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Herbs and Herbal Constituents Active against Arthritis

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Abstract

Arthritis is one of the oldest diseases of the universe and a major bone-joint related syndrome among the aged people. Arthritic patients are found all over the world and there are hundred types of arthritic conditions which can be classified under three major categories: Rheumatoid Arthritis (RA), Osteoarthritis (OA) and gouty arthritis. The management and treatment of arthritis and conditions affecting the articular cartilage represent one of the most challenging problems. The main aim for the treatment of this disease is to reduce pain and to minimise the damages occur during the process. Physiotherapy, physical exercise and analgesics are often prescribed by the rheumatologists. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line of defence against arthritis. But the NSAIDS and disease modifying anti-rheumatic drugs (DMARDs) have certain side effects like GI tract irritation, inhibits PGI biosynthesis, defective platelet aggregation, etc. Since the available therapeutics has their own limitations, a worldwide demand for the alternative therapy against arthritis is warranted. Use of traditional medicine is expanding to a new dimension and herbs are still remaining a novel source of compounds from which new innovative drugs could be discovered. From the traditional and folk medicine, it is well known that different herbs and herbal extracts have been used for the treatment of arthritis but enough scientific evidence are lacking. In recent times, several herbal compounds have shown their effectiveness in experimental arthritis. The present review is an effort to establish the use of herbs and herbal constituents in the treatment of arthritis.

Keywords: Herbs; Herbal constituents; Alternative therapy; Arthritis; Inflammation

Introduction

Arthritis is one of the oldest diseases of the society and has been documented since the beginning of civilization. The first known case of human arthritis date back as far as 4500 BC in the fossils of Native Americans, found in Tennessee, USA. The ancient classic Ayurvedic text has described painful deforming polyarthritis called “amavata” and “sandhighatvata” that bears resemblance to rheumatoid arthritis and inflammatory arthritis [1]. Arthritis has been mentioned in the ancient Hindu and Greek mythology [2]. The first written reference on arthritis was found in the Indian holistic book *Charaka Samhita* where it has been described as swollen painful joints, initially occurring in hands, feet, causing loss of appetite and occasionally related with fever [3]. The history of arthritis has been marked with a continuous search for better therapy, less toxicity and a reasonable cost. To understand the magnitude of the problem of rheumatic disorders, several strategies have been launched by American College of Rheumatology [4]. It has been found that soft tissue rheumatism and osteoarthritic disorders were the commonest community ailments. Inflammatory arthritic disorders including rheumatoid arthritis are less than 10% in the community, whereas osteoarthritis is the most predominant one. Although there are hundred types of arthritic conditions which could be classified under three major categories: rheumatoid arthritis, osteoarthritis and gouty arthritis. The present review is an effort to establish the effectiveness of herbs and herbal constituents in the management of arthritis and joint related disorders.

Osteoarthritis and pathophysiology

Osteoarthritis (OA) has been derived from the Greek word *osteo* meaning the bone *arthro* meaning joint and *itis* meaning

inflammation. It is the most common form of arthritis and one of the leading causes of chronic disability in the elderly person. OA is classified into primary or idiopathic, when there is no obvious pre disposing cause and in secondary OA when there is clearly defined pre disposing cause. Idiopathic osteoarthritis is the most common form of arthritis. OA is a painful degenerative condition that can affect one or more of the joints and specially the weight-bearing joints (e.g. spine, hip, knee, ankle). Obesity is one of the preliminary factors and increased weight translates to increased force on the weight-bearing joints leading to disability. Losing weight, though not always easy, is of paramount importance in slowing OA progression [5]. The incidence of overweight children has increased over the past 25 years and, among children 6 to19 years old, 16% were overweight, and 31% were at risk for being overweight [6]. The major known causes of hip OA include primary inflammatory arthritis, ankylosing spondylitis, rheumatoid arthritis, metabolic diseases, developmental dysplasia of the hip, Legg–Calvé–Perthes disease, and slipped capital femoral epiphysis. The fixed risk factors for OA are mainly age, sex, family history, and race.

In India, osteoarthritis (OA) is the second most common rheumatological problem with prevalence of 22% to 39% [7]. It has been reported that for age group of 65-74 years, prevalence of OA were 33% for males and 49% for females. The percentage is higher upto 37% for males and 51% for females for age group of 75 years and above. As OA is not reversible, the prevalence of OA increases indefinitely with age and it has been noticed that males are affected more often than females below age 45 years, while females are affected more frequently after age 55 years. It is now considered as a debilitating malignant disease with increase in mortality, morbidity and poor prognosis but also limit the patient from daily activities. Life expectancy decreases by 3-10 years according to severity and age of onset of disease. It is also associated with serious co morbid conditions like infections (common cause of death in developing countries) cardiovascular disease, respiratory disease etc. [8].

In OA, the factors which include the changes in the expression of collagen and other matrix molecules had not been yet identified, but may include changes of the chondrocyte environment, mechanical loading, cytokines, growth factors and perhaps molecular fragments produced by the matrix metabolism [9]. It was accepted that chondrocyte is the target of cytokines action but the sources responsible for generating the cytokines are less understood in the context of OA pathogenesis. The degradation of cartilage and proteoglycans in OA is due to an imbalance in the proteinases and the inhibitors synthesised by the chondrocyte [10]. Matrix metalloproteinases (MMPs) have been detected in the synovial fluids and cartilage of OA patients. It has been found that the increased levels of inhibitors of metalloproteinases in the synovial fluid of OA reflect an adaptive response to the increased levels of active MMPs [11]. Genetic and hormonal factors also play an important role in the pathogenesis of OA. It has been established that the mutations in collagen genes (types II, IX, X) appear to contribute to the development of premature idiopathic OA [12]. Along with the MMPs, the gelatinases also play an important role in the pathogenesis of OA [13]. The gelatinases are best known for their involvement in pulmonary, myocardial, and neoplastic diseases that have emerged as important enzyme implicated in the OA progression. It has been reported that gelatinases involved in the pathogenesis of OA through the regulation of subchondral bone resorption and microvascular invasion. In OA, subchondral bone shows dysregulated osteoblast and osteoclast phenotype and it is not known whether osteocyte cells undergo phenotypic changes during OA progression [14]. Jaiprakash *et al.* reported that OA osteocyte phenotype has distinctive changes both phenotypically and morphologically and it has also been reported that osteocyte phonotypic changes participate in OA subchondral bone pathogenesis [15]. These characteristic OA changes could be caused by the activation/deactivation of osteocyte signalling molecules in the OA microenvironment.

Healthy cartilage is maintained by a delicate balance between the anabolic and catabolic activities of articular chondrocytes. This involves actions of numerous cytokines and growth factors that regulate the synthesis and degradation of extracellular matrix components which maintain the functional integrity of the joint. An imbalance between the activities of these anabolic and catabolic factors leads to cartilage degradation resulting in OA, through chronic degenerative joint disorder characterized by destruction of articular cartilages, alterations of subchondral bone and synovial fibrosis. Transforming growth factor-β (TGF-β) has emerged as an important molecule that plays a critical role in the development, growth, maintenance and repair of articular cartilage. The alterations in the molecular events of TGF-β signaling and responses that may contribute to OA progression shows the potential of targeting the TGF-β signaling pathway for the development of novel therapies for OA [16]. Binding of stromal cell-derived factor-1 (SDF-1) to C-X-C chemokine receptor type 4 (CXCR4) induces OA cartilage degeneration [17]. Together, these findings raise the possibility that disruption of the SDF-1/CXCR4 signaling can be used as a therapeutic approach in cartilage degeneration. Prasadam *et al.* reported that a down-regulation of chondrogenic and upregulation of hypertrophic gene expression occurs in the normal chondrocytes, when p38 is neutralized by a pharmacological inhibitor thus indicating the importance of this pathway in the regulation of cartilage physiology and its relevance to OA pathogenesis [18]. IL-17 is a proinflammatory cytokine, secreted primarily by activated memory CD4+ T cells and binds to specific receptors that are expressed by virtually all cells and tissues. CD4+ T cells have been detected in the sublining layer of the synovium of patients with OA. T-cell reactivity against chondrocyte surface antigens has also been detected in patients with OA.

In chondrocytes, IL-17 has been shown to induce IL-1β, TNF and IL-6 to upregulate the production of nitric oxide and matrix metalloproteinases and to reduce proteoglycan levels [19]. TNF α, IL-17 and IL-18 contribute to pain transmission and also have been found to magnify pain in osteoarthritis [20]. The pro-inflammatory cytokines are mainly targeted for therapeutic intervention because of their role in promoting harmful inflammation. Dysregulation in the synthesis of the pro inflammatory cytokines occur in OA. Inflammasome, a protein complex of mainly three proteins IL-1, IL-18 and High Mobility Group Box 1 protein (HMGB1) plays a critical role in the inflammatory diseases. It has been observed that during arthritis the synthesis of IL-18, IL-1

gets increased and as a result of which there is an increase in the expression and synthesis of IFNγ, VCAM 1 proteins. Moreover it has been observed that HMGB1 protein expression also increased during arthritis and this protein mainly interacts with p53 thus cause apoptosis through NFκβ pathway. Regulation of the inflammasome activation in osteoarthritis disease may cause less susceptibility to the pathogenesis of the disease since complete deactivation of this protein complex causes increased susceptibility to the pathogens [21]. It has been reported that there is a close relation between osteoarthritis and metabolic diseases like obesity, hypertension, cardiovascular diseases etc [22]. Although it has been observed that there are mainly three types of mechanoreceptors are present in the chondrocytes and these receptors due to obesity overload gets activated thus causing liberation of cytokines, growth factors and metalloproteinaeses. A very reactive aldehyde derived from lipid peroxidation 4-hydroxynonenal (HNE), has been reported to play an important role in the pathogenesis of osteoarthritis (OA) *in vivo*. It has been observed that due to intra-articular injection of HNE there are cartilage lesions but treatment with carnosine ameliorates the action of HNE *in vivo* [23]. Takayama *et al.* suggested that DNA damage occurs during OA and excision repair cross complementation group 1 (ERCC1) is an endonuclease which has important role in DNA damage repair [24]. It has been reported if inhibition of ERCC1 in chondrocytes occurs, then there is an increase in the expression of OA related proteins, apoptosis, cellular senescence, and hypertrophic-like changes suggesting that ERCC1 is critical for protecting human chondrocytes (HCs) from catabolic stresses thus providing insights into the pathophysiology of OA and a potential target for its treatment. Although the aetiology of osteoarthritis is yet not well established but main risk factors include mechanical, biochemical and genetic factors out of which obesity is considered to be a prominent one.

Rheumatoid Arthritis & Pathophysiology

Rheumatoid arthritis (RA) is a chronic immune inflammatory joint disease characterised by symmetrical, destructive and deforming polyarthritis affecting small and large synovial joints with associated disturbances and multisystem involvement. There is swelling, tenderness and limitation of movement with heat and redness of the skin around the joint. Small joints of hands, feet elbow, knee and shoulder are more involved but hip joints are less involved. It has been observed that swelling occurs due to accumulation of synovial fluid, hypertrophy of synovium and thickening of joint capsule. Various deformities also occur due to laxity of supporting soft tissue structures, destruction of ligaments, tendons cartilage etc. Muscle weakness also occurs during this time [25]. Most of these features are seen in the patients with high titre value of rheumatoid factor. Muscle wasting, tenosynovitis, bursitis and osteoporosis is common in RA. Rheumatoid nodule formation occurs in about 20% of RA patients those who are seropositive for IgM rheumatoid factor especially in Caucasians. Nodule formation is very rare in case of Indian and Africans. There are two types of nodule formation, superficial and deep. Superficial nodules are usually formed on areas subjected to repeated pressure and extensor surfaces. These nodules are usually painless and occur in single or multiple forms. Deep nodules mainly occur in pleura, pericardium heart. These types of nodules sometimes ulcerate and create secondary infection [25].

The etiology and pathophysiology of RA is not fully understood yet. Autoimmune and genetic factors are involved in the occurrence of the disease. The inflammation and tissue destruction results from complex cell-cell interaction in the rheumatoid synovium. Activation of T cells results in activation of macrophages and monocytes, causing them to secrete abundant cytokines. Arachidonic acid metabolism in macrophages increases COX 2 activation and prostaglandin production which cause pain, fever and inflammation. Studies on synovium of RA patients demonstrated mitogen activated protein kinase kinase (MAPKK) make independent contribution to p38 MAPK activation after cytokine stimulation [26]. Pathophysiological features of RA can also be explained by activation of limited number of transcription factor and its activation signal such as NF-κβ. NF-κβ induces gene expression of cell growth promoting factors such as cyclin D 1 and c-myc besides causing upregulation of inflammatory cytokines [27]. Synovial fibroblasts and activated T lymphocytes from patients with rheumatoid arthritis also express RANKL, which appears to trigger bone destruction in rheumatoid arthritis as well. Recent studies have shown that T lymphocytes produce cytokines other than RANKL such as IL-17, granulocyte–macrophage colony-stimulating factor and IFN-ã, which regulates osteoclastogenesis [28]. It has been reported that Th17 a new type of helper cells has a great importance in rhodents studies with arthritis [29]. It has been found that T cells which develop under the influence of IL-6 and IL-23, IL-17 is secreted and they are important in setting of arthritis. IL-17 in synergy with TNF and IL-1 is responsible for sustaining inflammation and causing damage to the bone and cartilage. In RA, chemokines like IL 18 promote chemotaxis of leucocytes which in turn promote angiogenesis. Koch reported that chemokines and their receptors are more expressed in the synovial tissues of the RA [30]. A number of other cells like TREG cell subset, suppressive macrophages, regulatory dendritic cells, CD 8+ supppresor T cells have been reported also to downregulate the disturbance in T-cell response which is caused by the pathogenesis of RA [31]. Chemokine ligands like CXCLS are notable for being chemotactic for neutrophils and CCLs are notable for monocyte chemotaxis. In RA, the pro inflammatory cytokines TNFα and IL-1β are the two most important mediators in the pathophysiology of RA [32]. The detection of rheumatoid factor, as well as high titers of other auto-antibodies signified the role of B cells in RA pathology, and this is further emphasized by clinical improvement in patients receiving rituximab, an anti-CD20 antibody [33]. Osteoprotogerin (OPG) is secreted by osteoblast and competes with RANKL for binding with RANK on osteoclast, thus causing bone loss. RA synovium exhibit an increase ratio of RANKL/OPG mRNA expression indicating pro osteoclastic condition dominant in synovial micro environment [34]. It has been observed that T helper cell responses depend upon the pleiotropic activity of cytokine IL 18. IL 18 mRNA and protein has been reported to be found in higher levels in the synovial tissues of rheumatoid arthritis than osteoarthritis [35]. Burmester *et al.* reported that cytokines IL 20 & IL 21 plays an important role in the pathogenesis of rheumatoid arthritis and are also potential targets for the treatment [36].

A number of other cells like TREG cell subset, suppressive macrophages, regulatory dendritic cells, CD 8+ supppresor T cells have been reported also to downregulate the disturbance in T-cell response which is caused by the pathogenesis of RA [37]. It has been observed that 14-3-3η, a specific isoform of a family of proteins that mainly regulate processes such as cellular signalling, activates cell-signalling pathways and induces factors have been observed to contribute to the pathogenesis of rheumatoid arthritis. It has been also reported that 14-3-3η induce MMP1 activity *in vitro*, also activate ERK and JNK, but not p38MAPK and high levels of this protein has been observed in the serum of the RA patients. Radiographic studies showed that high levels of this protein in the serum of RA patients cause damage to joints and bones [38].

Therapeutic Management of Arthritis

The aim of the management of rheumatism is to reduce pain and to minimize the change occurs during arthritis development. Physiotherapy, physical exercise and analgesics are often prescribed by the rheumatologists. Non-steroidal anti-inflammatory drugs (NSAIDS) like accelophenac, dichlophenac are the first line of defence against arthritis. But NSAIDS work through cyclooxygenase (COX 1 and COX 2) inhibition that inhibit prostaglandins. COX 1 inhibition causes side effects like G.I tract irritation, platelet aggregation and cardiovascular problems. The COX inhibition helps to protect against arthritic inflammation, pain and rheumatic fever. Glucocortiocoid therapy also shows certain side effects such as softening or destruction of the hip, knee, wrist or foot joint, cataract etc. For this reason disease modifying anti rheumatic drugs (DMARDS) are better advised. But DMARDS like methotrexate, cyclosporine A , anti cytokine therapies all have certain side effects like sepsis, pulmonary and extra pulmonary tuberculosis etc. The p38 pathway is a potential therapeutic target in RA because it functions as a regulator of pro-inflammatory cytokine production both *in vivo* and *in vitro*. Blocking intracellular signalling cascades is a promising therapeutic target in RA. Orally available inhibitors of Syk and JAK kinases have proven clinical efficacy in RA trials although much more work is needed before these drugs reach the clinic for routine use. Clinical trials have established that long term continuing treatment with anti-TNF agents is required to control rheumatoid disease. Experimental evidence suggests that TNF does play an important part in host defence mechanisms against certain infections (with organisms such as listeria, mycobacteria and pathogenic protozoa). While anti-TNF treatment in the murine collagen induced arthritis model was found to protect joints from damage, it is not yet established that anti-TNF treatment protects rheumatoid joints from structural damage. Measurement of circulating matrix metalloproteinases (MMP1and MMP3) in their inactive form has been noted to be reduced after infliximab in a dose related fashion.

In the preliminary research, the cholinergic anti-inflammatory pathway was activated by direct electrical stimulation of the efferent vagus nerve, which may inhibit the synthesis of TNF in liver, spleen, and heart, and attenuate serum concentrations of TNF during endotoxemia [39]. The α7 nicotinic acetylcholine receptor (α7 nAChR) was found to be the molecular linker between the cholinergic nervous system and the innate immune system [40], which mainly expresses on the membrane of immune cells, including monocytes, macrophages, T and B lymphocytes, and dendritic cells. Anti-tumour necrosis factor-a therapies have set a new standard for symptom control in rheumatoid arthritis, and blockade of tumour necrosis factor has the potential to protect joints from structural damage. Other targets for therapeutic antibodies include the cytokines interleukin (IL)-1, IL-6, IL-8, IL-15, IL-17 and IL-18. There is preliminary evidence for the clinical efficacy of both keliximab, a mAb targeting the T cell antigen CD4, and rituximab, a chimeric mAb against the B cell antigen CD20 and CTLA4-Ig, which blocks the CD28/B7 interaction. Cytokines are immune mediators that play an important role in the pathogenesis of rheumatoid arthritis (RA). The cytokine environment in the peripheral lymphoid tissues and the target organ (the joint) has a strong influence on the outcome of the initial events that trigger autoimmune inflammation. In susceptible individuals, these events drive inflammation and tissue damage in the joints. The discovery of interleukin-17 (IL-17) and its association with inflammation and autoimmune pathology has reported the pathogenesis of arthritis, which previously was based on a simplistic T helper 1 (Th1)-Th2 paradigm. The role of the newer cytokines, particularly those associated with the IL-17/IL-23 axis in arthritis. Ongoing studies examining the role of the newer cytokines in the disease process would improve understanding of RA as well as the development of novel cytokine inhibitors that might be more efficacious than the currently available options [41]. It has been predicted that anti-TNF treatment might slow down the destructive process in RA joints. Long term observations in the clinic will be required to establish whether other molecular and cellular processes can compensate for loss of this defence mechanism. T_{REG} cell has got potential interventions in the treatment of rheumatoid arthritis. IL 2 treatment has been observed to enhance the functionality and potentially increase the T_{REG} cell as reported in the mouse models of autoimmunity and patients with graft versus host disease37 and hepatitis C associated vasculitis [42]. Cauusens *et al.* stated that Tregitopes which are derived from Fc region of human IgG sequences have high affinity in binding to human HLA class II molecules, and also induce the expansion of CD4+/CD25hi/FOXP3+ T cells, suppressing antigen-driven T cell acti¬vation responsiveness *in vitro* thus showing if these Tregitopes are properly characeterised can be used in the treatment of many autoimmune diseases (which includes RA also) [43]. Like other soluble inflammatory cytokines, granulocyte-macrophage colony-stimulating factor (GM-CSF) is mainly involved in the generation, survival, and activation of cells from the myeloid com¬partment. It regulates the function of neutrophils, eosinophils, and macrophages, and is the part of pro-inflammatory network in RA. Expression of GM CSF and its receptor are detectable within synovial fluid and synovial tissue of patients with RA (Hamilton *et al.* 2008). MOR103, a neutralising agent for GM-CSF have shown its efficacy in the treatment of patients of RA in Phase I & Phase II clinical trials. Burmester *et al.* reported that IL 6 and its receptor, IL 17, IL 20, IL 21, IL 23 are potential targets in the near future for the treatment of rheumatoid arthritis [36]. IL 1β reported to play an important central role

in the pathogenesis of osteoarthritis (OA). IL 1β antagonists given directly or via gene therapy have been shown to partially prevent cartilage breakdown. TNF is a potent proinflammatory cytokine that has been reported to show elevated levels in the serum of the OA patients. Furthermore, Zhang *et al.* reported that in a rabbit model of OA, intra-articular treatment with infliximab, a monoclonal antibody against TNF in the rabbit model of OA showed to decrease the extent of the cartilage lesions [44]. Excess production of nitric oxide and its metabolites in OA have been found to cause inhibition of type II collagen and proteoglycan synthesis, activa¬tion of metalloproteinases and chondrocyte apoptosis [45]. Hellio Le Graver *et al.* reported that treatment with iNOS inhibitor, cindunistat did not improve joint pain or function only to reduce the joint space in the medial tibio-femoral compartment [46]. Bone morphogenic protein (BMP 7) has been observed as a potential therapeutic target for the treatment of OA. Hunter *et al.* reported that intra articular injection of BMP-7 has shown to contribute to embryonic development and repair of mature tissues, including cartilage [47]. OA is associated with progressive and irreversible destruction of the joint tissues and it has been observed that all joint tissues contain mesenchymal stem cells which are capable of differentiating into bone, cartilage, and other tissues. OA has been reported to be associated with the changes in quantity and phenotype in the resident MSC cells. *Ex vivo* preparations of MSCs in the OA joints have been found to evoke a useful repair response of the cartilage in animal models of OA. Intra articular injections of MSCs have shown to prevent the OA progression and at the same time also help to repair the joint destruction causing the paracrine effect [48]. But it is not well known whether these new therapeutic managements have any side effects. As a result the past decades or two have seen a dramatic increase and growing interest in the use of alternative treatments and herbal therapies by arthritic patients. There has been a dramatic increase among the researchers to find out the anti-arthritic activity of different herbs and herbal constituents around the world.

Alternative Treatment of Arthritis with herbs and herbal constituents

Despite the availability of conventionally used drugs for arthritis, their limited efficacy in a proportion of patients coupled with their high cost and severe adverse effects has necessitated the search for novel therapeutics for this debilitating disease. The control of both inflammation and bone damage is essential for effective management of arthritis. There is a need to search for alternative natural therapy against arthritis with lesser side effects. Many traditional medicinal systems had herbal remedies against rheumatoid arthritis and osteoarthritis, although their proper scientific evaluation was pending till recent decades. In a broad sense, traditional herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products, processed by various local procedures including steaming, roasting, or stir-baking with honey, alcoholic beverages or other materials. The basis for 'herbal preparations' includes powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials produced by extraction, fractionation, purification, concentration, or other physical or biological processes.

The past decades or two have seen a dramatic increase and growing interest in the use of alternative treatments and herbal therapies by arthritic patients (Table 1). Topical application of *Aloe vera* extract resulted in reduction of inflammation and arthritis in adjuvant induced arthritis [49]. The willow bark tree extract also capable of reducing pain and improvement of movements in case of OA [50]. Appleboom *et al.* stated that Avocado soybean unsaponifiables significantly decrease the pain in OA patients [51]. This group compared the symptomatic effects of 300 and 600mg daily dose of avocado/soybean unsaponifiables in patients with knee osteoarthritis in a multicenter, double blind study for 3 months. The study involved patients (both male and female) aged 45 to 80 years. It was observed that the efficacy of avocado/soybean unsaponifiables at a dosage of 300mg/day and 600mg/day was consistently superior to that of placebo at all endpoints, with no differences observed between the two doses. Herbal extract of Pine bark when tested on OA patients showed reduced pain and improvement in movement than the NSAIDS drugs and also showed no gastrointestinal complications. *Pycnogenol* is a powerful antioxidant and anti-inflammatory compound made from the highest quality French maritime pine bark. In this study, osteoarthritis symptoms were evaluated by WOMAC scores, mobility by recording their walking performance (treadmill).Treatment (77 patients) and placebo group (79) were comparable for age, sex distribution, WOMAC scores, walking distances and use of antiinflammatory drugs. The global WOMAC score decreased by 56% (significant, $P<0.05$) in the treatment group versus 9.6% in the placebo group. Pycnogenol offered an option for reduction of treatment costs and side effects by sparing antiinflammatory drugs [52].

Herbs and herbal constituents	Use in arthritis/ inflammation	References
Willow bark extract	Reduced pain and improvement in movement in osteoarthritis	Schmid *et al.* [50]
Avocado soybean unsaponifiables	Reduced pain in osteoarthritis	Appleboom *et al.* [51]
Pine bark extract	Reduced pain and improvement in movement in osteoarthritis	Belcaro *et al.* [52]
Methanolic extract of the root of *Ricinus communis*	Anti nociceptive activity against acetic acid induced writhing test, formalin induced paw licking test	Taur *et al.* [53]
Ethanolic and ethyl acetate extract of *Tripterygium wilfordii*	Antirheumatoid arthritis	Tao *et al.* [55]
Ginger extract	Antiarthritis	Wigler *et al.* [56]
Seeds and husks of *Rosa canina*	Antiarthritis	Christensen *et al.* [58]
Curcumin	Upregulation of MMP3 and suppress matrix synthesis	Shakibaei *et al.* [60]

Herbs and herbal constituents	Use in arthritis/ inflammation	References
Resveratrol from grapes	Suppression of NFκβ dependent pro inflammatory products like PGE2, MMP 1, MMP 3	Csaki *et al.* [61]
Piperine isolated from black pepper	Inhibition in the inflammation and decreased in the symptoms of carragenin induced paw edema arthritic model	Bang *et al.* [62]
Root powder of *Withenia sommifera Linn*	Anti arthritic property in adjuvant induced arthritis	Pathwardhan *et al.* [63]
Ethanolic extract of *Tinospora cordifolia Willd*	Anti arthritic activity against adjuvant induced arthritis and bovine induced arthritis	Paval *et al.* [64]
Lawsonia innermis	Anti arthritic activity against adjuant induced and formaldehyde induced arthritis	Kore *et al.* [65]
Methanolic leaf extract of *Urtica pilulifera*	Anti arthritic activity against Freund's complete adjuvant induced arthritis	Abudoleh *et al.* [66]
Methanolic extract of *Ficus bengalensis*	Anti rheumatic activity	Manocha *et al.* [67]
Cedrus deodara	Anti arthritic activity	Chandur *et al.* [68]
Bartogenic acid isolated from *Barringtonia racemosa Linn*	Anti arthritic activity	Patil *et al.* [69]
Green tea polyphenols	Increased bone mineral density, serum osteocalcin level	Shen *et al.* [71]
Theaflavin from tea	Antiarthritic activy Blockade of MAPK and NF κβ pathway	Datta *et al.* [80] Kim et al. [70]
80% alcoholic extract of leaves of *Aloe vera, Bacopa monnieri, Moringa oleifera* and rhizome of *Zingiber officinale*	Anti inflammartory activity	Padmanabhan *et al.* [72]
Myrtus communis, Smilax aspera, Lavandula stoechas and *Calamintha nepeta*	Anti-inflammatory activity	Amira *et al.* [73]
Phenolic compounds-rich fraction from *Urtica atrichocaulis*	Anti rheumatoid arthritis	Wang *et al.* [74]
Petroleum ether extract, ethyl acetate extract and methanolic extract of the leaves of *Cassia uniflora*	Anti arthritic, anti inflammatory and anti analgesic activity in rat models	Chaudhuri *et al.* [76]
Black tea and Green tea	Anti inflammatory activity	Chatterjee *et al.* [77]
Dried tea root extract	Anti inflammatory, analgesic and anti pyretic activities	Chattopadhyay *et al.* [78]
Aqueous black tea extract	anti arthritic property in adjuvant induced rheumatoid arthritis	Datta *et al.* [79]
4-methoxy-5- hydroxycanthin-6-one isolated from *Picrasma quassioides*	Anti-inflammatory and antiarthritic effect	Fan *et al.* [81]
Duhuo Jisheng Decoction	Anti osteoarthritic activity	Zheng *et al.* [82]
Huo-luo-xiao-ling dan	Anti rheumatoid arthritis, suppressed inflammatory arthritis and reduced bone and cartilage damage in the joints of arthritic animals	Nanjundaiah *et al.* [83]
Huang-Lian-Jie-Du-Tang	Effective against collagen induced arthritis in rat	Hu *et al.* [84]
Scutellaria baicalensis Georgi	Anti-arthritic agent	Yang *et al.* [85]
Sida cordifolia L. and Piper longum L.	Effective against collagen induced arthritis	Nirmal *et al.* [86]
Allium sativum	Anti inflammatory and anti rheumatoid arthritic agent	Majewski [88]
Xanthium strumarium extract	FCA-induced arthritis	Lin *et al.* [90]
Extract of *Boswellia serrata*	Anti inflammatory activity, decrease of the release of pro inflammatory cytokines	Kumar *et al.* [93]
Schefflera octophylla	Antinociceptive and anti-inflammatory activities	Chen *et al.* [95]
Calotropis procera latex proteinC	Acute inflammation	Kumar *et al.* [96]

Table 1: Herbs and herbal constituents active against rheumatoid and osteoarthritis

Ricinus communis is a small tree distributed throughout the tropics and warm temperate regions of the world. Taur *et al.* reported that methanol extract of this plant showed anti nociceptive activity against acetic acid induced writhing test, formalin induced paw licking test [53]. The methanol extract of *Ricinus communis* leaves was evaluated in antinociceptive model in mice at doses of 100, 125 and 150 mg/kg body weight. The results indicated that the extract exhibited considerable antinociceptive activity against pain model in animals. *Spilanthes acmella Murr.*, an indigenous herb growing throughout the tropics and it has been reported that the crushed plant has anti-inflammatory activity [54]. *Tripterygium wilfordii*, a perennial vine plant grown in China, has been reported to have anti-rheumatoid arthritis activity. An ethanol/ethyl acetate extract from the roots of *Tripterygium wilfordii Hook F* was used in a double-blind, placebo-controlled study in patients with longstanding rheumatoid arthritis (in whom conventional therapy had

failed) at dose 180 mg/day and 360 mg/day. It showed therapeutic benefit in patients with treatment-refractory rheumatoid arthritis [55]. In a study, ginger extract showed much better efficacy in improvement of arthritis than ibuprofen drug. The effect of a ginger extract (Zintona EC) on patients suffering from gonarthritis was evaluated at dose of 250mg for 6 months. In the first 3 months, there was no significant effectiveness of Zintona EC when compared to placebo group, but at the end of 6 months the ginger extract group showed a significant superiority over the placebo group [56]. Extract of *Boswellia serrata* have natural anti-inflammatory activity and it can switch off the release of pro inflammatory cytokines which plays an important role in case of arthritis. The double-blind placebo controlled clinical study on the patients receiving *Boswellia serrata* extract reported decrease in knee pain, increased knee flexion and increased walking distance. The frequency of swelling in the knee joint was also decreased [57]. Rosehip powder was extracted from the seeds and husks of *Rosa canina* and it has been used extensively in traditional medicine. Christensen *et al* treated arthritic patients with rosehip powder and reported that there is significant improvement [58]. Curcumin (diferuloylmethane) is the principal biochemical component of the spice turmeric and has been shown to possess potent anti-catabolic, anti-inflammatory and antioxidant properties. Henrotin *et al.* reviewed the anti-inflammatory activities of Curcumin. Curcumin protects chondrocytes from catabolic effects of IL 1β that are responsible for pathogenesis of OA [59]. Curcumin is a potent anti-inflammatory agent capable of suppressing the production and catabolic actions of IL-1β and TNF-α. In a study, the effect of curcumin in human articular chondrocyte culture treated with IL-1β and TNF-α was evaluated for up to 72h. Collagen type II, integrin β1, cyclo-oxygenase-2 (COX-2) and matrix metalloproteinase-9 (MMP-9) expressions were evaluated by western blotting. The results indicated that curcumin acted as a naturally occurring anti-inflammatory agent against osteoarthritis through suppression of NF- κβ mediated IL-1β/TNF-α catabolic signalling pathways [60]. Resveratrol is a natural compound found in red grape skin with many beneficial actions. *In vitro* study with this compound showed inhibition of IL 1β induced apoptosis and down regulation of NFκβ pathway. It has also been reported that due to inhibition of NFκβ pathway there is suppression of NFκβ dependent pro inflammatory products like PGE2, MMP 1, MMP 3 [61]. Piperine isolated from black pepper when feed orally to carragenin induced paw edema arthritic model of rats showed inhibition in inflammation and decrease in the symptoms of arthritis in a dose dependant manner at concentrations of 10-100 μg/ml [62]. Root powder of *Withenia sommifera* Linn showed anti arthritic property in adjuvant induced arthritis [63]. *Tinospora cordifolia Willd* (Menispermaceae) is distributed throughout tropical Indian subcontinent and China and its ethanol extract showed anti arthritic activity against adjuvant induced arthritis and bovine induced arthritis [64]. Hydroalcoholic extract of *Lawsonia innermis* showed anti arthritic activity against adjuant induced and formaldehyde induced arthritis [65]. *Urtica pilulifera* has been used in folk medicine to decrease the inflammation and arthritis. Abudoleh et al reported that methanolic leaf extract of this plant has anti arthritic activity against Freund's complete adjuvant induced arthritis [66]. Manocha *et al.* reported that methanolic extract of *Ficus bengalensis* has anti rheumatic activity [67]. *Cedrus deodara* is a native plant of western Himalayas and showed its anti-arthritic activity effectively in polyarthritis phase of adjuvant induced arthritis [68]. Bartogenic acid isolated from *Barringtonia racemosa Linn* showed to protect arthritic symptoms in case of adjuvant induced arthritis. It protects rats against the primary and secondary arthritic lesions, body weight changes and haematological perturbations induced by adjuvants at dose 2, 5 and 10 mg/kg [69]. Kim *et al.* reported that theaflavin inhibit LPS-induced interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and intercellular adhesion molecule-1 (ICAM-1) expression in bone derived macrophages through blockade of MAPK and NF κβ pathway [70]. Shen *et al.* reported that green tea polyphenols showed increased bone mineral density, serum osteocalcin level thus indicating its role in bone health [71]. Regulation of osteoclast activity is essential in the treatment of bone diseases. Padmanabhan *et al.* reported 80% alcoholic extract of leaves of *Aloe vera, Bacopa monnieri, Moringa oleifera* and rhizome of *Zingiber officinale* was used to prepare an herbal preparation [72]. This herbal preparation showed anti inflammartory activity in case of *in vitro* study. Amira *et al.* studied the potential anti-inflammatory activity of myrtle (*Myrtus communis*), sarsaparilla (*Smilax aspera*), Arabian or French lavender (*Lavandula stoechas*), and calamint (*Calamintha nepeta*) along with their apoptotic effects on the pro-inflammatory cells, and the correlation of these effects with the plants' potential anti-oxidant activity. It has been found that Myrtle extract exhibited the highest inhibitory activity in the paw oedema induced by carrageenan [73]. Wang *et al.* reported that the phenolic compound-rich fraction from *Urtica atrichocaulis*, an endemic plant to China, is commonly used to treat rheumatoid arthritis inhibited the experimental arthritis induced by FCA [74]. It has been found that leaf methanol extract of *Cotyledon orbiculata L.* was investigated for antinociceptive and anti-inflammatory activities using acetic acid writhing and hot-plate tests and carrageenan-induced oedema test in mice and rats. Amabeoku *et al.* stated that *C. orbiculata* has antinociceptive and anti-inflammatory activities, justifying the folk use of the plant species by traditional medicine practitioners in the treatment of painful and inflammatory conditions like inborn diseases [75]. In this study, the selected dose of C. orbiculata was 100-400 mg/kg (i.p.). *Cassia uniflora* is an herb and its leaves were used as food whereas its stem was used as a fuel. The leaves of this plant has medicinal property and its use has been known from folk medicine. Chaudhuri *et al.* reported that the petroleum ether extract, ethyl acetate extract and methanolic extract of the leaves have anti arthritic, anti-inflammatory and anti analgesic activity in rat models [76]. Three extracts of *C. uniflora* was examined for analgesic (Eddy's hot plate and acetic acid induced writhing), anti-inflammatory (Carrageenan induced paw edema) and anti-arthritic (Complete Freund's Adjuvant induced arthritis) potential at 100 and 200 mg/kg doses. It was observed in the study that the extracts possessed analgesic, anti-inflammatory and anti-arthritic activity in experimental animals. Therapeutic value of Tea has been recognized in different systems of traditional medication for the treatment of different diseases and ailments. In Ayurvedic medicine, tea is well known as an anti inflammatory, anti oxidant, anti diabetic agent. Chatterjee *et al.* studied the anti inflammatory effect of Black tea and Green tea *in vitro* model [77]. For this study they evaluated anti inflammatory effect of black tea and green tea against denaturation of egg albumin. The results showed a concentration-dependent inhibition of albumin denaturation by both the tea

extracts. Green tea was found to be more active than black tea, probably due to the higher flavonoid contents of green tea. Pharmacological studies had shown that methanol-water extract (1:1) of dried tea root possess anti inflammatory, analgesic and anti pyretic activities [78]. Datta *et al* reported that aqueous black tea extract has anti arthritic property in adjuvant induced rheumatoid arthritis animal models and acted through the urinary markers and serum markers [79]. Animals were divided into 5 groups: group 1- sham control, group 2- arthritis control, group 3- standard drug treated (indomethacin, 0.25mg/100 g weight of rat, p.o.), group 4- black tea extract treated (250mg/100 g weight of rat, p.o.) and group 5- black tea extract treated (500mg/100 g weight of rat, p.o.). Antiarthritic activity of black tea extract was evaluated in animal models (through physical, urinary and serum parameters) and in clinical study (through serum cytokine study). The results showed the efficacy of black tea extract against arthritis in animal model and clinical study. It has also been reported that aqueous black tea extract has anti inflammatory and anti arthritic activity in clinical studies. Theaflavin, the chief flavonoid of black tea extract has showed anti arthritic activity in experimental animal model of rheumatoid arthritis [80]. Theaflavin at dose 0.1mg/kg and 0.5mg/kg dose normalized serum enzymes, serum cytokines, synovial cytokines and bone ash mineral levels. It significantly arrested the cell cycle of white blood cells at G_0/G_1 phase.

Fan *et al* evaluated the anti-inflammatory and antiarthritic effect of a natural alkaloid, 4-methoxy-5- hydroxycanthin-6-one isolated from *Picrasma quassioides* [81]. This alkaloid significantly inhibited lipopolysaccharide induced NO production, TNF-α release in macrophage RAW 264.7 and down-regulated iNOS expression. Oral administration of 4-methoxy-5- hydroxycanthin-6-one (3, 9, and 27 mg/kg) reduced carrageenan-induced paw edema and complete Freund's adjuvant (CFA)- induced chronic arthritis in rats, indicating the efficacy of 4-methoxy-5- hydroxycanthin-6-one against inflammatory diseases including chronic arthritis. Duhuo jisheng decoction (DHJSD) is a widely used traditional Chinese medicine against osteoarthritis. Zheng *et al.* identified multiple active compounds from DHJSD and suggested that the DHJSD had drug and lead like compounds with potential synergy and polypharmacology against OA [82]. Another traditional Chinese medicine, huo-luo-xiao-ling dan has long been used for the treatment of rheumatoid arthritis and other inflammatory disorders. Nanjundaiah *et al.* evaluated the efficacy of huo-luo-xiao-ling dan against arthritic bone damage in adjuvant induced rheumatoid arthritis model [83]. In this study, huo-luo-xiao-ling dan treatment suppressed inflammatory arthritis and reduced bone and cartilage damage in the joints of arthritic animals. It was proposed that protection against bone damage was mediated primarily via inhibition of mediators of osteoclastic bone remodeling (e.g., receptor activator of nuclear factor kappa-B ligand; RANKL), skewing of RANKL/osteoprotegerin (OPG) ratio in favor of antiosteoclastic activity, reduction in the number of osteoclasts in the arthritic joint's bone, and inhibition of cytokine production and MMP activity. Another traditional Chinese herbal remedy Huang-Lian-Jie-Du-Tang, consisting of Rhizoma coptidis (*Coptis chinensis Franch, Ranunculaceae*), *Radix scutellariae* (*Scutellaria baicalensis Georgi, Labiatae*), *Cortex phellodendri* (*Phellodendron amurense Rupr. Rutaceae*) and *Fructus gardeniae* (*Gardenia jasminoide Ellis, Rubiaceae*) in a weight ratio of 3:2:2:3, has been used to treat inflammation, hypertension, gastrointestinal disorders, and liver and cerebrovascular diseases in the clinical practice of traditional Chinese medicine, especially in treating inflammation for nearly two thousand years. Hu et al showed its efficacy against collagen induced arthritis in rat. It effectively ameliorated arthritis and suppressed the immune response against collagen [84].

T-helper-17 (T_h17) cells are involved in a number of inflammatory disorders including rheumatoid arthritis. T_h17 cell antagonism serves as a treatment option for arthritis. A compound baicalin, isolated from a Chinese herb huangqin (*Scutellaria baicalensis Georgi*), was evaluated as an alternative anti-arthritic agent active against T_h17 cell population [85]. The herb itself relieved ankle swelling and protected the joint against inflammatory destruction. Baicalin inhibited splenic T_h17 cell population expansion *in vivo*, prevented IL17-mediated lymphocyte adhesion to cultured synoviocytes, and blocked IL-17-induced intercellular adhesion molecule 1, vascular cell adhesion molecule 1, IL-6, and tumor necrosis factor-alpha mRNA expression in cultured synoviocytes. Baicalin downregulated the joint inflammation caused by IL-17 produced by an expanded population of splenic Th17 cells in experimental arthritis. Nirmal *et al.* examined the efficacy of six herbal remedies, *Sida cordifolia L., Piper longum L., Zingiber officinale Rosc., Ricinus communis L., Vitex negundo L.* and *Tribulus terrestris L.* against collagen induced arthritis [86]. In this study it was observed that *S. cordifolia* and *P. longum* possessed potent anti-osteoarthritic activity.

African traditional medicinal system has a wide variety of herbal remedies to treat rheumatoid arthritis (RA) and inflammation. Cock and van Vuuren investigated thirty four extracts from 13 South African plant species with a history of ethnobotanical usage in the treatment of inflammation for their ability to control two microbial triggers for rheumatoid arthritis (*Proteus mirabilis* and *Proteus vulgaris*) [87]. Twenty nine extracts inhibited the growth of P. mirabilis and twenty three of them inhibited the growth of *P. vulgaris*. Methanol and water extracts of *Carpobrotus edulis, Lippia javanica, Pelargonium viridflorum, Ptaeroxylon obliquum, Syzygium cordatum leaf* and bark, *Terminalia pruinoides, Terminalia sericea, Warburgia salutaris* bark and an aqueous extract of *W. salutaris* leaf were effective Proteus inhibitors. The extracts with Proteus inhibitory activity were also either non-toxic, or of low toxicity in the *Artemia nauplii* bioassay. The low toxicity of these extracts and their inhibitory bioactivity against *Proteus* sp. indicated their potential role in blocking the onset of rheumatoid arthritis. Garlic (*Allium sativum*) is also a well-known remedy against inflammation and rheumatoid arthritis [88]. Wu *et al.* reported the anti-arthritic potential of petroleum ether extract of hips of *Rosa multiflora* in collagen-induced arthritis model in rats [89]. In this study rheumatoid arthritis was induced in animals by intradermal injection of bovine type II collagen, and dexamethasone was used as positive control. Animals were treated with petroleum ether extract of *Rosa multiflora* (12, 36 or 120mg/kg bw per day, p.o.) for 28 days and it was observed that it had significant anti-arthritic activity. Lin et al reported the anti-arthritic property of *Xanthium strumarium* extract on FCA-induced arthritis in rat model [90]. *Cynodon dactylon* is a traditionally used herb to treat rheumatism. Its ethanolic extract has been proved to be effective

against FCA-induced arthritis [91]. Gupta & Singh reported the anti-inflammatory effect of *Withania somnifera* on collagen-induced arthritis in rats [92]. Treatment with *W. somnifera* root powder at 600 mg/ kg dose to the collagen-induced arthritic rats decreased the severity of arthritis by effectively suppressing the symptoms and improving the functional recovery of motor activity and radiological score. Kumar *et al.* has reported that ayurvedic herbal preparation caused improvement of pain in patients. Ayurvedic treatment with Ashwagandha powder and Sidh Makardhwaj had a potential for the treatment of rheumatoid arthritis in clinical study [93]. Antinociceptive activity of *Hedyotis corymbosa Linn.* whole plant ethanolic extract has been established [94]. *Hedyotis corymbosa Linn*. extract produced antinociceptive effect against heat-induced and chemical-induced pain model in animals at dose 100 and 200mg/kg. Antinociceptive and anti-inflammatory activities of *Schefflera octophylla*, a traditional Chinese herb have been reported. Ethanolic extract of *S. octophylla* had significant dose-dependent anti-inflammatory and antinociceptive activities in rat model [95]. *Calotropis procera* have been known to exhibit anti inflammatory, anti fungal, anti oxidant activity. Kumar et al isolated a protein from *C. procera* latex with anti-inflammatory and analgesic properties [96]. The study evaluated the effect of latex protein on inflammation, oxidative stress and tissue histology in rat model. Treatment with latex protein produced a dose dependent inhibition of edema formation.

Limitations of alternative therapeutics

Present research directions of alternative therapeutics of arthritis using herbs and herbal products have many limitations, which are as follows-

1. In many of the cases the crude herbs are being used against arthritis. Active compounds isolated from the herbal products are needed to be examined. Sometimes more than one active compound in a single herbal extract is effective against arthritis which should be explored.

2. The research of alternative therapeutics against arthritis has been mainly focused on osteoarthritis and rheumatoid arthritis (and on gout in a few cases). Besides this, there are many types of arthritis (such as septic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis etc.) which should be considered during design of alternative therapeutics.

3. Toxicity studies of herbs and herbal constituents active against arthritis should be worked out.

Recommendations of using herbs and herbal constituents against arthritis

The following recommendations may be followed while experimenting with alternative therapeutics using herbs and herbal constituents against arthritis-

1. Pure compounds of herbal origin may be used in alternative therapeutic research against arthritis.

2. Combination of different herbs or herbal constituents may be useful against arthritis.

3. Toxicity studies of the herbs and herbal constituents may be carried out as many of the herbs possess toxicity.

4. In Ayurveda, there has been mention of combination of metals along with herbs, which potentiated the efficacy of herbs. Gomes et al reported the efficacy of herb-metal nanoparticle (Herbonanoceuticals) against many pathophysiological conditions [97]. It may open new direction of research with herbs and herbal constituents against arthritis using metal nanoparticle.

Conclusion

This review tried to focus on different herbs and herbal constituents which have been traditionally used in the treatment of arthritis. Though research on experimental animal models showed interesting observations but very few clinical and toxicological studies have been done in this area. Future research opportunities are open in this area which may yield new drug clues against arthritis, a major socio-economical medical problem among the senior persons around the world. We are hopeful that herbal compounds will be an alternative treatment against arthritis and bone-joint related problems in the near future.

Conflict of interest

Authors declare no conflict of interest.

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Contribution of authors

Sourav Ghosh and Poulami Datta, Post-doctoral fellow, equally contributed in writing the manuscript. Kalyani Saha, Pre-doctoral fellow, partially contributed in writing the manuscript. Amrita Sarkar, Post-doctoral fellow, partially contributed in writing the manuscript. Dilip Chandra Muhuri, Assistant Professor, partly edited the manuscript. Aparna Gomes and Antony Gomes provided the concept, edited the whole manuscript including the bibliography.

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