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Rheumatoid arthritis and herbal drugs: A review

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ABSTRACT

Rheumatoid Arthritis (RA) is a chronic autoimmune disease of unknown aetiology that affects 0.5% of the population and can result in disability owing to joint destruction, characterized by joint synovial inflammation and progressive cartilage and bone destruction resulting in gradual immobility. The greatest disadvantage in the presently available potent synthetic drugs lies in their toxicity and reappearance of symptoms after discontinuation. With limitations of existing drug molecules herbal drugs are gaining interest among RA patients. Medicinal plants are plants containing inherent active ingredients used to cure disease or relieve symptoms of arthritis. The aim of this review is to update information on RA including causes, epidemiology, prevalence, symptoms and diagnosis, classification, medications, toxicities of allopathic anti-rheumatic drugs and importance of herbal drugs for the management of RA. The present review also focuses on the medicinal plants that interact with the mediators of inflammation and are used in the treatment of rheumatoid arthritis (RA).

Keywords: Rheumatoid Arthritis, causes, medications, classification, medicinal plants.

INTRODUCTION

Arthritis, generally inflammation of joints is a one of the oldest known diseases occurring almost in all age groups. In India, more than about 20% of total population is suffering from arthritis [1]. Rheumatoid Arthritis (RA) is a chronic autoimmune disease of unknown aetiology, characterized by joint synovial inflammation and progressive cartilage and bone destruction resulting in gradual immobility [2].

It was first found in early Native American population several thousand years ago but might have appeared in Europe after 17th century [3]. Pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , and IL-6 are important mediators of the disease perpetuation [4]. The arthritis usually begins in the small joints of the hands and the feet, spreading later to the larger joints, the inflamed joint lining or synovial extends and then erodes the articular cartilage and bone, causing joint deformity and progressive physical disability. Extra-articular features include nodules, pericarditis, pulmonary fibrosis, peripheral neuropathy and amyloidosis [5].

Causes

Arthritis involves the breakdown of cartilage. Cartilage normally protects a joint, allowing it to move smoothly [6]. The process produces an inflammatory response of the synovial (sinusitis) secondary to hyperplasia of synovial cells, excess synovial fluid, and the development of panes in the synovial. The pathology of the disease process often leads to the destruction of articular cartilage and alkalosis of the joints. Rheumatoid arthritis can also produce diffuse inflammation in the lungs, pericardium, pleura, and sclera, and also nodular lesions, most common in subcutaneous tissue. Although the cause of rheumatoid arthritis is unknown, autoimmunity plays a pivotal role in both its chronicity and progression, and RA is considered a systemic autoimmune disease.

Epidemiology

About 1% of the world's population is afflicted by rheumatoid arthritis, women three times more often than men [7]. Arthritis represents one of the most prevalent chronic health problems and is a leading cause of disability. Arthritis affected 43 million U.S. adults in 2002 and by the year 2020, this number is expected to reach 60 million [8]. It is up to three times more common in smokers than non-smokers, particularly in men, heavy smokers, and those who are rheumatoid factor positive. A study in 2010 found that those who drank modest amounts of alcohol regularly were four times less likely to get rheumatoid arthritis than those who never drank [9].

Prevalence of RA

RA is strongly associated with the inherited tissue type Major histocompatibility complex

(MHC) antigen HLA-DR4 (most specifically DR0401 and 0404)—hence family history is an important risk factor. The risk of first developing the disease appears to be greatest for women between 40 and 50 years of age, and for men somewhat later [10]. The incidence and prevalence of RA generally rises with increasing age until about age 70, then declines [11-13]. Around twice as many women as men are affected. The prevalence of RA is generally lower in developing countries, with few or no cases found in some African surveys [14]. The prevalence in native American groups can be considerably higher [15-17].

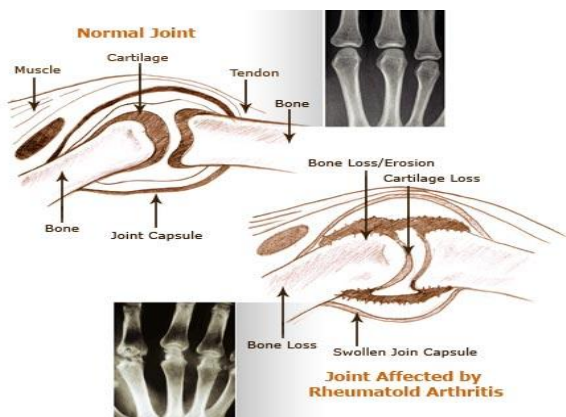


Figure 1: Comparison of normal joint and joint affected by rheumatoid arthritis

Symptoms and diagnosis

The pervasive nature of arthritis symptoms and their effect on physical, social and occupational activities can be discouraging, resulting in psychological sequelae such as anxiety, depression and helplessness [18].

RA can be hard to detect because it may begin with subtle symptoms, such as achy joints or a little stiffness. The stiffness seen in active RA

is most often worst in the morning. It may last one to two hours (or even the whole day). Stiffness for a long time in the morning is a clue that one may have RA, since few other arthritic diseases behave this way [19].

Other signs and symptoms that can occur in RA include:

Joint pain and swelling; reduced ability to move the joint; redness of the skin around a joint; warmth around a joint; loss of energy and appetite; low fevers; dry eyes and mouth from a related health problem; Sjogren's syndrome Firm lumps, called rheumatoid nodules, which grow beneath the skin in places such as the elbow and hands.

Methods to detect RA include clinical assessment, imaging and laboratory tests. Clinical assessment and opinion is considered the 'gold standard' [20]. Diagnosis of RA depends on the symptoms and some blood tests can also help to confirm RA. Telltale signs include:

Anemia (a low red blood cell count); rheumatoid factor (an antibody, or blood protein, found in about 80% of patients with RA in time, but in as few as 30% at the start of arthritis); antibodies to cyclic citrullinated peptides (pieces of proteins), or anti-CCP for short (found in 60– 70% of patients with RA); Elevated erythrocyte sedimentation rate (a blood test that, in most patients with RA, confirms the amount of inflammation in the joints).

X-rays can help in detecting RA, but may not show anything abnormal in early arthritis. Even so, these first X-rays may be useful later to show if the disease is progressing. Often, MRI and ultrasound scanning are done to help judge the severity of RA. There is no single test that confirms an RA diagnosis for most patients with this disease.

Medications

Medications may be prescribed along with lifestyle changes. All medications have risks, some more than others [21-22].

Table 1: Medications available for treatment of rheumatoid arthritis

Treatment	Drugs
Over The Counter	Acetaminophen (Tylenol), Aspirin, ibuprofen, or naproxen
Disease-modifying anti-rheumatic drugs (DMARDs)	Methotrexate, gold salts, penicillamine, sulfasalazine, and hydroxychloroquine. Common combinations of DMARDs include methotrexate – hydroxychloroquine, methotrexate – sulfasalazine, sulfasalazine – hydroxychloroquine, and methotrexate – hydroxychloroquine – sulfasalazine.
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Paracetamol, ibuprofen, naproxen, meloxicam, etodolac, nabumetone, sulindac, tolementin, choline magnesium salicylate, diclofenac, diflusal, indomethicin, ketoprofen, oxaprozin, and piroxicam.
Biological agents	Tumor necrosis factor alpha (TNF α) blockers -etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi) Monoclonal antibodies against B cells – rituximab (Rituxan)

Generally, over-the-counter medications are recommended first:

- Acetaminophen (Tylenol) is usually tried first. It is advisable not to take more than the recommended dose or do not take the drug along with a lot of alcohol. Doing so may damage liver.
- Aspirin, ibuprofen, or naproxen are nonsteroidal anti-inflammatory drugs (NSAIDs) that can relieve arthritis pain. However, they have many potential risks, especially if used for a long time. Potential side effects include heart attack,

stroke, stomach ulcers, bleeding from the digestive tract, and kidney damage.

Surgery and other treatments

In some cases, surgery may be done if other treatments have not worked. This may include:

- Arthroplasty to rebuild the joint
- Joint replacement, such as a total knee joint replacement

Classification

Classification criteria for RA were first proposed by the American Rheumatism Association (ARA) in 1958 [23]. The 1958 ARA criteria

were revised in 1987 by the American College of Rheumatology (ACR) [24].

Table 2: The 1987 revised ARA/ACR criteria for the classification of rheumatoid arthritis*

Criterion	Short title	Definition
1.	Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement. At least 3 joints.
2.	Arthritis of 3 or more joint areas	Areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3.	Arthritis of hand Joints	At least 1 area swollen (as defined above) in a wrist, MCP or PIP joint.
4.	Symmetric Arthritis	Simultaneous involvement of the same joint areas [as defined in (2)] on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
5.	Rheumatoid Nodules	Subcutaneous nodules, over bony prominences, or extensor in juxtaarticular regions, observed by a physician.
6.	Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor or any method for which the result has been positive in <5% of normal control subjects.
7.	Radiographic Changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

*For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least four of these seven criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with two clinical diagnoses are not excluded.

Need for herbal drugs for the management of RA:

Conventional treatments for rheumatoid arthritis (RA) present a number of problems, in terms of both safety and efficacy [25]. Owing to side effects of synthetic drugs as shown in table 2, many patients

look for complementary and alternative medicine (CAM) options in coping with this debilitating disease.

Table 3: Showing toxicities of allopathic anti-rheumatic drugs [26]

Sr. No.	Drug	Toxicities
1.	Methotrexate (DMARD's)	Stomatitis, rash, alopecia, infrequent myelosuppression, hepatotoxicity, rare but potentially life-threatening pulmonary toxicity
2.	Oral Gold Salts	Diarrhoea
3.	Injectable Gold Salts	Stomatitis, myelosuppression, rash, thrombocytopenia
4.	Cyclosporine	Renal impairment, hypertension, gingival overgrowth
5.	D-penicillamine	Rash, stomatitis, dysgeusia, proteinuria, myelosuppression
6.	Nonsteroidal Antiinflammatory Drugs	Gastrointestinal symptoms (indigestion, ulceration, hemorrhage, stomatitis); renal abnormalities; pulmonary neurological abnormalities; abnormalities; dermatologic abnormalities; hematologic abnormalities; hepatic abnormalities; displacement of protein-bound drugs; possible systemic complications

Research has indicated that people suffering from chronic pain, as in RA, and those dissatisfied with current treatment are very likely to seek alternative treatments, and an estimated 60–90% of persons with arthritis use CAM. With the growing interest in herbal therapies among persons with rheumatoid arthritis, there exists a need for investigation into their safety and efficacy [27].

The management of rheumatoid arthritis is a multidisciplinary approach in order to lessen the pain, reduction of inflammation and restoration of joints function. In practical terms suppression of inflammation is the target intensive therapy. Herbal medicines have become popular for the treatment of rheumatoid arthritis worldwide recently [28].

Herbal medicinal drugs that interact with the mediators of inflammation are used in the treatment of rheumatoid arthritis (RA) which are shown in below listed table:

Table 3: List of plant species and their families, constituents/isolated compounds, therapeutic uses and parts used in pain-inflammatory disorders including rheumatoid arthritis

Sr. No.	Biological Source	Part Used	Active Ingredient	Therapeutic Uses	Extract	Reference
1.	<i>Annona montana</i> (Annonaceae)	Leaves, fruit, seeds, bark, roots	Cyclomontanins A-D (1- 4), annonuricatin C (5), and (+)-corytuberine	Anti-rheumatic, anthelmintic, anticonvulsant, antidepressant, antimicrobial, antineoplastic, antiparasitic, antispasmodic, antiviral, astringent, cardiodepressant, cytostatic, cytotoxic, febrifuge, hypotensive, insecticide, nervine, pectoral, sedative, stomachic, vasodilator, vermifuge	Methanol	[29]
2.	<i>Abrus precatorius</i> (Fabaceae/ Leguminosae)	Fresh leaves	Triterpenoids (abrusosides A-D)	Colds, cough, convulsion, fever, rheumatism, conjunctivitis and ulcers by traditional healers	Methanol	[30-31]
3.	<i>Aristolochia bracteolata</i> (Aristolochiaceae)	Whole plant	Ceryl alcohol, β -sitosterol, aristolochic acid, alkaloid, myristic, palmitic, stearic, lignoceric, oleic and aristolochic acid, aristolochic acid aristolactam a nitrogen containing compound and magnoflorine	Anthelmintic, fever, purgative and painful joints.	Petroleum ether, chloroform and Methanol	[32]
4.	<i>Alpinia conchigera</i> Griff. (Zingiberaceae)	Rhizomes	Galangoflavonoid, 1'S-1'-acetoxychavicol acetate, 1'-acetoxychavicol acetate (galangal acetate), β -Sitosterol diglucoside (AG-7) and β -sitsteryl Arabinoside	Analgesic and anti-inflammatory	Ethanol	[33-34]
5.	<i>Alchornea cordifolia</i> (Euphorbiaceae)	Leaf	Tannins, phenolic acids: gallic acid, ellagic acid, protocatechic acid, flavonoids: quercetin, hyperin and guaijaverin and an alkaloid: triisopentenylguanidine	Anti-inflammatory: chancre, yaws wounds, cicatrisation, ulcers, caries, toothache, gum inflammation and conjunctivitis	Aqueous decoction and methanol extract	[35]
6.	<i>Asparagus racemosus</i> (Liliaceae)	Roots, Leaves, flowers and fruits	Steroidal glycosides including shatavarins I-IV, diosgenin and various sterols, alkaloid asparagine A, flavonoids: quercetin, rutin and hyperoside, an isoflavone, and a mucilage	Ulcerogenesis, antioxidant, treatment of thirst, fainting, dyspnoea, and gout	Methanol	[36]
7.	<i>Anacardium occidentale</i> (Anacardiceae)	Leaves	Myricetin, quercetin, kaempferol, apigenin and glycosides	Diarrhoea, diabetes, swelling, skin diseases, mouth ulcers, anti-inflammatory	Ethanol extract and its petroleum ether, solvent ether, ethyl acetate, butanol and butanone fraction	[37]
8.	<i>Azadirachta indica</i> (Meliaceae)	Leaf	alkaloids, flavonoids, triterpenoids, phenolic compounds, carotenoids, steroids and ketones	Anti-inflammatory, antipyretic, antimalarial, antitumour, antiulcer, antidiabetic, antifertility	hydro-alcoholic extract, ethyl acetate and n-butanol fractions	[38-39]
9.	<i>Allium cepa</i> (Liliaceae)	Bulbs	Organic sulfur compounds, including trans-S-(1-propenyl) cysteine sulfoxide, S-methyl-cysteine sulfoxide, S-propylcysteine sulfoxide and cycloalliin; flavonoids; phenolic acids; sterols including cholesterol, stigma sterol, β -sitosterol; saponins; sugars and a trace of volatile oil composed mainly of sulfur compounds, including dipropyl disulfide, fructans	Antimicrobial, anti-inflammatory	Petroleum ether, methanol and aqueous extracts	[40-42]
10.	<i>Antrodia cinnamomea</i> (Fomitopsidaceae)	(Fungus) Fruiting bodies	Antrocamphin A, ergostane-type triterpenoids and polyacetylenes	Cancer, inflammatory disorders and antioxidant	Methanol extract	[43-44]
11.	<i>Butea frondosa</i> (Fabaceae)	Roots and leaves	Flavanoids, glucosides and lectins	Anti-inflammatory	Aqueous extract	[45-46]

12.	<i>Barringtonia racemosa</i> (Lecythidaceae)	Fruits, leaves	Diterpenoids and triterpenoids, lycopene, bartogenic acid	Anti-inflammatory, anti-tumor, anti-nociceptive, α -glucosidase inhibitory, anti-bacterial and anti-fungal	Hexane, ethanol and methanol, ethyl acetate	[47]
13.	<i>Boswellia serrata</i> Roxb. (Burseraceae)	Oleogum resin	Resin which is pentacyclic triterpenoid in nature in which boswellic acids (β -boswellic acid, acetyl- β -boswellic acid, keto- β -boswellic acid and acetyl-11-keto- β -boswellic acid)	Cancer, inflammation, arthritis, asthma, psoriasis, colitis and hyperlipidemia	Petroleum ether	[48]
14.	<i>Borassus flabellifer</i> L. (Arecaceae)	Male flowers (inflorescences)	Alkaloids, terpenoids, spirostane-type steroid saponins and phenolic compounds	Anti-inflammatory, anti-laprotic, diuretic, antiphlogistic, stomachic, sedative, laxative, aphrodisiac, immunosuppressant	Ethanol	[49]
15.	<i>Aegle marmelos</i> (Rutaceae)	Roots, leaves and fruits	Glycoside, alkaloids, coumarins, fatty acid and sterols, tannins, skimmianine, essential oil (mainly caryophyllene, cineole, citral, eugenol), sterols and or triterpenoids, including lupeol, β -sitosterol and α -amyrin, flavanoids (mainly rutin) and coumarins, including aegeline, marmesin and umbelliferone	Vata diseases, insomnia, seizures, and hysteria, for diarrhoea, dysentery, colitis, loss of appetite and abdominal dull pain, anti-inflammatory	Aqueous extract and alcoholic	[50]
16.	<i>Commiphora mukul</i> (Burseraceae)	Stem	Guggulsterones (E- and Z-stereoisomers) and gugulipid	Arthritis, obesity, and other disorders	Ethyl acetate	[51]
17.	<i>Calluna vulgaris</i> (Ericaceae)	Aerial parts	Kaempferol-3-O- β -D-galactoside, a common flavonol derivative	Anti-inflammatory and antinociceptive, antirheumatic, diuretic, astringent and treatment of urinary infections	Ethanol, chloroform, ethyl acetate, <i>n</i> -butanol and water, methanol	[52]
18.	<i>Cistus laurifolius</i> (Cistaceae)	Leaves	Favonoids; 3-O-methylquercetin (1), 3,7-O-dimethylquercetin (2) and 3,7-O-dimethylkaempferol	Inflammatory ailments including rheumatism and renal inflammations	Ethanol	[53]
19.	<i>Cardiospermum helicacabum</i> (Sapindaceae)	Leaves	Saponins, alkaloids, (+)-pinitol, apigenium, luteolin and chrysoeriol.	Anti-inflammatory activity	Alcoholic	[54]
20.	<i>Cyperus rotundus</i> (Cyperaceae)	Tubers	β -sitosterol, 1,8-cineole, 4- α ,5- α -oxidoeudesm-11-en-3- α -ol, alkaloids, alpha-cyperone, alpha-rotunol, beta-cyperone, beta-pinene, beta-rotunol, beta-selinene, calcium, camphene, copaene, cyperene, cyperenone, cyperol, cyperolone cyperotundone D-copadiene, D-epoxyguaiene, D-fructose, D-glucose, flavonoids, gamma-cymene, isocyperol, isokobusone, kobusone, limonene, linoleic-acid, magnesium, mnganese, mustakone, myristic-acid, oleanolic-acid, oleanolic-acid-3-o-neohesperidoside, oleic-acid, P-cymol, patchoulone, pectin, polyphenols, rotundene, rotundenol, rotundone, selinatriene, stearic acid, sugeonol, sugetriol	Anti-inflammatory, cervical cancer, liver, menstrual disorders, menstrual pain, as a digestive stimulant and for memory	Methanol	[55]
21.	<i>Cleome rutidosperma</i> (Capparidaceae)	Aerial parts	Alkaloids, steroids, flavonoids	Stimulant, antiscorbutic, anthelmintic, vesicant, rubifacient, carminative, antiplasmodial, analgesic, locomotor, antimicrobial, diuretic, laxative	90% Ethanol, petroleum ether, diethyl ether and ethyl acetate	[56]
22.	<i>Callophyllum innophyllum</i> (Clusiaceae)	Nuts	Xanthone dehydrocylogua-nadine, callophllin-B	Anti-inflammatory	Methanol	[57]
23.	<i>Ficus religiosa</i> (Moraceae)	Leaves, stem	Sterols, glycosides, tannins and amino acids	Laxative, diarrhoea, asthma, cough, earache, toothache,	Methanol, Aqueous	[58]

			bark		migraine, gastric problems, haematuria and memory enhancing activity		
24.	<i>Justicia gendarussa</i> (Acanthaceae)	Leaves		Sterols and flavonoids	fever, hemiplegia, rheumatism, arthritis, headache, ear ache, muscle pain, respiratory disorders and digestive troubles	Ethanol (95%)	[59]
25.	<i>Moringa oleifera</i> (Moringaceae)	Flowers, leaves		Nitrile glycosides, niazirin, niazirin, sterol components –stigmasterol, campisterol	Anti-arthritis	Hydroalcoholic extract	[60]
26.	<i>Nyctanthes arbortristis</i> (Oleaceae)	Leaves, stems		Nyctanthoside, polysaccharides, iridoid glycosides, henylpropanoid glycoside, β -sitosterol, β -amyryn, hentri-acontane, benzoic acid, glycosides	Sciatica, arthritis and anti-inflammatory	Alcoholic extract	[61]
27.	<i>Premna serratifolia</i> (Verbenaceae)	Wood		Iridoid glycosides, alkaloids, phenolic compounds and flavonoids	Cardiovascular diseases, skin diseases, inflammatory diseases, arthritis, gonorrhoea, rheumatism, anorexia and jaundice.	90% Ethanol	[62]
28.	<i>Pistacia khinjuk</i> (Anacardiaceae)	Leaf		Flavonoid; galloylated compounds, gallic acid, methyl gallate, quercetin-3-O- β -D-(4)C(1)-galactopyranoside (hyperin), myricetin-3-O- β -L-(1)C(4)-rhamnopyranoside (myricitrin), 1,6-digalloyl- β -D-glucose, 1,4-digalloyl- β -D-glucopyranoside, and 2,3-di-O-galloyl-(β /?)-(4)C(1)-glucopyranose (nilocitin)	Anti-inflammatory	Aqueous methanol	[63]
29.	<i>Phyllanthus emblica</i> syn. <i>Emblica officinalis</i> (Phyllanthaceae)	Leaves, bark or fruit		Flavonoids, kaempferol, ellagic acid and gallic acid; vitamin C and other antioxidants like emblicanin A, emblicanin B, punigluconin, pedunculagin	Hypercholesterolemic, rheumatoid arthritis and osteoporosis	Water	[64]
30.	<i>Rosa multiflora</i> Thunb. (Rosaceae)	Hips		Fatty acid, mainly including dodecanoic acid (8.72%), hexadecanoic acid (9.24%), pentadecanoic acid (1.58%), linoleic acid (26.04%), oleic acid (22.58%) and octadecanoic acid (6.3%)	Dietary and medicinal purposes like cold, flu, inflammation, osteoarthritis, rheumatoid arthritis and chronic pain	Ethanol, petroleum ether, ethyl acetate	[65]
31.	<i>Vitex negundo</i> (Verbenaceae)	Roots, bark, leaves, flowers		C-glycoside, casticin, essential oil, vitamin c, benzoic acid, flavone	Antiseptic, ophthalmic, anti-gonorrhoeic, depurative, anti-inflammatory	Ethanol, water	[66]
32.	<i>Vernonia anthelmintica</i> (Asteraceae)	Seeds, dried seeds, leaves and Roots		Alkaloids, flavonoids, steroids, triterpenes and polyphenols	Anti-inflammatory, anti-arthritis	Ethanol (99.9%)	[67]

CONCLUSION

A large number of number of plants described in this review clearly demonstrated the importance of herbal plants in treatment of rheumatoid arthritis and also to consider one of good source for a new drug or a lead to make a new drug.

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