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Rheumatoid arthritis – Pharmacology and its management with traditional herbs

Premanand A Nighojkar[*1], Munira Momin[2] & Suvarna P Phadatare[3]

[1]Faculty of Pharmacy, Pacific Academy of Higher Education and Research University, Udaipur-313 00, Rajasthan, India;

[2]SVKM's Dr Bhanuben Nanavati College of Pharmacy, Mithibai college campus, Vile Parle (W), Mumbai-400 056, Maharashtra, India;

[3]NCRD's Sterling Institute of Pharmacy, Mumbai University, Nerul, Navi Mumbai-400706, Maharashtra, India

E-mail: nighojkar.5683@gmail.com

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Rheumatoid arthritis (RA) is chronic, debilitating disease that follows a progressive course characterized by persistent inflammation and erosive joints damage leading to functional disability. The cause of rheumatoid arthritis remains unknown. Several disadvantages like serious side effects, high cost and requirement of parenteral administration still invite more research in this area to provide a convenient, affordable therapy with lesser or no side effects. The medicinal properties of plants have been investigated in the light of recent scientific developments throughout the world, due to their potent pharmacological activities, low toxicity and economic viability. The present review focuses on pharmacology of rheumatoid arthritis and traditional herbs which are potential candidate for treatment of rheumatoid arthritis. Due to effectiveness, safety, economical reasons herbal treatments will open doors for advanced research in treatment of rheumatoid arthritis.

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Rheumatoid arthritis (RA) is chronic, debilitating disease that follows a progressive course characterized by persistent inflammation and erosive joint damage leading to functional disability[1]. Rheumatoid arthritis is characterized by synovial inflammation and hyperplasia, autoantibody production, cartilage and bone destruction and systemic features, including cardiovascular, pulmonary, psychological and skeletal disorder[2].

Pathophysiology of rheumatoid arthritis

Many factors contribute for RA. There is persistent synovial inflammation and associated damage to articular cartilage and underlying bone. Inflammation associated with overproduction and over expression of tumour necrosis factor (TNF), which causes synovial inflammation and joint destruction, interaction between T&B lymphocytes, synovial-like fibroblasts, and macrophages which ultimately leads overproduction of cytokines like interleukin (IL)-6[3]. The dominant local cell populations in joints affected by RA are synovial and cartilage cells. Macrophages like synoviocytes and fibroblast like synoviocytes leads joint destruction. IgM and IgA rheumatoid factors are key pathogenic markers directed against the Fc fragment of IgG. Additional types of antibodies are those directed against citrullinated peptides. 50% of risk of developing RA is attributed to genetic factors[4].

Aetiology of rheumatoid arthritis

The cause of RA remains unknown. It has been suggested that RA might be manifestation of the response to an infectious agent in a genetically susceptible host. A number of possible causative agents have been suggested, including Mycoplasma, Epstein-Barr virus (EBV), cytomegalovirus, parvovirus, and rubella virus, but convincing evidence that these or other infectious agents cause RA has not emerged.

Signs and symptoms of RA

In RA pain, swelling and tenderness poorly localises to joints. Morning stiffness, weakness, easy fatigability, anorexia and weight loss are also seen in inflammatory arthritis. RA causes symmetric arthritis with characteristics like proximal interphalangeal and metacarpophalangeal joints. Persistent inflammation attributes pathogenic events like laxity of supporting soft tissue, damage of ligaments, tendons and joint

*Corresponding author

capsule, cartilage degradation, muscle imbalance. Extra articular findings may include; gradual appearance of rheumatoid nodules(subcutaneous, round or oval), non-tender masses, leg ulcers, and multiple systemic complications from infiltration of immune complexes and subsequent tissue damage and necrosis in the vasculature, pericarditis, pulmonary nodules or fibrosis, pleuritis, or inflammation of the sclera and overlying tissue of the eye peripheral neuropathy with numbness or tingling in the feet or weakness and loss of sensation in the fingers from infiltration of the nerve fibres, stiff, weak, or painful muscles secondary to limited mobility and decreased use[5].

Treatment options for RA

The primary aim of the treatment is reduction of pain and inflammation, maintenance of joint mobility, and prevention of deformity.

I) Disease modifying anti-rheumatic drugs (DMARD)

1. Immunosuppressant's: Methotrexate, Azathioprine, Cyclosporine
2. Sulfasalazine
3. Purine/pyrimidine inhibitors: Azathioprine, 6-Mercaptopurine, Mycophenolate mofetil, Leflunomide
4. Gold sodium thiomalate, Auranofin
5. d-Penicilamine
6. Alkylating agent: Cyclophosphamide, Chlorambucil
7. Calcineurin inhibitors and macrolite regulators: Cyclosporine, Tacrolimus (FK 506), Sirolimus (Rapamycin)
8. Glutamic acid derivatives: Thalidomide[3-6]

II) Biological response modifiers (BRM)

1. TNF-α inhibitors: Etanercept (Enbrel), Infliximab (Remicade), Adalimumab (Humira)
2. IL-1 antagonist: Anakinra (Kineret)[4-6]

III) Antibiotics

Sulphone antimicrobials, Tetracyclines, Chloroquine or Hydroxychloroquine

IV) Anti-metabolite hormones

Corticosteroids: Cortisone acetate, Dexamethasone, Prednisone, Triamcinolone.

V) Non steroidal anti-inflammatory drugs (NSAID)

Salicylates: Aspirin and derivatives, Celecoxib, Rofecoxib

Long term use of corticosteroids carries serious disadvantages. Therefore, either low doses are used to supplement nonsteroidal anti-inflammatory drugs (NSAIDs) or high doses are employed over short period in cases with severe systemic manifestations while the patient awaits response from a remission inducting drug[3-6].

Traditional/herbal medicine for rheumatoid arthritis

The medicinal properties of plants have been investigated in the light of recent scientific developments throughout the world, due to their potent pharmacological activities, low toxicity and economic viability. In this article, we have compiled some medicinal plants which have great potential to treat RA. Most researchers worked with these plants and found to be effective and they are using these plants with different dosage forms, routes with combinations to treat RA.

***Boswellia serrata* Roxb. ex Colebr.**; Family: Burseraceae; Local name: *Shallaki*

The oleo-gum-resin and the bark are usable parts of *B. Serrata.* The volatile oils contain alpha thujene and p-cymene. The main constituents of *Boswellia serrata* are β-Boswellic acid, 3-O-acetyl β (ABA), 11-keto-β-boswellic acid, and 3-O-acetyl-11-keto-β-boswellic acid (AKBA) collectively called Boswellic acids. *Boswellia* decreased polymorph nuclear leukocyte infiltration, migration, decreased primary antibody synthesis, and almost totally inhibited the classical complement pathway[7]. In the clinical study of formulation containing *Boswellia serrata* on patient with rheumatoid arthritis (RA) shows greater relief of pain, decreased morning stiffness, decreased in Ritchie articular index and joint score, reduced levels of pro inflammatory mediators, increased level of intrinsic factor (IF-10), decreased arthritis scoring, bone histology, reduced level of β-glucuronidase, lactate dehydrogenase[8-11].

***Curcuma longa* L.**; Family: Zingiberaceae; Local name: *Haldi*

Turmeric is a medicinal plant extensively used in *Ayurveda*, *Unani* and *Siddha* medicine as home remedy for various diseases. Active constituents are curcumin (curcumin I), desmethoxycurcumin (curcumin II), bisdesmethoxycurcumin (curcumin III), and dihydrocurcumin[12]. Experimental antiarthritic activity shown by inhibition of the expression of cyclooxygenase (COX)-2, reduction of PGE_2,

preventing the activation on nuclear factor-kB (NF-kB) [13]. Studies carried out for antirheumatic activity showed absence of side effect, efficient, safe to use, suppress the fibroblast-like synoviocytes proliferation and DNA synthesis induced by platelet-induced growth factor[14-17].

***Zingiber officinale* Roscoe**; Family: Zingiberaceae; Local name: *Adrakh*

Ginger having ginger oil is constituted of monoterpene hydrocarbon, sequiterpene hydrocarbons, oxygenated mono and sequiterpenes, and phenyl propanoids. It shows anti-inflammatory effect by blocking the activities of both COX-1 and COX-2, suppressing leukotriene biosynthesis, IL-1β expression[18, 19]. Study carried out on rats and patients with RA on treatment with ginger shows effectiveness against RA and symptoms like inflammation, joint mobility, pain, morning stiffness related to it[20,21].

***Tripterygium wilfordii* Hook. f**.; Family: Celastraceae; Local name: *Three-wing-nut* or thunder god vine

Extracts of the roots of the medicinal vine *T. wilfordii* have shown therapeutic promise in treating autoimmune and inflammatory conditions. Three diterpenoids- triptolide, tripdiolide and triptonide are the most abundant and account for immunosuppressive and anti-inflammatory effect both *in vitro* and *in vivo* studies. Triptolide inhibit gene expression of IL-1α, IL-1β, TNF-α, and IL-6, as well as the production of IL-1β and IL-6, also inhibit production of COX-2, but not those of COX-1. Triptolide decreased viability, inhibited proliferation, and induced apoptosis of rheumatoid synovial fibroblasts in a concentration dependent manner, inhibit transcription of the inducible nitric oxide synthase (iNOS) gene. Randomized, controlled trial study was found well tolerated and significant in most patients[22-25].

***Withania somnifera* (L.) Dunal;** Family: Solanaceaea; Local name: *Ashgandh*

Ashwagandha is medicinal plant widely found in India and North America. Among the various alkaloids, withaninne is main constituent. Withanolide extracted from *Withania somnifera* can indeed inhibit the activation of nuclear factor-kB (NF-kB) which regulates gene expression which could explain their ant arthritic action. It has molecular targets NF-kB, COX-2, matrix metalloproteinase (MMP-9) and intercellular adhesion molecule (ICAM-1)[26]. *W. somnifera* root powder shows β-glucuronidase and lactate dehydrogenase levels reverted to near normal, reduced amplification and propagation of the inflammatory response without gastric damage[27].

Borage seed oil

Borage seed oil is extracted from the seeds of *Borage officinalis* (*Borago officinalis* L.; Family: Boraginaceae; local name: *Gojiva*). It contains about 25 % gamma linolenic acid (18:3n-6), GLA. Based on recent research, Kast *et al*.[28] hypothesized that borage oil's anti-inflammatory effects may be due to the gamma-linolenic acid component of borage oil, which suppresses tumour necrosis factor-alpha synthesis by increasing prostaglandin E and cyclic adenosine monophosphate (cAMP) levels. There are two double blind, placebo controlled trials of borage seed oil in RA, lowering of RA disease activity by daily oral administration of 1.4 gm and 2.8 gm of GLA were documented. Gamma-linolenic acids used in the study well tolerated and effective treatment for active rheumatoid arthritis[29].

Cat's claw

The two most prevalent species of cat's claw, *Uncaria tomentosa* (Willd. ex Schult.) DC. (Family: Rubiaceae; local name: *Una de Gato*) and *Uncaria guianensis* (Aubl.) J.F.Gmel. (Family: Rubiaceae) are used interchangeably in traditional medicine for their anti-inflammatory properties. Although the main active ingredient is not known, the anti-inflammatory activity of it may be due to multiple secondary metabolites working in synergy. For example, quinovic acid glycosides found in the bark and root have been documented to be the most potent anti-inflammatory constituents. Additionally, the steroidal fraction of it has shown the presence of β-sitosterol (60 %), stigmasterol, and campesterol all which have moderate anti-inflammatory activities. The anti-inflammatory activity appears to involve suppression of TNF-α synthesis, as well as the secretion of nitric oxide and interleukins[30, 31]. Small preliminary study show relative safety and modest benefit to the tender joint count of a highly purified extract from pentacyclic chemotype of *Uncaria tomentosa,* i.e., cat's claw in patients with active rheumatoid arthritis taking sulfasalazine or hydroxychloroquine[32].

Rose hip

It is incompletely ripe fruit of various species of rosa, including the common dog-roses *Rosa canina* L. (Family; Rosaceae; local name: Dog-rose and downy

leaved roses (*Rosa mollis*). They contain phenolic acids, proanthocyanidins, tannins, flavonoids, unsaturated and polyunsaturated fatty acids, phospholipids. In a particular, a galactolipid isolated from rose hip has been proved to inhibit chemotaxis of human peripheral blood neutrophils, linoleic and alpha-linolenic acids from rose hip exhibit COX-1 and COX-2 inhibitory activities *in vitro*, three triterpene acids also display COX and lipooxygenese inhibitory properties[33]. Randomized, double blind, placebo controlled trial on patients with RA may benefit from additional treatment with rose hip[34,35].

Willow bark

Willow bark (Family: Salicaceae) extracts have been used as source of willow from species of *salix purpurea* (purple willow), *Salix fragilis* (crack willow), *Salix alba* (white willow), *Salix daphnoids* (violet willow) and *Salix pentandra* (bay willow). These salix species are also considered the natural source of acetylsalicylic acid, also known as aspirin. It contains an ingredient called salicin, which is transformed in the body into another chemical substance called salicylic acid. Similar to acetylsalicylic acid reduces the production of certain prostaglandins in the nerves and this relives pain and discomfort[36]. Effective and safe open, randomized studies carried out on patients with RA using willow extract[37,38].

Cannabis

Cannabis sativa L. (Family: cannabinaceae or Moraceae; local name: *Marijuana*) comprises 15–20 % of resin (present in glandular trichomes) which contains the major active euphoric principle 1-3-4 trans tetra hydrocannabinol (commonly known as Δ^1 THC). The resin also contains cannabinol, cannabidiol, cannabidiolic acid, cannabichromene and cannabigerol. Several studies showed that cannabinoids down regulate cytokine and chemokine production and in some models, upregulate T-regulatory cells (Tregs) as a mechanism to suppress inflammatory responses[39]. In randomized, double blind, parallel group study in 58 patients over 5 weeks of treatment, significant analgesic effect and suppressed disease activity with no adverse effect related withdrawals or serious adverse effects in the active treatment group by Sativex treatment[40].

Other herbal drug used for RA

Researchers carried out studies on extract of *Aloe vera*, black pepper, black cohosh, milkweed, banyan tree, *Deodar cedar*, barringtonia, mango, *Tinospora gluancha*, night jasmine, chaste tree, *abuta*, *aginbuti*, black *adusa*, *kindal* tree, headache tree, clearing nut tree, ashok, myrobalam, *colchicum luteum*, *arthosansar* a polyherbal formulation, green and black tea and many *Siddha* drugs found potential candidate for treatment of rheumatoid arthritis[41].

Japanese traditional herbal *Kampo* medicine, which is covered by national health insurance, is applied as an alternative treatment for serious diseases such as RA. These formulae usually contain components from several medicinal plants that are thought to exert anti-inflammatory and immune regulator effects and are effective for treating RA[42-44]. *Kampo* shows it safe and well tolerated and effective with clinical and economic benefits. Patients with rheumatoid arthritis were successfully treated with traditional herbal medicine *Kampo* and demonstrated a decrease in their serum level of anti-cyclic citrullinated peptide antibodies and rheumatoid factor[45,46].

Other complementary therapies in treatment of RA include acupuncture, thermal baths, bath salts (deadsea), cognitive behavioural treatment, food intolerance, food supplements, hypnosis, laser therapy, *yoga*, etc.[47]

Animal drugs used for RA

Fish oil

Fish oil, i.e., fish body oil (made from tissue of fatty fish like sardines, sprat, salmon and mackerel) and/or fish liver oil (made by pressing the cooked liver of halibut, shark or most commonly cod) rich in vitamin A&D, omega-3-essential fatty acids which have strong anti-inflammatory properties. Firstly they significantly reduce the release of several proinflammatory elements from leucocytes. Secondly they form building blocks for prostaglandins[48,49]. Randomized, double blind, prospective study of dietary supplementation was found to be effective in suppressing clinical symptoms of RA[50,51]. Medicinal cod liver oil is a fixed oil prepared from the fresh liver of the cod fish of different *Gadus* species (Family: Gadidae). Its medicinal value is due to vitamin A and D. The oil contains glyceryl esters of oleic, linoleic, gadoleic, myristic, palmitic and other acids. It also contains 7% eicosapentaenoic acid and 7 % docosahexanoic acid which are omega-3- fatty acids. Dual centre, double blind, placebo controlled, randomized study for 9 months on 97 patients with RA, 10 gm of cod liver oil containing 2.2 gm n-3

essential fatty acids or air filled placebo capsule given and found to be effective by more than 40 % of patients without any worsening of their disease activity and risks associated with NSAIDs use[52,53].

Conclusion

The major benefit of using herbs and other natural products lies in their limited or no undesirable side effects. Numerous treatments for various forms of arthritis have been identified, researchers has to take initiative for application of traditional herbs to treatment of RA. Plant derived products offer much promise but they require extensive investigation in various preclinical and clinical setting to prove their usefulness. Those herbs shows good result in preclinical and clinical studies should be promoted to next level of investigation so that more and more patients get benefited to recover from RA. Novel approaches will enhances the effectiveness, safety, bioavailability, drug targeting, reduces side effects so as to become preferred choice for treatment of RA.

Conflict of interest

The authors confirm that this article content has no conflict of interest.

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