

Recent Advances in Indian Herbal Drug Research

Guest Editor: Thomas Paul Asir Devasagayam

Indian Herbal Medicines: Possible Potent Therapeutic Agents for Rheumatoid Arthritis

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Received 18 October, 2006; Accepted 11 December, 2006

Summary Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology and is mainly characterized by the progressive erosion of cartilage leading to chronic polyarthritis and joint distortion. Although the exact pathogenesis of the disease has yet not been elucidated, however, studies suggest that cellular proliferation of synoviocytes result in pannus formation which damages the cartilage and bone. Recent reports also support the role of free radicals in its pathogenesis. Apart from the conventional treatment strategies using nonsteroidal anti-inflammatory drugs, disease modifying antirheumatic drugs and glucocorticoids, newer and safer drugs are continuously being searched, as long term usage of these drugs have resulted in adverse effects. Alternative medicine provides another approach for treatment of RA and currently a number of medicinal plants are under scientific evaluation to develop a novel drug. There is a dire need to investigate the complete therapeutic potential and adverse effects, if any, of these herbals for providing newer and safer treatment options with minimum side effects. In this review we have tried to explore various Indian ancient Ayurvedic, Unani and Tibbi, as also some Chinese and Korean, herbals for their potential to treat RA.

Key Words: rheumatoid arthritis, alternative medicine, Indian herbal, free radical, cytokine

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disorder which mainly affects the diarthrodial joint. It has societal effect in terms of cost, disability, and lost productivity. However the pathogenesis of disease is not well understood. Efforts are being made to understand the cellular and molecular mechanism for the pathogenesis of RA. It has been reported that proinflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , and IL-6 are important mediators of the disease perpetuation. Moreover, there are also reports that free radical generation worsens the disease and contribute towards damage to bone and cartilage. Immune cells such as T cells also impart their role in the progress of the disease. Apart from the conventional treatment strategies using nonsteroidal anti-inflammatory drugs (NSAIDs), disease modifying antirheumatic drugs (DMARDs) and glucocorticoids newer and safer drugs are continuously being searched, as long term usage of these drugs have resulted in the hepatic and gastrointestinal disorders. Alternative medicine is another therapeutic approach for treatment of the disease, which include herbal and folklore medicines. Many plants and plant products are under scientific exploration to develop a novel therapeutic agent. Here we have tried to review mainly various Indian ancient Ayurvedic, Unani and Tibbi, as also some Chinese and Korean, medicinal plants for their potential to treat RA.

Rheumatoid Arthritis: An Immunological Insight

RA is a chronic, autoimmune and systemic inflammatory disease which targets synovial joints [1]. Its prevalence is estimated at 2.5–3% in the adults above 50 years of age. Despite significant gains in knowledge of the immunopathology, the exact etiology of RA remains uncertain [2]. The genetic basis for RA is rather complex. It has been reported that RA does not aggregate in families with very high frequency [3]. In addition, the concordance rates in identical (monozygotic) twins are relatively low (12–15%) [4]. However, human leukocyte antigen (HLA) association supports the hypothesis that genetic factors are important for susceptibility to RA.

Joint damage occurs very early in RA [5]. Among the prominent symptoms pain, joint swelling, stiffness, deformity and weight loss are common, while palpation tenderness, synovial thickening, erythema, warmth and decreased mobility are the articular characteristics. An inflamed synovium is central to the pathophysiology of RA. The synovial tissue of patients with RA is characterised by mononuclear cell infiltration, neovascularisation and proliferation of synovial fibroblasts [6]. Synovial vessel endothelial cells transform into high endothelial venules early in the course of the disease. The formation of locally invasive tissue ‘pannus’ takes place,

which is an important characteristic feature of rheumatoid joint. This ‘pannus’ consists of mononuclear cells and fibroblasts with the expression of matrixmetalloproteinases, which later on turns into fibrous pannus comprising of vascularised layer [7]. It has been speculated that perpetuation of inflammation is associated with the production of pro-inflammatory cytokines [8]. Inflammatory cytokines are essential mediators in the pathogenesis of RA. IL-1 β and TNF- α are the principal mediators of tissue destruction in RA. These two cytokines induce, in synergy, the production of high levels of matrixmetalloproteinases by synovial cells and chondrocytes [9].

Association of Free Radicals with RA

In recent years, there are growing evidences of possible role of highly reactive products of oxygen and nitrogen termed as free radicals [10], in the pathogenesis of RA as well as other degenerative diseases [11, 12]. These reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced endogenously during aerobic metabolism and at the site of chronic inflammation. ROS such as super oxide radical, hydroxyl radical and hypochlorous acid contribute significantly to tissue injury in RA [13]. Several mechanisms are involved in the generation and action of ROS in the joint of RA patient, including increased pressure in synovium cavity, reduced capillary density, vascular changes and increased metabolic rate of synovial tissue. In addition activated leukocytes also produce ROS [14]. Super oxide radical and hydrogen peroxide do not directly damage the majority of biomolecules, they are converted into the highly reactive hydroxyl radicals, which reacts with almost all molecules in living cells. ROS can directly or indirectly damage basic articular constituents and lead to the clinical expression of the inflammatory arthritis [15]. Synovial cavity damage correlation with fluctuating oxygen pressure in the joint, overproduction of ROS, lack of oxygen-processing enzymes and free radical-scavenging molecules have been reported in RA [16]. RA patients have an increased plasma conjugated dienes and significantly decreased vitamins E and A levels, which increases oxidative stress and damages tissue [17, 18]. Moreover, there is growing evidence that oxidative stress exacerbates inflammation and worsens joint tissue [19].

Normal equilibrium between ROS production and anti-oxidant system of the cell is disturbed due to oxidative stress, thus resulting in the damage to vital cell components such as proteins, DNA and membrane lipids. There are number of reports depicting that ROS plays a major role in the inflammation and related diseases. There are several studies demonstrating increased levels of malondialdehyde in the RA patients [20]. Significant decrease in the activities of catalase has also been reported in RA patients. Similarly,

glutathione reductase activities also get disturbed in the synovial fluid of patients [21]. Moreover, the levels of thioredoxine, which is a marker of oxidative stress, are significantly higher in synovial fluid of RA patients. Findings of McInnes *et al.* 1996, reveals that production of nitric oxide (NO) is upregulated in arthritic tissue [22].

Treatment Strategies

In the past decade, there has been a transformation in the treatment of RA in terms of approach and choice of drugs too. Previous treatment strategies involved initial management by NSAIDs for several years. NSAIDs have represented an effective therapy for treating RA by eliciting their effects by inhibiting cyclooxygenase activity and blocking the downstream production of prostanoids and eicosonoids. The advantages of early management of rheumatoid arthritis with DMARDs were not well recognized, until recently, and treatment options were limited to mono- or combination therapy with a relatively restricted therapeutic armament. DMARD therapy showed decrease in the markers of inflammation such as erythrocyte sedimentation rate and swollen joint counts. The combination therapy comprises immunosuppressives and DMARDs. This may exacerbate the potential for hepatic enzyme disturbances. Additional side-effects include weight loss, diarrhea, skin rash and alopecia [23].

Although the recent years have brought new information for the researchers and clinicians, but the treatment of RA still remains a challenge. Cytokine research has led to idea for the use of anti-cytokine therapy for the treatment of RA. Etanercept (recombinant form of the p75 TNFR-II) and Infliximab (monoclonal antibody directed against TNF- α) were the first biological response modifiers approved for the treatment of RA in the year 1992 [24, 25]. Both drugs have been designed to bind with TNF- α and decrease its bioavailability. Apart from all the above described treatment approaches scientists are now trying to cure RA using gene therapy, but it is still not fully explored.

Alternative Approach

Because of the limitations and risks of conventional therapy, people are exploring alternative measures to treat the disease. Commonly used alternative approaches include dietary modifications, nutritional supplements and botanicals. The response to these treatments varies from patient to patient. Alternative treatments have been used both as adjunct and an alternative to conventional therapy. Most of the treatments are relatively free of side effects [26].

Herbal Therapies

Herbal medicine provides a foundation for various traditional medicine systems worldwide. Today, these herbs contribute approximately 25% of currently used crude drugs and another 25% is derived from chemically altered natural products [27]. Herbal therapies occupy a large section of alternative therapy. India, along with its wealth, is rich in wide variety of medicinal plants, a large number of popular remedies many of which are in common use even today. More than 2000 plants of medicinal value are mentioned in Indian ancient Ayurvedic, Unani and Tibbi systems of medicine [28]. We have also carried out a number of studies on possible intervention of herbal preparations with diabetic and arthritic conditions in experimental animals [29, 30].

Ginger (*Zinziber officinalis*, Zinziberacea) has been used for centuries in Indian ayurvedic medicine and traditional medicine system as an anti-inflammatory agent. It is cultivated all over tropic and subtropical Asia and 50% of the world's harvest is produced in India. Five constituents of ginger have been identified as inhibitors of prostaglandins. Another constituent of ginger, gingerol inhibited lipopolysaccharide (LPS) induced inducible nitric oxide synthase (iNOS) expression and production of NO *in vitro* [31]. According to a study, oral administration of ginger oil suppressed the induction of adjuvant induced inflammation [32].

Similarly, Pineapple has also been used as a medicinal plant after its recognition in late 18th century. Bromelain, an extract of pineapple stem, has been reported to possess anti-inflammatory property. It is a general name for a family of sulfhydryl proteolytic enzymes obtained from *Ananas comosus*, the pineapple plant. Active components of bromelain are peroxidase, acid phosphatase, several protease inhibitors. When bromelain was tried with RA patients, 72% of total patients reported reduced swelling and pain [33].

Turmeric (*Curcuma longa*), is commonly used in Chinese and Indian (Ayurvedic) medicine system, possess curcumin which is an active anti-inflammatory component. It is a perennial plant, grows 3 to 5 feet high in the tropical regions of Southern Asia. The rhizome, the root, of curcuma is used in medicinal and food preparations. Curcumin is the main active component of this herb, and exhibits antioxidant properties. Significant improvement in morning stiffness, walking time and joint swelling have been observed as anti-arthritic effects after regular curcuma consumption by RA patients [34].

Harshingar (*Nyctanthes arbor tristis* Linn., NAT) has been used widely as a decoction for the treatment of arthritis and sciatica in Indian ayurvedic system of medicine since centuries. The plant has its origin from the Bengal region of India while it is distributed all over sub tropical regions of country. Arbostrisoides, nyctanthic acid, and crocetin are the main active principals of NAT. Water soluble ethanolic extract

of NAT leaves have been reported to reduce significantly the levels of inflammatory cytokines (IL-1, TNF- α) in experimental arthritis [35].

Chirayita (*Swertia Chirayita*), a herb found abundantly in the temperate regions of Himalaya, is commonly used for chronic fever, anemia and asthma. The plant inhabits the pastures and slopes of the Himalayas and ranges upto the height of 3,000 metres. Chirayita comprises of swerchirin, swertanone and swertianin, as active components responsible for the anti-inflammatory activity. Chirayita is reported to reduce the elevated levels of IL-1 β , TNF- α and IL-6 (Pro-inflammatory cytokines) in experimental arthritis as well as in asthmatic conditions [36].

Saffron (*Crocus sativus*, Iridaceae) is commonly used as folk medicine for various purposes such as aphrodisiac, antispasmodic and expectorant. It is a perennial flowering plant with very less growing height upto 40 cm. Commonly cultivated in the Kashmir and ranges to Northern America, Greece and Spain. Saffron stigma possesses anti-inflammatory action due to presence of crocetin and carotenoids. Aqueous and ethanolic extracts of saffron petals exhibit radical scavenging as well as anti-inflammatory effects in xylene and formalin induced inflammation [37].

Karvi (*Strobilanthus callosus*, Acanthaceae), another Indian medicinal herb, commonly found in the Maharashtra state has been used by the local tribals for the treatment of inflammatory disorders. The Lupeol and 19 α -H Lupeol isolated from the roots of *Strobilanthus callosus* have demonstrated the anti-inflammatory as well as anti-rheumatic activity in carrageenan induced oedema [38].

Trewia polycarpa Benth (Euphorbiaceae) roots are also used in Indian Ayurvedic medicine for the treatment of rheumatism, arthritis and gastritis [39]. Two Indian species viz. *Trewia nudiflora Linn.* and *Trewia polycarpa Benth* are common. No toxicity has been observed after oral administration of alcoholic extract at different dose to wistar rats, also superoxide dismutase, glutathione peroxidase activities were found to be elevated thus indicating the free radical scavenging property [40].

Madimadi, a Korean folk medicine, is a kind of fermented alcohol prepared from water extracts of herbal medicines. It has also been used for the treatment of RA since long time by the natives of the Korea. Madimadi had inhibitory effects on pro-inflammatory cytokine, and dose dependently inhibited TNF- α , IL-1 β and IL-8 production in RA patients. Madimadi also downregulates the TNF- α and IL-1 β [41].

Among the Chinese traditional medicine system, 'Thunder God Vine' (*Tripterygium wilfordii* Hook F, TwHF) occupies the foremost place for the treatment of autoimmune and inflammatory diseases such as RA, systemic lupus erythematosus, psoriasis etc. It is a perennial vine like plant growing in southern China and Taiwan. Triptolide is the main active component which imparts the anti-inflammatory

and free radical scavenging potential. Dose dependent studies of ethyl acetate extract of TwHF roots have in symptomatic improvement in 50% of RA cases during the first 4 weeks of treatment. Suppression of adhesion molecules like E-selectin, intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) contribute for the anti-inflammatory action of the TwHF extract [42]. Inhibition of iNOS expression by TwHF extract downregulates nuclear factor-kappa B (NF- κ B) DNA binding activity and results in the ROS scavenging [43].

Another Chinese folk medicine *Shiraiia bambusicola* has long been utilized in the treatment of RA. The active component of *Shiraiia bambusicola*, Shiraiachrome A, significantly inhibits the proliferation, migration, and angiogenesis by blocking growth factor-stimulated autophosphorylation of receptor tyrosine kinases in diseased synovium [44]. Another Chinese herbal medicine Qin Jiao (*Gentiana macrophylla*, Gentianaceae) is also reported to be used in the treatment of diabetes, paralysis and rheumatism. It has been reported that roots of *Gentiana* have anti-inflammatory effect in RA patients, which is quite comparable to Prednisone, a conventional drug used to treat RA [45].

Conclusions

RA is a debilitating disease usually manifesting as inflammation of multiple joints. Severity of the disease ranges from minor pain to joint deformity. While the cause of the disease is still not known completely, the treatment includes the NSAIDs and DMARDs. However, the biologic response modifiers are available in the market but still under critical examination for their effects in RA patients. With increasing awareness, a large section of RA patients have started adopting the alternate therapeutic measures. There is a need for screening and scientifically evaluating number of known ancient Indian Ayurvedic and Unani medicinal plants for providing newer and safer treatment options with minimum side effects.

Acknowledgments

Authors are thankful to Indian Council of Medical Research, New Delhi, India for financial support vide sanction no. 3/1/2/1/ortho-2003 NCD-I.

Abbreviations

RA, rheumatoid arthritis; IL-1 β , interleukin-1 beta; IL-6, Interleukin-6; TNF- α , tumor necrosis factor alpha; NSAIDs, Non-steroidal anti-inflammatory drugs; DMARDs, disease modifying anti-rheumatic drugs; ROS, reactive oxygen species; RNS, reactive nitrogen species.

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