

Ayurvedic Medicine for Rheumatoid Arthritis

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Abstract Ayurvedic medicine is the traditional medicine of India, which originated over 5,000 years ago. Parts of this alternative medical system have become increasingly popular worldwide as patients seek approaches to medical care that they perceive as more holistic and less toxic than those offered by conventional Western medicine. Despite the advent of highly effective pharmacologic therapy, most individuals with rheumatoid arthritis (RA) continue to use alternative therapy at some point in the treatment of their disease. This report discusses some of the in-vitro data that suggest potential mechanisms through which Ayurvedic herbal medicines might have beneficial actions in rheumatoid arthritis, and the available clinical data evaluating the use of Ayurvedic medicine for RA.

Keywords Ayurvedic medicine · Rheumatoid arthritis · RA · Treatment

Introduction

Patients with rheumatoid arthritis have benefited greatly from recent advances in drug development that have led to the widespread use of targeted biological therapy. Yet patients continue to seek alternatives to these medications, in response to their cost, availability, and the possibility of side effects [1]. Herbal medicine from a variety of cultural traditions is used by some of these patients. According to the 2007 National Health Interview Survey from the Centers for Disease Control [2],

more than 200,000 US adults chose to use Ayurvedic medicine in the previous year to treat their health conditions. This report will review current evidence of the use of Ayurveda in the management of rheumatoid arthritis.

The derivation of the term Ayurveda comes from the words ayur, or “life”, and veda, or “science” [3, 4]. Ayurveda emerged from an oral tradition and was subsequently recorded in the ancient Indian texts known as the Vedas, originally written in Sanskrit. The Vedas detail aspects of a way of life, in addition to a system of medicine, that focuses on preventing and delaying aging and disease rather than simply treating disease once established. This fundamentally difference approach from conventional Western medical practice makes comparison with standard pharmacological therapy challenging. Ayurveda focuses on promoting health by taking a holistic view of mind, body, and spirit and with the help of natural remedies derived from medicinal plants and minerals. However, Ayurvedic practice includes the use of not just oral pharmacological agents but also topical preparations, massage, meditation, dietary recommendations, and exercises. Its purpose is to establish a dynamic equilibrium or balance of different forces in the body which are believed to be responsible for a person’s state of health.

According to Ayurveda, every living being is composed of five basic elements of the universe: space, air, earth, water, and fire. In the human body, these elements form “doshas” which are biophysical forces or energies that govern all biological processes. Their dynamic, continuous interactions are believed to be responsible for the state of being of the mind and body. The three main doshas are vata (space and air), kapha (earth and water), and pitta (fire and water). Vata governs those bodily functions that relate to movement; kapha governs structural aspects of the body; and pitta relates to transformative processes, for example digestion and metabolism. Each individual is born with a certain percentage of each dosha which determines their prakriti, or individual

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constitution, and that does not change over a lifetime. Indeed, Ayurveda teaches that doshas function in inanimate objects and plant and animal life on Earth, and in the universe beyond, linking humans to all of creation. Events in daily life, in addition to diet, lifestyle, geographic location, and the seasons of the year can affect the balance of the doshas, according to Ayurveda. A loss of the harmonious equilibrium of the doshas results in a state of imbalance, termed *vikriti*. Ayurveda seeks to maintain balance of the doshas and thereby ensure health and longevity. In doing so, the Ayurvedic practitioner will focus on characteristics of the individual as much as on their disease, so two patients afflicted by the same illness may be treated in different ways. Thus, trials investigating Ayurvedic medicine tend to focus on pharmacological aspects of care rather than the complete approach to the patient that might include instructions on sleep habits, diet, exercise, and cleansing rituals.

Ayurvedic Perspective on Arthritis

There is no exact correspondence of Ayurvedic disease classification to modern medical terminology. However, joint conditions that bear similarities to such diseases as rheumatoid arthritis and osteoarthritis, on the basis of symptoms and clinical findings, are described in Ayurveda. In fact, among the many disorders of the joints described in Ayurvedic texts [4•] is “*aamavata*”, a cause of polyarticular pain and swelling suggestive of rheumatoid arthritis. Because *vata* dosha governs motion, it is believed to be crucially important in causing arthritis. *Aamavata* is said to arise as a result of imbalances in the doshas linked to the gut, with particular attention to *vata* dosha. Diagnosis in Ayurvedic practice involves obtaining a detailed history, performing a thorough clinical examination, drawing conclusions regarding the patient’s *prakriti*, and determining the deranged doshas. Traditionally, laboratory and radiographic test results are not used in this assessment. However, investigators have recently begun to investigate the concept of “Ayurgenomics” in RA, hypothesizing that genetic susceptibility markers might differ among patients with *vata*, *kapha*, or *pitta* predominance in their presentation [5]. Subjects diagnosed with *aamavata* were evaluated by allopathic physicians and those meeting ACR criteria for RA underwent intensive *prakriti* analysis and laboratory testing. Genetic analysis was conducted for a total of 325 *aamavata* patients and 356 controls. The authors suggested that *vata*-predominant RA patients have disease mediated by inflammatory marker genes (CD40, IL-1 β) and those that are *pitta*-predominant have disease mediated by oxidative stress genes (SOD3).

When the patient’s condition has been assessed, treatment proceeds with use of herbal, dietary, and physical intervention in sequence and in combination [4•]. The Ayurvedic approach to RA has been characterized as “defensive” as opposed to the

“offensive” strategy of modern Western medicine [6]. In addition to balancing the doshas, Ayurveda is used to increase the digestive and metabolic fires (“*agni*”), stop the formation of “*aama*” and increase its digestion and excretion, and restore and balance damaged intestinal mucosa and absorption. Treatment is likely to begin with dual application of heat in some form (“*swedana*”), with medicines dissolved in oil (“*snehana*”) applied via different routes. A steam bath might be used and oily formulations given orally, as enemas, or massaged into the skin may be administered. The five processes of treatment with emetics, purgatives, medicated oily enemas, medicated dry enemas of herbal decoctions, and oleation and nasal purgation (“*panchkarma*”), are altered throughout the course of disease depending on the therapeutic response. Dietary restrictions, and even fasting in the initial acute stages of the disease, may be recommended, with the purpose of reducing accumulated “*aama*” and strengthening the digestive system. Local application of plant extracts or heated metal probes to induce burn-like skin reactions, massage, exercise, and yoga practice may be recommended. Application of leeches and venesection are also part of traditional practice. Evaluation of this multimodal approach has not been fully reported in the scientific literature. Rather, several trials have assessed the use of herbal ingredients in Ayurvedic practice, in part driven by laboratory evidence of relevance to the pathophysiology of the inflammation and immune responses seen in RA.

Ayurvedic formulations are often complex, containing several herb and mineral ingredients determined by the traditional principles of preparation, compatibility, and administration [4•]. Ayurvedic medicines are divided into two major types: those containing herbs only and “*rasa shastra*” (combination of herbs with minerals and/or metals). By use of an oxidation process, raw metals and minerals are converted into ashes, known as “*bhasmas*”, with presumed medicinal properties. These are regarded as non-toxic while retaining healing properties. One such commonly used preparation is the *Guggul* preparation that can contain ashes (“*bhasma*”) of minerals such as gold (known as *suvarna bhasma*), silver, copper, iron, mica, mercury, sulfur, zinc, and lead. It is of interest in the context of treating RA that gold ash has been used to treat arthritis since ancient times in Ayurveda.

An important sector in Ayurvedic medicine, from a rheumatologic perspective, is the “*Rasayana*” branch of Ayurveda which targets strengthening and rejuvenation of the body and, in the current context, is most relevant to chronic arthritis. A prime example of a *Rasayana* plant is *Withania somnifera* (*Aswagandha*) which is extensively used in Ayurvedic medicine because of its immunomodulatory and anti-inflammatory effects. Numerous other *Rasayana* plants are common components of anti-rheumatic medications. Other examples are *Ricinus communis* (Erand or castor oil) and *Guggul* extracts of *Commiphora mukul* and *Boswellia serrata*; these are important examples of anti-arthritic medicinal plants named in

“Charaka Samhita”, one of the well-known Ayurvedic texts. It should be noted that one medicinal plant might be used for several purposes, and that individual conditions might be treated with extracts from several medicinal plants.

Evidence of the Anti-Inflammatory and Immunomodulatory Effects of Ayurvedic Herbs

A wide variety of herbs have been tested under in-vitro and in-vivo conditions and found to have demonstrable and reproducible anti-inflammatory and immunomodulatory effects [7]. Numerous herbal extracts, including those of *Boswellia serrata*, *Curcuma longa*, and *Zingiber officinale*, target mediators within the arachidonic acid pathways that lead to the production of phospholipase A₂, cyclooxygenase-2, lipoxygenase, prostaglandin E₂, and leukotriene B₄. *Boswellia* and *Zingiber* also have effects on such cell signaling molecules as ERK, p38 MAP kinase, and JNK. Another herb commonly used in Ayurvedic arthritis treatments, *Withania somnifera*, has been shown to target such nuclear factors as NF-κB. In addition, several Ayurvedic herbs may be effective in changing the course of the disease in animal models of rheumatoid arthritis [8]. Treatment with turmeric extracts can reduce clinical expression of streptococcal cell wall-induced arthritis, and curcumin, a major component of turmeric, has been shown to reduce immunoglobulin and cytokine levels, and clinical signs of collagen-induced arthritis. Rheum Off Gold (RG), an herbo-mineral formulation (*Commiphora mukul*, *Strychnos nux-vomica*, *Boswellia serrata*, suvarna bhasma) used to treat RA was given to Wistar rats with complete Freund’s adjuvant-induced arthritis [9]. RG 100 mg kg⁻¹, dexamethasone 2 mg kg⁻¹, or no treatment was given from day 1 to day 21. Animals treated with RG or dexamethasone gained weight, had reduced paw volume and thickness, reductions in CRP, ESR, and RF, increases in hemoglobin, and improvements in synovial hyperplasia on histopathologic evaluation. Herbs used in Chinese and other traditional medicines have also been studied and found to have effects in these pathways, and on matrix metalloproteinase and nitric oxide production. Such observations have led to interest in studying the effects of herbal medicines on such diseases as rheumatoid arthritis. However, methodological concerns have arisen because of the complexity of the formulas used. This, in turn, has led to creative partnerships between the Indian government and Indian academics, and creative trial designs, to help address some of these concerns.

New Millennium Indian Technology Leadership Initiative

In 2002, the Indian government launched the New Millennium Indian Technology Leadership Initiative (NMITLI), a

public–private partnership for research and development under the auspices of the Council of Scientific and Industrial Research (CSIR) [10]. The NMITLI was intended to identify and support innovative projects showcasing Indian industry, technology, and academics. Study of poly-herbal treatments with traditional formulas for treatment of arthritis, diabetes, and liver disease are among the projects supported by NMITLI. A number of publications have resulted, including several on poly-herb treatment of osteoarthritis [10, 11]. Additional work has further investigated the immunomodulatory effects of *Withania somnifera* [12] in BALB/c mice. Investigators noted that substantial morphological variability is seen among *Withania* grown in different geographic locations, and in this trial used three NMITLI “chemotypes” of *Withania* derived from wild habitats and subsequently genetically altered. These chemotypes were found to differ in the amounts of different withanolides they contained and in their effects on the BALB/c mice. One subtype induced formation of reactive oxygen species, enhanced Th1 cytokine production and B and T cell proliferation, and increased foot pad swelling; another enhanced Th1 cytokine production but had little effect on humoral and cellular responses; a third led to a more predominant Th2 response. These findings emphasize the importance of standardization in preparations, and this has been one of the objectives of NMITLI sponsored arthritis research.

Clinical Trials on Rheumatoid Arthritis

The first clinical trial assessing the efficacy and safety of Ayurveda for RA was conducted over a 7-year period from 1977–1984. Complete records of 160 of the 290 patients originally enrolled were available for review and analysis and a report of the findings for 33 of the subjects was published in 2011 [13]. This remarkable trial was sponsored by the World Health Organization in collaboration with the Indian Council for Medical Research (ICMR), a governmental agency directing biomedical research efforts, and the Ayurvedic Trust, a public charitable organization promoting Ayurveda. The original longitudinal, unblinded study was entitled “The WHO/ICMR Study of the Efficacy of *Ayurvedic* Treatment for Rheumatoid Arthritis”. Its purpose was to assess response to a complete Ayurvedic program of treatment for RA under the scrutiny of allopathic standards of the time. The ICMR team was responsible for the study design, confirmation of RA diagnosis, and enrollment of patients, and for evaluation of the efficacy of the *Ayurvedic* treatment. However, the initial selection of patients was by three Ayurvedic physicians who agreed that the subject seen in the outpatient department of the Ayurvedic Trust hospital met Ayurvedic criteria for “vatarakti” which could include any cause of acute rheumatism and did not exclude gout. Subjects were then reviewed for RA, by four allopathic physicians, on the basis

of clinical, serological, and radiological testing. Approximately two thirds were confirmed to have RA and entered the trial. Individualized therapy was administered with herbal medications, enemas, purgations, external applications of herbal pastes and medicinal oils, dietary modification, and lifestyle changes. Evaluation was performed every six weeks on the basis of American Rheumatism Association criteria: grip strength, walking time, number of swollen and tender joints, functional class, erythrocyte sedimentation rate, results from biochemical analysis, complete blood count, and rheumatoid factor. There was no control group. Patients remained in inpatient treatment until they were regarded as well enough for discharge, which varied between one and six months after admission. Almost two thirds of the 33 subjects were women, 75 % were from age 15–44 and most were in functional class III or IV. One quarter had had RA for >5 years, half had had the disease for 1–4 years and a quarter for <1 year. At the end of the first year, the 33 subjects studied had trends toward improvement in most of the criteria assessed. In general, functional class improved and sedimentation rates fell. However, improvement was worst for women and those with longstanding disease, and some patients were being treated with corticosteroids and had them abruptly withdrawn at the study outset. Nonetheless, this early attempt to study Ayurveda for RA remains of great historical interest.

The first report of the use of a poly-herbal Ayurvedic medicine in a randomized, controlled trial (RCT) was published in 2000 [14]. A standardized formulation, called RA-1, was prepared from purified plant extracts of *Withania somnifera*, *Boswellia serrata*, *Zingiber officinale*, and *Curcuma longa*, and given orally over 16 weeks in a randomized, double-blind, placebo-controlled, parallel efficacy, single-center trial. One-hundred and eighty-two participants with active RA were enrolled. Subjects were permitted to remain on a fixed dose of prednisolone <7.5 mg daily and use paracetamol as a rescue analgesic. However, nonsteroidal anti-inflammatory drugs (NSAIDs) were not allowed and no changes in diet or exercise were advocated. At the end of 4 months, responses to RA-1 were indistinguishable from those to placebo for most measures of outcome. The proportion of subjects with a 50 % reduction in swollen joint count was higher in the treatment group than for the placebo, but there were no other significant changes in ACR20 or ACR 50 responses. Side effects were reported to be minor, but were not reported in detail. They did not differ between the treatment and placebo groups and did not lead to any withdrawals from the trial.

A subsequent study using a different formulation was summarized in a review article [4]. In this trial, a preparation called IRA-01 was used. It contained extracts of *Boswellia serrata* (Salai Guggul), *Trigonella foenum-graecum* (Fenugreek), *Linum usitatissimum* (Flaxseed), *Camellia sinensis* (Green tea), *Curcuma longa* (Turmeric), *Tribulus terrestris* (Gokshur), and *Piper nigrum* (Black pepper). A

12-week multicenter, randomized, double-blind, placebo-controlled phase was undertaken, followed by a 28-week, single-center, open-label phase. One hundred and thirty participants entered the study. Paracetamol, as needed, was allowed as a rescue analgesic but no NSAIDs, prednisolone, or disease modifying agents were permitted during the entire one-year study. During the initial RCT phase, IRA-01 was not significantly different from placebo for any outcome measure except physician global assessment of disease activity at 12 weeks. Once again, a strong placebo response was evident, with ACR20 response for 60 % of subjects receiving IRA-01 and for 53 % receiving placebo. Only minor side effects were reported but 30 % of those enrolled withdrew. At 12 weeks, 70 patients entered the open-label phase. After one year, 58 (83 %) remained in the study with 80 % having achieved an ACR20 response and 40 % achieving an ACR50 response. However, given the absence of controls, interpretation of these findings is difficult. Although the authors argued that these observations support considering IRA-01 as a slow-acting DMARD with an excellent safety profile, no radiographic data demonstrating a disease-modifying effect were reported.

The following year, the first-ever, double-blind, randomized, placebo-controlled pilot study comparing Ayurveda, methotrexate (MTX), and their combination for RA was published [15]. Forty-three seropositive RA patients diagnosed by use of American College of Rheumatology (ACR) classification criteria and with disease duration <7 years were assigned to the one of three groups:

- MTX plus placebo Ayurveda ($n=14$);
- Ayurveda plus MTX placebo ($n=12$); or
- Ayurveda plus MTX ($n=17$).

The initial dose of MTX was based on the patient's weight and was increased by 2.5 mg per week every 8 weeks, as tolerated, to a total dose of 25 mg per week. The mean dose of MTX at 36 weeks was 20.3 mg per week. A unique feature of this study was the development of six different placebos for each Ayurvedic pharmacological dosage form, including powders, liquids, pills, jams, and oils. This enabled individualization of the placebo Ayurvedic therapy. Testing demonstrated that subjects were unable to distinguish between the Ayurvedic treatment and the placebo Ayurvedic treatment and that blinding was maintained [16]. The protocol was approved by the academic institutions involved, and by the Ayurvedic Trust, and the subjects were screened by allopathic physicians. All subjects met ACR criteria for diagnosis of RA and had either a positive RF or a positive anti-cyclic citrullinated protein antibody test. Outcomes included the Disease Activity Score (DAS28-CRP), ACR20/50/70, and the Health Assessment Questionnaire-Disability Index (HAQ-DI) monitored every 12 weeks for 36 weeks. At baseline, the demographics and disease characteristics for each group were comparable.

Three subjects left the trial at 24 weeks because of neuropathy, femoral fracture, and pregnancy. There were no statistically significant differences between DAS28-CRP or HAQ-DI among the three groups. Only the ACR70 results at 24 weeks were superior for MTX alone compared with the other two groups (MTX 29 %, Ayurveda 0 %, and combination 6 %). Differences between adverse events among groups were not statistically significant and no deaths occurred. This study demonstrated that a double-blind, placebo-controlled, randomized study was possible for testing of individualized classic Ayurvedic versus allopathic treatment but was unable to show differences in efficacy among the treatment groups within the confines and limitations of a pilot study.

In 2012, results from an NMITLI-based study comparing standardized Ayurvedic formulations, chosen for their Rasayana attributes, with hydroxychloroquine for treatment of RA were published [17]. In this trial, 121 participants meeting ACR criteria for active moderate to severe RA were enrolled and randomized to receive either one of two Ayurvedic treatments or hydroxychloroquine. During the initial 16 weeks of this 24-week investigator-blind, parallel efficacy, multicenter exploratory study all subjects also received a fixed dose of meloxicam. One Ayurvedic group received a poly-herb preparation (*Tinospora cordifolia*, *Zingiber officinale*, *Withania somnifera*, and *Tribulus terrestris*), referred to as B formulation, and the other Ayurvedic group received a monoherb preparation of *Semecarpus anacardium*, referred to as Bhallataka Parpati or BPRT. Each was administered orally in capsule form twice daily. Hydroxychloroquine was given at a dose of 200 mg twice daily. Patients on prednisolone continued on a fixed stable dose of <7.5 mg daily. Paracetamol was permitted, as needed, but no other analgesics, NSAIDs, or DMARDs were allowed. No exercise or dietary restrictions were imposed and subjects already participating in exercise and/or physical therapy programs were permitted to continue. Reductions in the physician global score were noted for both the B formulation group and the hydroxychloroquine group compared with their baseline. However, the treatment groups did not differ in ESR or other laboratory data, joint counts, visual analogue scale pain, or HAQ scores. ACR20 (poly-herb 44 %, monoherb 36 %, and HCQS 51 %) and ACR50 (poly-herb 12 %, monoherb 3 %, and HCQS 10 %) responses were not significantly different. Only mild adverse side effect were reported without differences between the groups, but forty-two patients dropped out. The authors concluded that Ayurvedic B formulation was comparable with hydroxychloroquine for treatment of moderately severe RA.

Toxicity of Ayurvedic Medicines

There is a paucity of data on the safety of, and potential drug interactions with, Ayurvedic medicines. However, because

minerals and metals are frequently used as ingredients of Ayurvedic formulations, consumers should be aware of the possibility of adverse effects as a result of these. In 2008, the National Center for Complementary and Alternative Medicine (NCCAM) funded a study which examined the content of 193 Ayurvedic products purchased over the internet and manufactured either in the US or India. They found that 20 % of the products contained detectable levels of lead and mercury and/or arsenic that exceeded US Environmental Protection Agency (EPA) and WHO limits for acceptable daily intake [18]. Although US and foreign companies are required to register their facilities with the Food and Drug Administration (FDA), they are not required to obtain FDA approval before selling their products. Under the Dietary Supplemental Health and Education Act (DSHEA) of 1994, manufacturers of dietary supplements are not required to prove a product safe or effective and post-marketing surveillance is not required, as it is for prescription pharmaceuticals. Lead poisoning as a result of prolonged use of Ayurvedic medications has been well documented [19]. Symptoms can include anemia, abdominal pain, constipation, arthralgias, myalgias, headache, mood disorder, and encephalopathy, and can occur within weeks of exposure if the amount is sufficient. Although arsenic poisoning has been reported less frequently, it, also, has occurred as a result of chronic use of Ayurvedic medicines [20]. Serious side effects include the characteristic cutaneous raindrop pigmentation, hyperkeratosis of the palms and soles, transverse white bands on nails, predisposition to premalignant and malignant lesions especially of the skin, peripheral neuropathy, and hepatotoxicity.

Conclusion

In summary, despite the many millennia over which Ayurvedic practice has been used and the numerous laboratory observations of potential anti-inflammatory and immunomodulatory mechanisms of action of Ayurvedic herbs, little in the scientific literature currently supports the use of Ayurveda for RA. In part this is because of the complexity of the intervention by Ayurvedic practitioners seeking to restore the balance of the doshas. The multiple modalities used and the length of time over which they are implemented and adjusted make study design challenging. Nonetheless, several committed academics, and officials in India, have an interest in investigating and understanding more deeply the place of Ayurveda in the treatment of a host of disorders. Larger and increasingly sophisticated clinical trials are likely to be conducted as patients continue to

seek holistic and comprehensive strategies for coping with chronic disease.

Compliance with Ethics Guidelines

Conflict of Interest Shristi Basnyat and Sharon L Kolasinski declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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