and treatment outcomes. Casp J Intern Med. 2011;2(1):161-170. Accessed 29 October 2021. /pmc/articles/PMC3766928/
15. Rheumatoid arthritis and osteoarthritis are different types of arthritis. Although they share some I Rheumatoid arthritis remedies, Rheumatoid arthritis, Arthritis. Accessed 29 October 2021.
Available: https://www.pinterest.com/pin/7388786876692255/
16. Ashwlayan DVD, Nimesh S. Cutting Edge of Herbal Drugs over Allopathic Drugs in Clinical Treatment of Rheumatoid Arthritis. J Bone Biol Osteoporos. 2018;4(1):43-50. doi:10.18314/JBO.V4I1.1194
17. MP van der L, D van der W, A I-F, et al. Value of anti-modified citrullinated vimentin and third-generation anti-cyclic citrullinated peptide compared with second-generation anti-cyclic citrullinated peptide and rheumatoid factor in predicting disease outcome in undifferentiated arthritis and rheumatoid arthritis. Arthritis Rheum. 2009;60(8):2232-2241. doi:10.1002/ART.24716
18. The nature and origins of synovium: experimental approaches to the study of synoviocyte differentiation - PubMed. Accessed 30 October 2021.
Available: https://pubmed.ncbi.nlm.nih.gov/7928638/
19. Rheumatoid arthritis | Sparrow. Accessed 29 October 2021. https://www.sparrow.org/departments-conditions/conditions/rheumatoid-arthritis
20. Rheumatoid arthritis | Causes, symptoms, treatments. Accessed 29 October 2021. https://www.versusarthritis.org/about-arthritis/conditions/rheumatoid-arthritis/
21. Diagnosis and differential diagnosis of rheumatoid arthritis - UpToDate. Accessed 29 October 2021.
Available:https://www.uptodate.com/contents/diagnosis-and-differential-diagnosis-of-rheumatoid-arthritis
22. Rheumatoid arthritis - Diagnosis and treatment - Mayo Clinic. Accessed 30 October 2021.
Available:https://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/diagnosis-treatment/drc-20353653
23. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Accessed 30 October 2021.
Available:https://my.clevelandclinic.org/health/drugs/11086-non-steroidal-anti-inflammatory-medicines-nsaids
24. Biologic Response Modifier Agents as First-line Treatment for Patients with Rheumatoid Arthritis: A Review of the Clinical Efficacy, Cost-effectiveness, and Guidelines. Published online 2013.
25. Rheumatic diseases--surgical treatment. A systematic literature review by SBU--the Swedish Council on Technology Assessment in Health Care - PubMed. Accessed 30 October 2021.
Available: https://pubmed.ncbi.nlm.nih.gov/11029978/
26. Kumar P, Banik S. Pharmacotherapy Options in Rheumatoid Arthritis. Clin Med Insights Arthritis Musculoskelet Disord. 2013;6(6):35. doi:10.4137/CMAMD.S55`58
27. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol. 2011;335(1):2. doi:10.1016/J.MCE.2010.04.005
28. Yasir M, Goyal A, Bansal P, Sonthalia S. Corticosteroid Adverse Effects. StatPearls. Published online July 8, 2021. Accessed 30 October 2021.
Available: https://www.ncbi.nlm.nih.gov/books/NBK531462/

29. Raza K, Buckley CE, Salmon M, Buckley CD. Treating very early rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2006;20(5):849. doi:10.1016/J.BERH.2006.05.005
30. Choudhary M, Kumar V, Malhotra H, Singh S. Medicinal plants with potential anti-arthritic activity. J Intercult Ethnopharmacol. 2015;4(2):147. doi:10.5455/JICE.20150313021918
31. Hajja G, Bahlouli A. Medicinal plants in the prevention and treatment of rheumatoid arthritis. MOJ Bioequivalence Bioavailab. 2018;Volume 5(Issue 1). doi:10.15406/MOJBB.2018.05.00084
32. Saini S. Review on achyranthes aspera L. Int Educ Res J. 2016;2(2). Accessed 30 October 2021.
Available: http://ierj.in/journal/index.php/ierj/article/view/156
33. Li M, He J, Jiang LL, Ng ES, Wang H, Lam FF, et al. The anti-arthritic effects of Aconitum vilmorinianum, a folk herbal medicine in Southwestern China. J Ethnopharmacol. 2013;147(1):122-127. doi:10.1016/J.JEP.2013.02.018
34. Dey A. Alstonia scholaris R.Br. (Apocynaceae): Phytochemistry and pharmacology: A concise review Abhijit Dey.
35. A review on plants having anti-arthritic potential. Accessed 30 October 2021.
Available: https://www.researchgate.net/publication/285729677_A_review_on_plants_having_anti-arthritic_potential
36. Gokhale AB, Damre AS, Kulkami KR, Saraf MN.Preliminary evaluation of anti-inflammatory and anti-arthritic activity of S. lappa, A. speciosa and A. aspera. Phytomedicine. 2002;9(5):433-437. doi:10.1078/09447110260571689
37. Antipyretic activity of whole aerial part from Argyreia nervosa. Accessed 30 October 2021. Available: https://www.researchgate.net/publication/237176030_Antipyretic_activity_of_whole_aerial_part_from_Argyreia_nervosa
38. Ngoc DD, Catrina AI, Lundberg K, Harris HE, Ha NT, Anh PT, et al.Inhibition by Artocarpus tonkinensis of the development of collagen-induced arthritis in rats. Scand J Immunol. 2005;61(3):234-241. doi:10.1111/J.1365-3083.2005.01560.X
39. Babushetty V. Evaluation of Anti-Arthritis Activity of Asystasia Dalzelliana Leaves. undefined. Published online 2012.
40. Bhattacharya S, Mandal SK, Akhtar MS, *et al*. Phytochemicals in the treatment of arthritis: Current knowledge. Int J Curr Pharm Res. 2020:1-6. doi:10.22159/IJCPR.2020V12I4.39050
41. Vijayan V, Shyni GL, Helen A.Efficacy of Bacopa monniera (L.) Wettst in alleviating lysosomal instability in adjuvant-induced arthritis in rats. Inflammation. 2011;34(6):630-638. doi:10.1007/S10753-010-9272-6
42. Sudheer WN, Praveen N. Phytochemical, pharmacological and tissue culture studies of some important species of the genus Barleria L. (Acanthaceae) - a review. Plant Sci Today. 2021;8(3):491–500-491–500. doi:10.14719/PST.2021.8.3.1117
43. Singh K, Sharma D, Gupta RS. A comprehensive review on barleria prionitis (L.). Asian J Pharm Clin Res. 2017;10(12):22-29. doi:10.22159/AJPCR.2017.V10I12.18587
44. Bodakhe SH, Ram A. Hepatoprotective properties of Bauhinia variegata bark extract. Yakugaku Zasshi. 2007;127(9):1503-1507. doi:10.1248/YAKUSHI.127.1503
45. Nazir N, Koul S, Qurishi MA, Taneja SC, Ahmad SF, et al.Immunomodulatory effect of bergenin and norbergenin against adjuvant-induced arthritis--a flow cytometric study. J Ethnopharmacol. 2007;112(2):401-405. doi:10.1016/J.JEP.2007.02.023
46. Fan AY, Lao L, Zhang RX, Wang LB, Lee DY, Ma ZZ, et al. Effects of an acetone extract of Boswellia carterii Birdw. (Burseraceae) gum resin on rats with persistent inflammation. J Altern Complement Med. 2005;11(2):323-331. doi:10.1089/ACM.2005.11.323
47. Muralidhar. Evaluation of wound healing properties of bioactive fractions from the extract of Butea monosperma (Lam) Stem Bark. Int J Phytomed. Accessed 30 October

2021. *(In press)*
Available: https://www.arjournals.org/index.php/ijpm/article/view/269
48. Wu SQ, Otero M, Unger FM, Goldring MB, Phrutivorapongkul A, Chiari C, et al. Anti-inflammatory activity of an ethanolic Caesalpinia sappan extract in human chondrocytes and macrophages. J Ethnopharmacol. 2011;138(2):364. doi:10.1016/J.JEP.2011.09.011
49. Wang YZ, Sun SQ, Zhou YB. Extract of the dried heartwood of Caesalpinia sappan L. attenuates collagen-induced arthritis. J Ethnopharmacol. 2011;136(1):271-278. doi:10.1016/J.JEP.2011.04.06149.
50. Feng X, Lu J, Xin H, Zhang L, Wang Y, Tang K. Anti-arthritic active fraction of Capparis spinosa L. fruits and its chemical constituents. Yakugaku Zasshi. 2011;131(3):423-429. doi:10.1248/YAKUSHI.131.423
51. Jeyadevi R, Sivasudha T, Rameshkumar A, Dinesh Kumar L. Anti-arthritic activity of the Indian leafy vegetable Cardiospermum halicacabum in Wistar rats and UPLC-QTOF-MS/MS identification of the putative active phenolic components. Inflamm Res. 2013;62(1):115-126. doi:10.1007/S00011-012-0558-Z
52. Chippada SC, Volluri S, Bammidi SR, Vangalapati M. In vitro anti-arthritic activity of methanolic extract of Centella asiatica. Biosci Biotechnol Res Asia. 2011;8(1):337-340. doi:10.13005/BBRA/868
53. Ethnomedical value of Cissampelos pareira extract in experimentally induced diarrhoea - PubMed. Accessed October 30, 2021. https://pubmed.ncbi.nlm.nih.gov/15050042/
54. Lee YC, Kim SH, Roh SS, Choi HY, Seo YB.Suppressive effects of Chelidonium majus methanol extract in knee joint, regional lymph nodes, and spleen on collagen-induced arthritis in mice. J Ethnopharmacol. 2007;112(1):40-48. doi:10.1016/J.JEP.2007.01.033
55. Narendhirakannan RT, Subramanian S, Kandaswamy M.Anti-inflammatory and lysosomal stability actions of Cleome gynandra L. studied in adjuvant induced arthritic rats. Food Chem Toxicol. 2007;45(6):1001-1012. doi:10.1016/J.FCT.2006.12.009
56. Kaushik ML, Jalalpure SS. Effect of Curcuma zedoaria Rosc root extracts on behavioral and radiology changes in arthritic rats. J Adv Pharm Technol Res. 2011;2(3):170. doi:10.4103/2231-4040.85537
57. Yeom MJ, Lee HC, Kim GH, Lee HJ, Shim I, Oh SK, Kang SK, Hahm DH., et al. Anti-arthritic effects of Ephedra sinica STAPF herb-acupuncture: inhibition of lipopolysaccharide-induced inflammation and adjuvant-induced polyarthritis. J Pharmacol Sci. 2006;100(1):41-50. doi:10.1254/JPHS.FP0050637
58. Manocha N, Chandra SK, Sharma V, Sangameswaran B, Saluja M. Anti-rheumatic and antioxidant activity of extractof stem bark of Ficus bengalensis. Res J Chem Sci. 2011;1(2):2-8.
59. Han Y. Ginkgo terpene component has an anti-inflammatory effect on Candida albicans caused arthritic inflammation. Int Immunopharmacol. 2005;5(6):1049-56. doi: 10.1016/j.intimp.2005.02.002. PMID: 15829420.
60. Petchi RR, Kathiresan V. Anti-diabetic and anti-arthritic potential of glycosmis pentaphylla stem bark in FCA induced arthritis and streptozotocin induced diabetic rats. Int J Pharma Bio Sci 2012;3(3):P328-P336.
61. Bstia S, Mishra G, Patra S. Anti-arthritic activity of Glycyrrhiza glabra, Boswellia serrata and their synergistic activity in combined formulation studied in freund's adjuvant induced arthritic rats. undefined. Published online 2011.
62. Mehta A, Sethiya NK, Mehta C, Shah GB. Anti-arthritis activity of roots of Hemidesmus indicus R.Br. (Anantmul) in rats. Asian Pac J Trop Med. 2012;5(2):130-135. doi:10.1016/S1995-7645(12)60011-X
63. Srivastava S, Singh P, Jha KK, Mishra G, Srivastava S, Khosa RL. Evaluation of anti-arthritic potential of the methanolic extract of the aerial parts of Costus speciosus. J Ayurveda Integr Med. 2012;3(4):204. doi:10.4103/0975-9476.104443
64. Paval J, Kaitheri SK, Potu BK, et al. Anti-Arthritic Potential of the Plant Justicia

Gendarussa Burm F. Clinics (Sao Paulo). 2009;64(4):357. doi:10.1590/S1807-59322009000400015
65. Kaithwas G, Majumdar DK. Therapeutic effect of Linum usitatissimum (flaxseed/linseed) fixed oil on acute and chronic arthritic models in albino rats. Inflammopharmacology. 2010;18(3):127-136. doi:10.1007/S10787-010-0033-9
66. Lee J-H, Han Y. Antiarthritic effect of lonicerin on Candida albicans arthritis in mice. Arch Pharmacal Res 2011 345. 2011;34(5):853-859. doi:10.1007/S12272-011-0520-6
67. Chinaka O. Nwaehujor, Maxwell I. Ezeja, Nkeiruka E. Udeh, Dozie N. Okoye, Rita I. Udegbunam, Anti-inflammatory and anti-oxidant activities of Mallotus oppositifolius (Geisel) methanol leaf extracts, Arab. J Chem. 2014;7(5):805-810.
68. Rajendran R, Krishnakumar E. Anti-Arthritic Activity of Premna serratifolia Linn., Wood against Adjuvant Induced Arthritis. Avicenna J Med Biotechnol. 2010;2(2):101-6. PMID: 23407688; PMCID: PMC3558150.
69. Gupta S, Ved A. Operculina turpethum (Linn.) Silva Manso as a Medicinal Plant Species: A Review on Bioactive Components and Pharmacological Properties. Pharmacogn Rev. 2017;11(22):158. doi:10.4103/PHREV.PHREV_6_17
70. Lee J Il, Park KS, Cho IH. Panax ginseng: a candidate herbal medicine for autoimmune disease. J Ginseng Res 2019;43(3):342-348. doi:10.1016/J.JGR.2018.10.002
71. Mali SM, Sinnathambi A, Kapase CU, Bodhankar SL, Mahadik KR. Original article. Biomed Aging Pathol. 2011;3(1):185-190. doi:10.1016/J.BIOMAG.2011.09.004
72. Kumar S, Kishore G, Sivakumar G, Priya S. In-vitro anti-inflammatory and anti-arthritic activity of leaves of physalis angulata L. Published online 2012.
73. Tsubata M, Takagaki K, Hirano S, Iwatani K, Abe C. Effects of flavangenol, an extract of French maritime pine bark on collagen-induced arthritis in rats. J Nutr Sci Vitaminol (Tokyo). 2011;57(3):251-257. doi:10.3177/JNSV.57.251
74. Pandey A, Bani S, Dutt P, Suri KA. Modulation of Th1/Th2 cytokines and inflammatory mediators by hydroxychavicol in adjuvant induced arthritic tissues. Cytokine. 2010;49(1):114-121. doi:10.1016/J.CYTO.2009.08.015
75. Kyei S, Koffuor GA, Boampong JN. Antiarthritic effect of aqueous and ethanolic leaf extracts of Pistia stratiotes in adjuvant-induced arthritis in Sprague-Dawley rats. J Exp Pharmacol. 2012;4:41. doi:10.2147/JEP.S29792
76. Ratheesh M, Shyni GL, Sindhu G, Helen A. Protective effects of isolated polyphenolic and alkaloid fractions of Ruta graveolens L. on acute and chronic models of inflammation. Inflammation. 2010;33(1):18-24. doi:10.1007/S10753-009-9154-Y
77. Freire RB, Borba HR, Coelho CD. Ruta graveolens L. toxicity in Vampirolepis nana infected mice. Indian J Pharmacol. 2010;42(6):345-350. doi:10.4103/0253-7613.71898
78. Sharma S, Sahu D, Das HR, Sharma D. Amelioration of collagen-induced arthritis by Salix nigra bark extract via suppression of pro-inflammatory cytokines and oxidative stress. Food Chem Toxicol. 2011;49(12):3395-3406. doi:10.1016/J.FCT.2011.08.013
79. MP Schwellnus, DN Patel, C Nossel, M Dreyer, S Whitesman & EW Derman Healthy lifestyle interventions in general practice Part 11: Lifestyle and arthritic conditions-rheumatoid arthritis. SA Fam Pract. 2010;52(3),176-183.
80. Allah ESA, Hagrass SAA, Hassanin OA. Effect of lifestyle modification intervention program among adults suffering from osteoarthritis knee. J Nurs Healthc Sci. 2017;6(1):01-08.
81. Sheila O' Reilly, Michael Doherty. Lifestyle changes in the management of osteoarthritis. Rheumatology. 2001;15(14):559-568.
82. Managing Arthritis Through Lifestyle Modifications.
Available: https://sa1s3.patientpop.com /assets/docs/1650.pdf
83. Chehade L, Jaafar ZA, El Masri D, Zmerly H, Kreidieh D, Tannir H, et al. Lifestyle modification in rheumatoid arthritis: dietary and physical activity recommendations based on evidence. Curr Rheumatol Rev. 2019;15(13):209-214.
84. Lifestyle changes to help with your arthritis pain. Accessed 28 October 2021.

Available:https://coloradopaincare.com/lifestyle-changes-to-help-with-your-arthritis-pain/
85. Zaccardelli A, Friedlander HM, Ford JA, Sparks JA. Potential of lifestyle changes for reducing the risk of developing rheumatoid arthritis: is an ounce of prevention worth a pound of cure? Clin Ther. 2019;41(7):1323-1345
86. Versus Arthritis: Herbal Medicine. Accessed 2 December 2021. Available: https://www.versusarthritis.org/about-arthritis/complementary-and-alternative-treatments/types-of-complementary-treatments/herbal-medicine/
87. EP2952201A1 - Compositions of Alpinia galanga or Alpinia conchigera with high content of 1'S-1'-acetoxychavicol acetate suitable for pharmaceutical processing - Google Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/EP2952201A1/en
88. US6589516B1 - Compositions containing Boswellia extracts - Google Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/US6589516B1/en
89. US8192768B2 - Synergistic anti-inflammatory and antioxidant dietary supplement compositions - Google Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/US8192768B2/en
90. US7205011B2 - Anti-inflammatory activity of a specific turmeric extract - Google Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/US7205011B2/en
91. CN102697887A - Traditional Chinese medicine composition for treating rheumatoid arthritis - Google Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/CN102697887A/en
92. WO2007056811A1 - Zingiber plant extract - Google Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/WO2007056811A1/en
93. US5494668A - Method of treating musculoskeletal disease and a novel composition therefor - Google Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/US5494668A/en
94. KR101055172B1 - Pharmaceutical composition for inhibiting or treating arthritis, containing piperine or a plant extract containing the same as an active ingredient - Google Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/KR101055172B1/en
95. EP0935964A1 - Pharmaceutical compositions containing NSAIDs and piperine - Google Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/EP0935964A1/en
96. US7943184B2 - Process for preparing an extract from ivy leaves - Google Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/US7943184B2/en
97. CN102091104B - Method for obtaining refined extract from capparis spinosa and application of extract - Google Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/CN102091104B/en
98. US20020136784A1 - Selective COX-2 inhibition from plant extracts - Google Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/US20020136784A1/en
99. CA2744514C - Vitis vinifera plant extract for use as a phytochemical - Google Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/CA2744514C/pt-PT
100. US20100173028A1- Process for preparing vitis vinifera pip extract and pharmaceutical composition for preventing or treating rheumatoid arthritis comprising the sameGoogle Patents. Accessed 20 November 2021. Available: https://patents.google.com/patent/US20100173028A1/en