

Natural products in treatment of rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic, progressive, sustained inflammatory autoimmune disease associated with articular, extraarticular, and systemic effects. It is characterized by synovial inflammation, hyperplasia, leading to destruction of articular cartilage, bone erosion, and ultimately permanent deformities. Conventional treatments for RA include non-steroidal anti-inflammatory drugs, disease modifying antirheumatoid drugs, corticosteroids, and biological agents. All these therapeutic agents are associated with one or more side-effects, and none of the available treatments are able to achieve the ultimate therapeutic goal, i.e., drug-free remission. Herbal remedies are alternative source to relieve symptoms in patients having RA as well as to overcome the drawbacks associated with present treatment methods. A study conducted by the World Health Organization had reported that about 80% of world's population relies on traditional medicine. More than 450 plants belonging to 100 families are used traditionally in management of arthritis. Some of the important natural compounds reported to exhibit anti-arthritis potential includes anthroquinone (*Aloe barbadensis*), withanolides (*Withania somnifera*), terpenes (*Zingiber officinale*, *Boswellia serrata*), polyphenols (*Camellia sinensis*), stilbene (*Vitis vinifera*, *Tripterygium wilfordii*). Although a number of herbal medicines are recommended for RA, further research is required to investigate their safety, efficacy, and potential drug interactions.

Key words: Disease modifying antirheumatoid drugs, Herbal medicines, non-steroidal anti-inflammatory drugs, remission, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA), a complex autoimmune inflammatory disorder, affects multiple joints of the body in a systematic manner.^[1] Initially, there is a chronic inflammation of synovial membrane which often leads to articular cartilage destruction, bone erosion, and permanent deformity.^[2,3] RA commonly affects the synovial-lined joints of feet, wrists, and knees, as well as cervical spine, shoulders, and hips.^[4] The destruction of cartilage and bones is due to proliferation of synovium membrane which results in formation of pannus, i.e., the hypertrophied synovium.^[5] Radiologic manifestations of such damage appear as loss of joint space and juxta-articular bone erosion. RA may have other systemic manifestations such as bone marrow alteration, comorbidities (pericarditis, osteoporosis, and lung disease), and psychosocial (depression and cognitive dysfunction) effects.^[6]

According to the World Health Organization (WHO), the prevalence of RA is estimated to be

0.5-1% worldwide, with women at three to five times more risk than men.^[7] RA can start at any age; however, the mean age of onset is 40-60 years. Furthermore, people suffering from RA have diminished functioning and shortened life expectancy up to 5-10 years; however, it also depends upon severity of disease and genetic factors.^[8]

Exact cause of the disease is not clear precisely but hormonal, genetic, and environmental factors are important contributors in the development of disease.^[9] RA is immune cell-mediated disease with progressive nature and is initiated and promoted by release of inflammatory

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cytokines by macrophages, B-cells, and T-cells.^[10] The various proinflammatory cytokines involved in articular cartilage destruction are tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, and transforming growth factor- β (TGF- β).^[11] Degrading enzymes secreted by fibroblast-like synoviocytes and macrophages play a key role in cartilage and bone destruction.^[6] Elevated levels of vasoactive amines, arachidonic acid metabolites, proinflammatory cytokines, and neuropeptides activate the RA synovium.^[11] McInnes and Schett reported production of autoantibody (rheumatoid factor and anti-citrullinated protein antibody).^[4] The HLA-DR4 allele is also an important genetic factor in development and severity of disease.^[7]

The current review presents detail discussion on various agents used for treatment of RA and role of herbal drugs in treatment and cure of RA.

DRUGS USED IN TREATMENT OF RA

The goals of currently used antirheumatic drugs are to reduce pain and swelling, delay the progression of disease, minimize the disability, and ultimately improving patient life and expectancy.^[12] Most of these objectives are achieved by combination of non-steroidal anti-inflammatory drugs, disease modifying antirheumatic drugs, corticosteroids, and biological agents. In addition to conventional therapies, some unconventional therapies such as superoxide dismutase, antisense oligonucleotide, boron neutron capture therapy, and radioisotopes have been explored for the management of arthritis.^[13] The various classes of drugs used for treatment of RA along with their molecular targets and complications have been summarized in the Table 1.

HERBAL PRODUCTS

Herbal products are being used worldwide for various ailments. A number of natural products including flavonoids, terpenes, quinones, catechins, alkaloids, anthocyanins, and anthoxanthins modulate inflammatory response and hence are considered as gold mine for treatment of RA. They act by multiple mechanisms such as suppression of TNF- α , IL-1 β , cyclooxygenase (COX), lipoxygenase (LOX), nuclear factor- κ B (NF- κ B), adhesion molecules, and metalloproteinases.^[25,26]

Curcumin

Curcumin (*Curcuma longa*) possesses various biological activities such as anti-inflammatory, hepatoprotective, antibacterial, antidiabetic, antidepressant, analgesic, and anticarcinogenic.^[27,28] The anti-inflammatory action of curcumin is attributed to inhibition of LOX, suppression of activation of NF- β , TNF- α , molecular adhesion, and inhibition of upregulation of matrix metalloproteinase (MMP-9) mRNA. It also promotes suppression of expression of TNF- α -induced MMP-13 in chondrocytes.^[29] Various *in vivo* and *in vitro* studies have been carried out to explore the antiarthritic potential of curcumin. *In vivo* evaluation of curcuminoid was found to reduce both acute and chronic inflammation by 75% and 68%, respectively.^[30] Oral administration of curcumin provides symptomatic relief in exercise-induced muscle damage due to its anti-inflammatory property.^[31]

Guggulosterone

Guggul is a common name for *Commiphora* species and contains a bioactive oleo-gum-resin which is responsible for various pharmacological activities. Gum contains various constituents such as guggulosterone [4,17(20)-pregnadiene-3,16-dione],

Table 1: Therapeutic agents used in RA and their complications

Pharmacological class (drugs)	Mechanism of action	Complications	References
NSAIDs (diclofenac, ibuprofen, indomethacin, ketoprofen, and naproxen)	COX inhibitors	Peptic ulcer, renal toxicity, liver damage, abdominal cramps, and CVS complications	[14,15]
DMARDs (methotrexate, leflunomide, chloroquine, and cyclosporine)	TNF- α and IL-17 signaling inhibitors	Tuberculosis, osteoporosis, cushing syndrome, leukopenia, and alopecia	[16-19]
Glucocorticoids (prednisone, triamcinolone dexamethasone, and cortisone)	Macrophage accumulation inhibitors	Osteogenesis, adrenal insufficiency, muscle atrophy, peptic ulcer, and cataract	[20]
Biologicals (infliximab, etanercept, golimumab, and tocilizumab)	IL and TNF- α inhibitors	Bacterial and fungal infection, non-Hodgkin lymphoma, myositis, hepatitis, and tuberculosis	[21-23]
Surgical treatment	-	Post-operative site specific infections, psychological disadvantages	[24]

NSAIDs: Non-steroidal anti-inflammatory drugs, remission, DMARDs: Disease modifying anti-rheumatoid drugs, TNF- α : Tumor necrosis factor- α , IL: Interleukin, COX: Cyclooxygenase, CVS: Chorionic villus sampling

diterpene, Gallic acid, and flavanoids. The resin has been used for the treatment of various types of ailments including cardiovascular disease, ulcer, diabetes, cancer, leprosy, obesity, and RA.^[32-34] Guggulosterone act by inhibiting MAP kinase, which further inhibit NF- κ B, and also by downregulating expression of cytokines such as IFN- γ , IL-12, IL-1 β and nitric oxide (NO).^[35] *In vivo* anti-inflammatory activity of guggulosterone was found to be comparable to phenylbutazone and ibuprofen in rats.^[36,37]

Resveratrol

Resveratrol (trans-3,4',5-trihydroxystilbene), a polyphenolic compound, has been found in various plants such as grapes, peanuts, mulberries, and rhubarb. It exhibits various health benefits such as antiaging, antioxidant, antihypercholesterolemic, antiarthritis, antidiabetic, antiviral, and neuroprotective.^[38] The role of resveratrol in treatment of joint disorder is due to suppression of NF- κ B, c-Jun N-terminal kinase (JNK)/extracellular signal-regulated kinase (ERK)-activator protein-1 (AP-1), iNOS-NO, COX-2-PGE₂, MMP-13, TNF- α , and IL-1 β genes.^[39,40]

Withanolides

Withanolides (Ashwaganda), obtained from extract of *Withania somnifera*, are reported to have analgesic, anti-inflammatory, antibacterial, immunomodulatory, anticancer, diuretic, antiulcer, antidiabetic, and antiarthritic properties.^[41] The *in vivo* antiarthritic potential of aqueous extract of *W. somnifera* roots was evaluated in rats and was found to reduce anticyclic citrullinated peptide antibody (a-CCP), collagen Type II antibody (a-CII), inflammatory marker such as C-reactive protein (CRP), lipid peroxidation, and glutathione-S-transferase activity.^[42] Withanolides also inhibit NF- κ B and NF- κ B-regulated gene expression. The clinical evaluation of *W. somnifera* extract at two different doses (250 mg, 125 mg) has been found to reduce inflammation significantly in dose-dependent manner and was devoid of any side effects.^[43]

Boswellic acid (BA)

BA (*Boswellia serrata*, Burseraceae), pentacyclic terpene, is found in plants in the forms of various derivatives such as acetyl-11-keto-BA and 11-keto-BA.^[44] Therapeutically BA and its derivatives are used in various ailments such as ulcerative colitis, cancer, hepatitis, inflammation, pain, cough, bacterial infection, and osteoarthritis.^[45] In pre-clinical evaluation, BA was reported to reduce cartilage loss, synovitis, and osteophyte formation and hence has beneficial role in osteoarthritis and other joint disorder.^[46] Clinical investigation of *B. serrata* extract was found to provide statistically significant improvement in patients suffering osteoarthritis and was well tolerated with minor gastric disturbance.^[47] The antiarthritic activity of BA is due to inhibition of NF- κ B, COX-2, LOX-5.^[48]

Procyanidine

Procyanidine (*Cinnamomum zeylenicum*, Lauraceae), a polyphenol derivative, has been explored in various pharmacological conditions such as atherosclerosis, diabetes, fungal infection, inflammation, alzheimer disease, and arthritis.^[49,50] Type-A procyanidine polyphenols are reported to have immunomodulatory and anti-inflammatory potential without analgesic activity in both *in vitro* and *in vivo* studies.^[51] In another study, *C. zeylenicum* extract was found to reduce inflammation and arthritis in rats by suppressing intracellular release of TNF- α in dose-dependent manner and; hence is an effective remedy for treating RA.^[52,53]

Shagoal

Conventionally, ginger (*Zingiber officinale*) is used in treatment of various diseases such as pain, arthritis, cough, hepatotoxicity, oxidative stress, and cardiovascular problems.^[54] The major phytochemical constituents of ginger are 6-,8-,10-gingerol, 6-,8-,10-shagaol and zingiberine.^[55] The antiarthritic activity of shagoal is due to suppression of IL-1 β , IL-6, TNF- α , and INF- γ .^[56,57]

The efficacy and tolerability of ginger in management of arthritis has been tested in patients with knee joint pain. Ginger powder exhibited significant reduction in arthritis index and visual analog scale scores and it is attributed to reduced production of NO and CRP.^[58,59] 6-shagoal is most potent antioxidant and anti-inflammatory agent among other shagaols and gingerols.^[60] Ginger essential oil, a secondary metabolite of ginger, also prevented chronic joint inflammation, and granuloma formation. The antirheumatic effect of ginger are not only due to phenolic compounds (gingerol and shagoal) but also attributable to secondary metabolites.^[61]

The chemical structures of some of the active constituents responsible for anti-inflammatory activity have been given in Figure 1.

Others

In addition to above-discussed natural products, several other herbal compounds are found to have antiarthritic activity. Clinical trials have been carried out with several natural products and their combination preparation. The anti-inflammatory activity of extract of ten herbs, including Japanese creeper, Chinese honeylocust spine, datchmanspipe herb, pubescent angelica, garden balsam, antonese buttercup, giant typhonium tuber, euphorbia, semen hyoscyami, and sesame oil was investigated in oxazolone-induced inflammation in mice. It has been observed that extract of these herbs has ability to reduce inflammation by inhibiting TNF- α level.^[25] Black sage, *Salvia mellifera*, is employed in form of topical preparation for treatment of pain associated

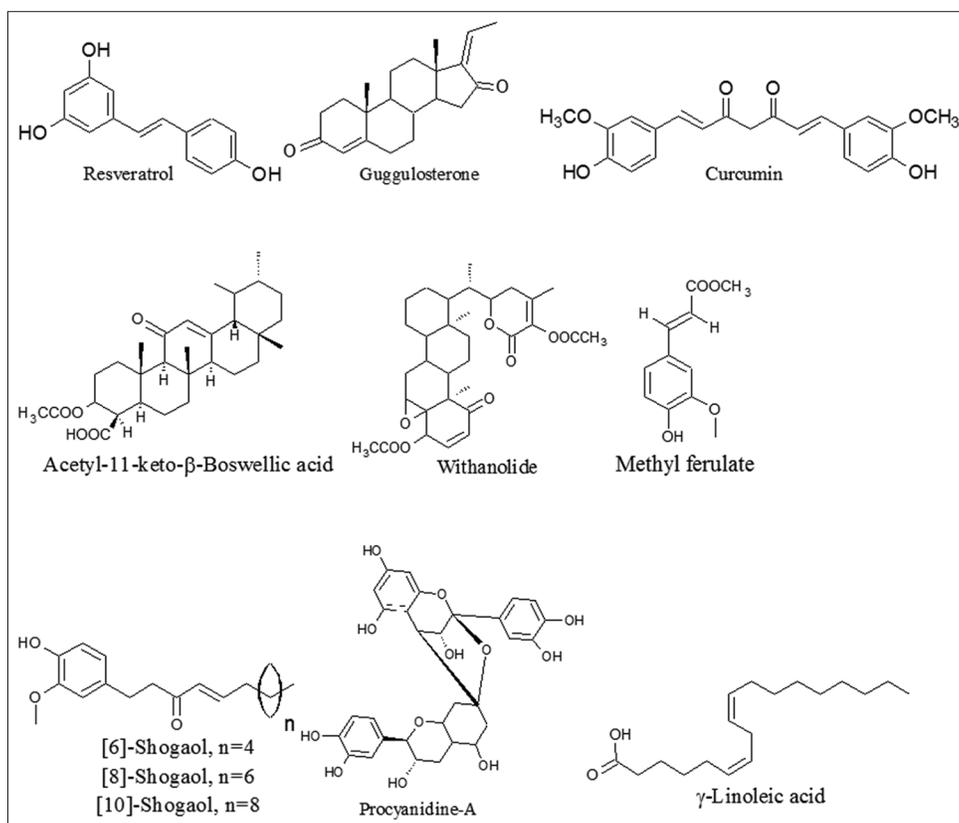


Figure 1: Chemical structures of active constituents having anti-inflammatory activity

with RA.^[26] Two clinical studies have been carried out to investigate efficacy of borage seed oil, *Borago officinalis*, for RA. The active constituent of *Borago officinalis* is γ -linolenic acid which is responsible for significant improvement in joint pain and swelling.^[62]

The antiarthritic potential of ethyl acetate fraction of chloroform extract of *Barleria prionitis* was investigated in formaldehyde-induced and Freund's complete adjuvant-induced chronic arthritis in rats. Significant inhibition of oedema formation in dose-dependent manner was observed.^[63]

The safety and efficacy of ethanol/ethyl acetate extract of *Tripterygium wilfordi* hook F were evaluated in rheumatic patients unresponsive to conventional therapy. A dose-dependent effect was seen in the rheumatic patients and the extract was well tolerated in therapeutic dosages.^[64,65]

Anti-inflammatory activity of active constituent, methyl ferulate (MF) from *Stemona tuberosa*, was tested by measuring cytokine release, NO generation, expression of COX-2, and protein kinase pathway. MF strongly inhibited release of proinflammatory cytokines IL-6, TNF- α , IFN- γ but has no effect on IL-10. MF is also a potent inhibitor of nitrogen activated kinase.^[66]

Therapeutic efficacy of petroleum ether extract of *Celastrus paniculatus* has been investigated in adjuvant-induced arthritis in rats. Arthritic severity was evaluated by arthritis

score, paw volume, joint thickness, knee flexion, body weight, and index of thymus and spleen and rate of motility. *C. paniculatus* alleviated arthritic progression due to significant suppression of overproduction of inflammatory cytokines, oxidative stress markers, and cellular enzyme levels.^[67]

The antiarthritic activity of three herbal extract, namely, modified Huo-luo-xiao-ling dan, *Celastrus aculeatus*, and green tea (*Camellia sinensis*) have been tested in adjuvant-induced arthritis in rats. The reduction in disease severity is due to inhibition of inflammatory cytokines such as IL-1 β , IL-6, IL-17, NO, MMP-9, monocyte chemotactic protein-1 (MCP-1), mediators of bone modeling (receptor activator of nuclear factor- κ B ligand (RANKL)) and TNF- α .^[68] The antiarthritic activity of various herbal products has been summarized in Table 2.

Even though, a large number of trials have been carried out with various natural products, they could not find clinical efficacy as in most of the cases comparison with standard drugs have not been made. Hence, more clinical trials should be carried out to access potential of herbal products in arthritis. In case of RA, comparison should be done with MTX because it is the first line of drug used for treating RA. In addition, the safety profile of natural products should be accessed in patients with significant adverse effects with conventional therapies. Moreover, identification of active constituent of herbal products could help in identifying better molecules.

Table 2: Herbal products having antiarthritic potential along with their molecular targets

Component	Family	Chemical class	Source	Target	References
Curcumin	Zingiberaceae	Diarylheptanoid	<i>Curcuma longa</i>	NF- β , TNF- α , AMs, MMP-9, TLR-9, IL-6, IL-8, COX-2, LOX	[29,30]
Guggulosterone	Burseraceae	Sterol	<i>Commiphora mukul</i>	IFN- γ , IL-12, IL-1 β , NO, NF- κ B, COX-2	[35]
Resveratrol	Melanthiaceae	Polyphenol	<i>Veratrum grandiflorum</i>	JNK, NF- κ B, TNF- α , 5-LOX, AMs COX-2, PGE ₂ , MMP-13	[39]
Withanolide	Solanaceae	Steroidal lactone	<i>Withania somnifera</i>	NF- κ B, COX-2, MMP-9, ICAM-1, α -CII, CRP	[42,43]
Boswellic acid	Burseraceae	Pentacyclic triterpene	<i>Boswellia serrata</i>	NF- κ B, COX-2, LOX-5, MMP-9	[48]
Procyanidin	Lauraceae	Monoterpenoids	<i>Cinnamomumzeylenicum</i>	TNF- α , COX-2, LOX	[53]
Shagoal	Zingiberaceae	Phenol	<i>Zingiber officinale</i>	IL-1 β , IL-6, TNF- α , INF- γ , NO, PGE2	[56,59]
Tea polyphenols	Theaceae	Polyphenol	<i>Camellia sinensis</i>	NF- κ B, COX-2, TNF- α , 5-LOX, AMs, MMPs	[69]
Ursolic acid	Lamiaceae	Pentacyclic triterpenoid	<i>Ocimumtenuiflorum</i>	TNF- α , IL-2, IFN- γ	[70]
Celastrol	Celastraceae	Penatcyclictriperpene	<i>Tripterygium wilfordii</i>	NF- κ B, COX-2, MMP-9, TNF- α , AMs	[67]
Myristicin	Apiaceae	Monoterpene	<i>Trachydiumroylei</i>	IL-6, IL-1 β , TNF- α , NO, PGE ₂	[71]
Linalool	Lamiaceae	Monoterpene	<i>Lavandula officinalis</i>	COX-2	[72]
Punicalagins	Punicaceae	Ellagitannins	<i>Punicagranatum</i>	TNF- α , IL-1 β , MCP1, iNOS, COX-2	[73]
Methyl ferulate	Stemonaceae	Methyl cinnamate	<i>Stemona tuberosa</i>	IL-6, TNF- α , IFN- γ	[74]
Shanzhiside methyl ester	Acanthaceae	Flavanoid	<i>Barleria prionitis</i>	COX-2, PGE ₂ , TNF- α	[63]
γ -Linolenic acid	Boraginaceae	Omega-6-fatty acid	<i>Borago officinalis</i>	COX-2, IL	[62]
Calycosin	Apiaceae	Isoflavone	<i>Angelica sinensis</i>	IL-6	[75]
Silibinin (Silymarin)	Asteraceae	Flavolignan	<i>Silybum marianum</i>	NF- κ B, COX-2, TNF- α , 5-LOX, AMs	[76,77]
Berberine	Berberidaceae	Benzylisoquinoline alkaloid	<i>Berberis vulgaris</i>	NF- κ B, COX-2, TNF- α , IL-6 IL-1 β	[78]
Quercetin	Amaryllidaceae	Flavonoid	<i>Allium cepa</i> (onions)	NF- κ B, COX-2, TNF- α , 5-LOX, TNF- α , IL-1 β , AMs, RANKL	[79]

NF- κ B: Nuclear factor- κ B, AMs: Adhesion molecules, MMP-9: Matrix metalloproteinase-9, LOX: Lipoxegenase, IFN- α : Interferon- γ , ICAM-1: Intracellular adhesion molecule-1

CONCLUSION

Although many conventional and non-conventional treatments for arthritis have been identified, all of these are associated with few limitations such as long-term efficacy, safety, and cost. Herbal remedies are alternative drugs to relieve symptoms in RA patients as well as to overcome the drawbacks associated with present treatment methods. A study conducted by the WHO had reported that about 80% of world's population relies on traditional medicine. More than 450 plants belonging to 100 families are used traditionally in the management of arthritis.

Plant-derived products are much promising agent for RA but still extensive investigation is required to prove their usefulness. Although a number of herbal medicines are recommended for RA, further research is required to investigate their safety, efficacy, and potential drug interactions.

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