Review Article

Utility of Herbal plants for treating osteoarthritis and rheumatoid arthritis

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ABSTRACT

Background: Arthritis is a chronic inflammatory disorder. Arthritis is of more than a hundred types but the major two forms of arthritis are osteoarthritis (OA) and rheumatoid arthritis RA. Both of these major forms of arthritis are associated with deformation in the joints along with a decrease in overall quality of life. **Aim:** The primary aim of this review is to determine the safety and efficacy of various herbal plants which have a positive impact on OA and RA. This review summarized the mechanism, trials, and treatment of various herbal plants on OA and RA. **Methods:** Different databases present in PubMed, Google Scholar, and ClinicalTrials.gov were evaluated in extracting the information on various types of herbs used in OA and RA. Conclusion: The herbs showed promising results in the treatment of OA and RA. Despite the given studies more studies and clinical trials are required to determine the exact safety and efficacy of herbs in the treatment of OA and RA.

Keywords- *Osteoarthritis, rheumatoid arthritis, inflammation, herbal, herbs*

Arthritis is a chronic health condition. Arthritis is of different types and the two major types of arthritis are osteoarthritis (OA) and rheumatoid arthritis (RA). Arthritis is one of the leading causes of disability in the United States (US) and has affected an estimated population of 52.5 million [1]. Arthritis mainly targets the joints, both OA and RA impair the joint structure but have different symptoms, pathophysiology, and effective treatment. OA is a degenerative or "wear and tear" health condition, it is an inflammatory disease that is caused by various factors such as age, gender, obesity, genetics, etc. [2].

OA degenerated the cartilage of the joint which changes the underlying bone structure. Pro-inflammatory cytokines along with pro-catabolic mediators are present in the synovial fluid which are associated with the degeneration of cartilage [3]. OA begins gradually and eventually leads to disability of the limbs. Symptoms of OA include inflammation and tenderness of the joints along with morning stiffness.

RA is a disease that involves dysregulation of the immune system affecting multiple joints. The most common risk factors for RA are gender (females are more likely to be affected) and smoking [4]. RA arises due to anti-citrullinated protein antibody (ACPA), this protein causes inflammation of the bones leading to bone erosion and chronic pain [5]. RA possesses a high prevalence of disability after the onset of the disease affecting almost 60%of the patients in the span of 10 years [6]. Symptoms of RA are inflammation and tenderness of the joints along with morning stiffness. To date, there isn't a complete cure for Arthritis.

The treatment options for OA include non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids, and norepinephrine reuptake inhibitors however, NSAIDs have gastrointestinal, cardiovascular, and nephrotoxic side effects in the long term [7]. Corticosteroids that are injected into the joints to treat OA have a different efficacy which may lead to further deterioration of the joints [7]. Common treatment options for RA are disease-modifying antirheumatic drugs (DMARD) [8]. DMARDs also have a high risk of

gastrointestinal disturbance along with toxicity of the liver and kidney. Biologics are also available for the treatment of RA but they have low levels of tolerance and also have a high risk of cancer and chronic infections [9]. The side effects of the above drugs limit their use in the treatment of OA and RA and the risk outweighs the benefit.

A constant concern for modifying the side effects of the drugs has been provoked in the herbal remedies. Herbal therapies are an alternative method for the risk-free treatment of Arthritis. In this review, we summarize the herbal therapies available in the management of OA and RA. We specifically determine the safety and efficacy of the herbal medicines available in the treatment of OA and RA.

MATERIALS AND METHODS

Databases such as PubMed, Google Scholar, and ClinicalTrials.gov were explored using the keywords such as osteoarthritis, rheumatoid arthritis, herbal, herb, and inflammation. A search was carried on using by using the name of specific traditional herbs such as Boswellia serrata, Curcuma Serrata, *Eremostachys laciniata,* Eucommia ulmoides, and Zingiber Officinale. Scientific articles and internet sources published after the year 2000 were included. Various clinical trials performed on the herbs were included.

RESULTS

In the late 21st century the traditional therapy for OA and RA has gained recognition. Herbal medicines found all over the world are extensively being studied and investigated for their ability to cure diseases. Some recent studies reported the mechanism of herbal plants in the reduction of inflammation in OA and RA. Numerous clinical trials have shown a positive effect on the response of herbal plants. This section gives an overview of the role of herbal plants in treating OA and RA.

Clinical trials using different herbs

Boswellia serrata: Boswellia has an alternative name called frankincense. Boswellia has been used in the past for decades in ayurvedic treatment [10]. Boswellia consists of various boswellic acids which give evidence of anti-inflammatory and anti-tumorigenic effects. This herb inhibits microsomal prostaglandin E2 (PGE2) synthase-1 and 5-lipoxygenase which aids in reducing the activation of various inflammatory mediators like matrix metalloproteinase (MMP)-9, MMP-13, cyclooxygenase (COX)-2, and nitric oxide (NO) [10]. Boswellia exerts a positive influence on OA by improving the degradation of the joints and decreasing the production of inflammatory mediators such as C-reactive protein and hyaluronic acid. Many researchers have investigated the safety and efficacy of Boswellia serrata.

Majeed et al conducted a study to determine the efficacy of Boswellia serrata. A double-blind, randomized, placebo-controlled trial was presented in the study [11]. The study was conducted for a period of 120 days. Male and female patients between the ages of 35-75 years suffering from OA were involved in the study. Patients suffering from hypertension, pregnant women, and other degenerative joint diseases were excluded from the study. The patients were administered boswellic tablets or a placebo in a 1:1 fashion. Two tablets of Boswellia Serra extract containing 169.33 mg each were administered daily. A Western Ontario McMaster Index (WOMAC) was used to evaluate the physical function, pain, and stiffness of the patients suffering from OA. A comparative analysis of X-rays was performed at the end of the study. Boswellia showed a significant decrease in the pain of the joints along with improvement in the ability to walk. No serious adverse effects were reported during the study.

A recent study was performed by Razwi et al to evaluate the effect of topical Boswellia serrata on OA [12]. The study was conducted on 154 patients suffering from OA. The participants were divided into three groups for the application of topical Boswellia for a period of six weeks. The degree of pain was evaluated by using a visual analog scale (VAS) along with Knee Injury and Osteoarthritis Outcome Score (KOOS). The topical application showed an improvement in the pain and symptoms however, the quality of life did not show any significant improvements. No serious side effects were observed in the study.

Curcuma Serrata: Curcuma is commonly known as turmeric. Curcumin is an extract of turmeric and it shows anti-inflammatory and anti-oxidant effects. Curcuma has been used in the history of Chinese and ayurvedic medicines. Curcuma inhibits interleukin (IL)-1, tumor necrosis factor-alpha (TNF-α), IL-8, and NO by activating NF-κB, protein kinase B (Akt), and MAPK signaling pathways [13]. Curcuma also inhibits prostaglandin synthesis. Curcuma is extensively studied for its effects on arthritis. Kuptniratsaikul et al conducted a randomized clinical trial on Curcuma to evaluate its safety and efficacy [14]. This study included 367 patients suffering from OA. The participants were divided into two groups and were randomly administered with ibuprofen or Curcuma extracts. WOMAC was used to evaluate the pain, stiffness, and baseline function. The WOMAC score demonstrated a

reduction in abdominal pain and discomfort in the curcumin group when compared to ibuprofen.

Another study was conducted by Nakagawa Y et al [15]. A double-blind, placebo-controlled, randomized clinical trial was conducted to evaluate the efficacy of Theracurmin and placebo on a group of 50 patients suffering from knee OA. Patients were administered theracurmin or placebo orally two times a day for eight weeks. Each capsule of theracurmin contained 180 mg of curcumin. The knee of the patient was evaluated after every 2 weeks. Adverse effects such as hypertension and tachycardia were observed in one patient on day 50 and another patient showed redness of the tongue. There was an overall reduction in the VAS scores in the group treated with theracurmin in comparison to the placebo group. There was also an advancement in the quality of life.

A recent study randomized trial performed by Dhaneshwar et al showed the efficacy of turmeric on OA. This study included 140 patients suffering from OA [16]. Half of the patients were administered with a curcuminoid complex of 500 mg in combination with diclofenac 50 mg twice a day and the rest of the patients were administered with diclofenac 50 mg twice a day. The primary measure for the efficacy of the treatment was performed by a Knee injury and OA outcome score (KOOS). Both the treatment group showed improved efficacy in treatment at the primary endpoint. Patients in the curcuminoid group had an improvement in the analgesic effect compared to that in the diclofenac group.

Eremostachys laciniata: E. laciniata is an herb from Iran. This plant helps in alleviating the symptoms of inflammation [17]. The exact mechanism of this herb is still unclear. However, one study was conducted by Salimullah et al which report that crude Methanol extracts of *E.* laciniata showed evidence of anti-inflammatory properties in vivo [18]. The aqueous extract of E laciniata has antioxidant properties due to the scavenging activity of the DPPH radical. A study conducted by Abbas et al investigated E. laciniata on arthritic pain and inflammation [19]. This study was a single-blinded, randomized trial. A total of 137 patients between the ages of 18-80 years suffering from OA and RA were included in the study. One group received topical E. laciniata and the other group received topical piroxicam. The ointment of both types was gently massaged on the affected joint for 2-3 minutes twice a day. This procedure was followed for 14 days. Patients were personally examined by the Physician during the course of treatment. The level of pain was recorded on VAS. The group of E. laciniata showed a much better therapeutic response when compared to the piroxicam group.

Eucommia ulmoides: E.ulmoide herb shows OA and RA properties. These herbs reverse the production of lipopolysaccharide (LPS) in IL-1β, IL-6, TNF-α, and COX-2 through modulation and activation of toll-like receptor (TLR) 4. E. ulmoides have proven to activate the phosphoinositol 3-kinase (PI3K)/Akt signaling pathway in rat modules containing OA and RA [20]. Hai Lu et al conducted a study on aqueous extract of E. ulmoides on the articular cartilage of OA rat models [21]. A total of fifty-four were collected in this study. Rats were housed in proper conditions with access to food and water. The rats were administered with an aqueous extract of E.ulmoide. The rats showed a reduction in serum MMP-1, MMP-3, and MMP-13 along with protection of the articular cartilage. A current double-blind, randomized, multicenter trial is being conducted to evaluate the safety of E. ulmoides in patients suffering from mild OA. A total of 100 participants will be recruited for the study. The subjects will be randomly allocated in a 1:1 fashion.

Zingiber officinale: Zingiber officinale is often known as ginger. It has the potency for reducing inflammation in various in vitro and in vivo subjects. Ginger shows a significant reduction in PGE2, NO, IL-1β, IL-12, and TNF-α. A study was conducted by Haghighi et al to evaluate the safety of ginger in patients suffering from OA. It was a double-blind, randomized, clinical trial. 120 patients from moderate to severe OA were included in this study. The patients were separated into 3 groups and were administered placebo, ginger extract, and ibuprofen. VAS was used to evaluate the gelling pain, swelling of the joint, and slope of the joint. The positive impact of the ginger extract was superior to that of placebo and ibuprofen [23]. One more trial was conducted that showed 250 mg of ginger was more effective when compared to the placebo. The trial demonstrated a reduction in VAS scores with reduced morning stiffness [24].

DISCUSSION

In this review, I have summarized various clinical trials which demonstrate the utility of herbal medicines in the treatment of OA and RA. A total of five herbs were included that showed promising results in reducing the symptoms of pain, inflammation, joint tenderness, morning stiffness, and oxidative stress. The main mechanism of action of these herbs includes alteration in the inflammatory signaling pathway along with management of immune cell activity.

Disease	Herbal medicine	Dosage (per day)	Mechanism of action	Clinical implication
Boswellia spp.	100, or 349.3 mg, or 10 drops (oil)	42–120	Inhibit the production of inflammatory mediators, such as iNOS, COX-2, TNF-α, IL-1β, and ROS → reducing apoptosis of chondrocytes and synovial fibroblasts	Herbal medications demonstrate powerful anti-inflammatory and antioxidative activities
Curcuma spp.	180 or 500 mg	28–56	Curcuma inhibits interleukin (IL)-1, tumor necrosis factor-alpha (TNF-α), IL-8, and NO by activating NF-κB, protein kinase B (Akt), and MAPK signaling pathways	Curcuma shows anti-inflammatory and anti-oxidant effects
Eucommia ulmoides	1 g extract or 36 g powder	28 or 84	Reduce the production of MMP-1, MMP-3, MMP-9, and MMP-13 → slowing degradation of the extracellular matrix of cartilage and bone and reducing osteoclast formation and bone resorption	Herbal medications mimic anti-arthritis activities, as shown in the treatment of current medications, with fewer adverse effects.
Zingiber officinale	Zingiber officinale powder: 250 or 1000 mg; Extract: 30, or 510 mg, or 5% of body weight	30–84	Promote collagen synthesis	Herbal medications could also enhance the anti-arthritis activities of current medications.
Eremostachys laciniata	0.5% topical ointment	14	Inhibit the production of PGE2, leukotriene B4, NO, ROS, and other pro-inflammatory mediators.	Unknown

Despite the different pathology and clinical symptoms of OA and RA, they have similar inflammation and oxidative stress properties. The inflammatory mediators of OA such as IL-1, IL-6, and TNF-α synthesizes collagenase and MMPs leading to the deterioration of collagen type – II. RA is an autoimmune disease in which the cytokines play a major role in regulating T-cells and B-cells. Herbs play a role in the reduction of anti-inflammatory properties of RA. These herbs inhibit the pro-inflammatory NF-κB, MAPK, and Akt along with PPARγ enhancement. This leads to inhibition of the inflammatory chemokines, NO, and PGE2 and promotion of the anti-inflammatory IL-10 and TGFβ [3]. These herbs also reduce the activity of collagenase and MMPs, therefore, causing an improvement in OA and RA symptoms. The herbal drugs which were reviewed in this review article showed improvement in OA and RA along with minimal or no adverse effects. Some studies however showed some adverse effects like nausea, vomiting, gastrointestinal defects, hepatotoxicity, and some negative effects on the menstrual cycle [25]. Poor bioavailability decreased absorption, and rapid metabolism may also contribute to the limited use of herbal medicines. The overall bioavailability of herbs used in the treatment of OA and RA is less, and there is a constant need for development in future studies to overcome this issue.

CONCLUSION

Various traditional herbs can also be used as an alternative therapy for OA and RA in decreasing the need for pharmacological drugs. More clinical trials are required in the future to determine the exact safety and efficacy of herbal medications in OA and RA. The proper development of herbal formulations with improved bioavailability is crucial for optimizing the overall treatment.

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