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File: ■ Phytomedicine
■ Joint Disorders

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RE: Review of Medicinal Plant Extracts Reveals Trends of Clinical and Biochemical Benefits in Patients with Osteoarthritis and with Rheumatoid Arthritis

Dragos D, Gilca M, Gaman L, et al. Phytomedicine in joint disorders. *Nutrients*. January 2017;9(1):70. doi: 10.3390/nu9010070.

Chronic joint inflammatory disorders, including osteoarthritis (OA) and rheumatoid arthritis (RA), are characterized by disabling symptoms and histological alterations caused by an increase in inflammation and oxidative stress. Risk factors for OA are older age, gender, overweight, increased body mass index, genetics, ethnicity, diet, trauma, and certain physical or occupational activities. RA, a chronic progressive systemic autoimmune disease, is associated with disability and an increased risk for cardiovascular disease, lymphoma, and death. Conventional treatment of OA and RA, while they may be effective, can cause serious adverse effects. Botanicals may help improve the symptoms and course of these diseases with fewer adverse effects than conventional treatment. These authors reviewed the scientific evidence available from medical databases and literature on medicinal plants that have been reported to have anti-arthritic activity in vitro, in animals, and in human clinical studies.

The authors conducted a literature search in PubMed, looking for only the following medicinal plants studied in human clinical studies: arnica (*Arnica montana*, Asteraceae), boswellia (frankincense; *Boswellia* spp., Burseraceae), *Curcuma* spp. (Zingiberaceae), horsetail (*Equisetum arvense*, Equisetaceae), devil's claw (*Harpagophytum procumbens* and/or *H. zeyheri*, Pedaliaceae), sanchi ginseng (*Panax notoginseng*, Araliaceae), willow (*Salix* spp., Salicaceae), sesame (*Sesamum indicum*, Pedaliaceae), comfrey (*Symphytum officinale*, Boraginaceae), ginger (*Zingiber officinale*, Zingiberaceae), and ashwagandha (*Withania somnifera*, Solanaceae). [Note: While there may be very good reasons for doing so, the authors do not make clear why they chose only these medicinal plants and not any others.]

Arnica has been used in traditional herbalism, primarily topically, to treat trauma-, strain-, and/or inflammation-related conditions of the musculoskeletal system and for rheumatologic conditions. It was shown to be beneficial in rats with collagen-induced arthritis and to improve knee OA in humans. Some investigators attribute the anti-arthritic efficacy to a synergism of phenolic and flavonoid compounds.

Many anti-arthritic formulations contain frankincense (predominantly *B. serrata*; also *B. sacra* and others). In vitro, a frankincense preparation slowed the breakdown of cartilage and blocked an inflammatory reaction. In another in vitro study, a combination of cat's claw (*Uncaria tomentosa*, Rubiaceae), *Boswellia* spp., maca (*Lepidium meyenii*, Brassicaceae), and an amino acid exhibited anti-inflammatory properties and protected articular cartilage. Animal studies report that frankincense, alone and in combination with other herbs, relieved inflammation and arthritis. A Cochrane systematic review of frankincense cited two high-quality and two moderate-quality studies demonstrating its superiority compared with placebo in reducing pain and increasing functionality, and one moderate-quality study reporting its safety. Among the bioactive principles of frankincense responsible for its anti-inflammatory activity is β-boswellic acid.

Turmeric (*C. longa*) is used in Ayurvedic medicine for its anti-inflammatory properties. In animal studies, turmeric preparations helped prevent the destruction of joints and, combined with ginger, alleviated histopathological changes of arthritis. In a human clinical study cited, a mixture of turmeric and frankincense was more effective than the nonsteroidal anti-inflammatory drug celecoxib in treating OA, with no toxicity. The active ingredient, diferuloylmethane, benefits various conditions through its influence on various signaling pathways and mediators.

Horsetail, used in European ethnomedicine as an anti-inflammatory remedy, exhibited downregulating effects on lymphocyte proliferation in an animal model of arthritis. In a clinical study of patients with RA, horsetail decreased the inflammation marker tumor necrosis factor-alpha (TNF-α) as a contributing mechanism. Its active ingredient kynurenic acid is suggested to be responsible for its anti-inflammatory and pain-relieving effects.

Devil's claw is approved by the European Medicines Agency (EMA) to treat degenerative disease of the musculoskeletal system. Devil's claw extracts have shown chondroprotective activity in vitro and anti-inflammatory activity in rats. In several human clinical trials, various devil's claw extracts significantly improved pain, movement, and joint crepitus in patients with knee and hip OA. The phytochemicals responsible for the plant's anti-OA effect are its iridoid glycosides harpagoside, harpagide, and procumbide, found mostly in its tubers and root.

Sanchi ginseng, which has long been used to treat traumatic injuries, swellings, and pains, was shown to inhibit pro-inflammatory mediators in vitro and suppress collagen-induced arthritis in mice. Combining sanchi ginseng with Chinese foxglove (*Rehmannia glutinosa*, Orobanchaceae) and eleuthero (*Eleutherococcus senticosus*, Araliaceae) improved physical function and pain in human patients with knee OA. Saponins are the main osteoactive phytochemicals in sanchi ginseng.

Various species from the genus *Salix*, or willows, have been used historically to relieve pain. In animal studies, willow bark extract exhibited anti-inflammatory and antioxidative properties. In a human clinical trial, a willow bark extract controlled the symptoms of patients with OA, especially pain, "although with rather subdued efficiency." Patients with OA and back pain experienced decreased pain when treated with a willow bark extract for six months. The active ingredient is salicin; other phytochemicals such as polyphenols and flavonoids also may contribute to its beneficial effects.

Used in Asian traditional medicines to alleviate inflammation-associated pain, sesame oil reportedly has helped alleviate joint pain in animal studies. In a human clinical study of patients with knee OA, oral administration of sesame together with standard therapy produced better results on subjective and objective measures than did the standard therapy alone. The lignans in sesame appear to be responsible for its protection against inflammation and oxidative stress.

Comfrey, used traditionally in Europe to treat inflammatory disorders, has shown anti-inflammatory potential in vitro and in animal studies. In patients aged 50-80 years with knee OA, a topical comfrey preparation decreased pain but did not decrease the rate of cartilage breakdown. Among its active phytochemicals, the phenolic acids, glycopeptides, and amino acids are considered to be at least partly responsible for its anti-inflammatory effects.

Ginger is traditionally used in Ayurveda for joint diseases. In mice, the oral administration of a squeezed ginger extract initially increased TNF-α synthesis but after repeated administration, decreased it. In a human clinical study, 1 gram of ginger powder daily for three months reduced inflammatory markers in patients with knee OA. Significant reductions in arthritic pain were seen in other human studies. The anti-inflammatory properties of ginger are attributed to its pungent constituents.

Ashwagandha is used in Ayurvedic medicine for its anti-inflammatory and anti-OA activities. Significant reductions in pain, stiffness, and disability were reported in patients with knee pain after treatment with an aqueous ashwagandha extract. A contributor to the beneficial effects of ashwagandha in patients with OA is the steroid withaferin A.

While the authors conclude that "medicinal plant extracts showed trends of clinical and biochemical benefits with low risk of side effects … .," they did not describe in detail the side effects of the botanicals in the human studies. This is a limitation of the study. Further study and more in-depth analysis with the inclusion of possible side effects are warranted.

—Shari Henson

Peer Reviewer's Comment:
An odd limitation of the original article is that it provides the doses used in human studies for some botanicals but not for others. In comparing animal to human data and, most particularly, clinical trials against one another, knowing the dose is essential.

Referenced article can be accessed at http://www.mdpi.com/2072-6643/9/1/70.