Update on complementary and alternative medicines for arthritis

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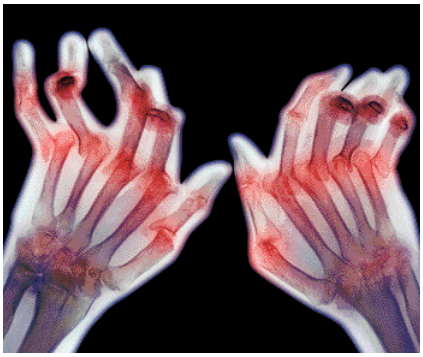
Although there is limited evidence to support their use, complementary and alternative medicines may offer promising results in patients with arthritis.



PHOTOLIBRARY

Figure. X-ray of arthritic hands.

Arthritis will affect most of us at some point in our lives, with up to 80% of people over the age of 70 years experiencing its effects. It is, therefore, appealing to hear of various nutritional or 'natural' therapies that may improve its symptoms or prevent its development, and such claims are often seen as headlines in the general media. Unfortunately, strong scientific evidence for most of these claims is lacking. This review looks at the current evidence available for the more popular of the complementary and alternative medicines marketed for the treatment of patients with arthritis (Table).

Glucosamine and chondroitin

Glucosamine is a component of O- and N-glycosaminoglycans, which are an important part of the cartilage matrix. For medicinal use, glucosamine can be extracted from crustacean shells as chitin or produced through fermentation of vegetable matter.

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Chondroitin, often combined with glucosamine in nutraceutical products, is a naturally occurring polysaccharide molecule that provides compressive resistance in healthy human cartilage. Chondroitin for supplements is usually derived from bovine trachea or shark cartilage. Ingested glucosamine and chondroitin are said to reach the joints and, therefore, have a potential role in pain relief and in slowing structural damage in individuals with osteoarthritis (OA).

Early clinical studies of glucosamine and chondroitin in patients with OA were extremely promising, showing symptom relief of up to 50% and suggesting retardation of cartilage loss over time compared with placebo. However, since those studies have been published, evidence from subsequent trials and indeed clinical experience has been variable. Latest research fails to show any significant benefits of glucosamine hydrochloride treatment on pain in patients with OA of the knee.

The large multicentre Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), published in 2006, randomised 1583 patients with OA of the knee to treatment with either glucosamine hydrochloride, chondroitin sulfate, both glucosamine and chondroitin, celecoxib alone or placebo.[1] There were no significant differences in knee pain between any of the non-celecoxib treatment arms and placebo after 24 weeks of treatment. Subgroup analysis suggested only a small benefit of glucosamine and chondroitin combination therapy on pain in those patients with moderate to severe pain at the beginning of the study. There was no significant difference in change in joint space width between treatment groups and placebo.[2]

In contrast, the 2007 Glucosamine Unum In Die (once a day) Efficacy (GUIDE) randomised controlled trial of glucosamine compared with placebo in 318 patients with OA reported favourable results for glucosamine sulfate at a dose of 1500 mg/day.[3] One theory is that the difference in efficacy seen between glucosamine sulfate and glucosamine hydrochloride may be because of an additional effect of absorbed sulfate on the synthesis of proteoglycans and metabolic intermediates that are important for chondrocyte metabolism.

The only published randomised controlled trial of glucosamine in patients with OA of the hip described 222 patients treated with glucosamine sulfate over a two-year period.[4] Compared with placebo, at the end of the study there were no significant differences in pain or function as measured on the Western Ontario and McMaster Universities OA (WOMAC) scale, and there was no difference in joint space narrowing with glucosamine sulfate treatment. There have not been any recent studies on glucosamine or chondroitin in patients with OA affecting other areas, such as the hands or spine.

Glucosamine and chondroitin use are regulated on prescription in many European countries; however, in the USA and Australia they are considered to be

Table. Evidence to support the use of complementary and alternative medicines in arthritis

Level of evidence/complementary or alternative medicine	Disease	Safety
5: Consistent evidence across several studies to suggest the compound is effective		
• Fish oils	RA	No safety signals
4: Some consistency on more than one study but still some doubts from the evidence; on balance, more likely to be effective than not		
• S-Adenosylmethionine	OA	No safety signals
3: Some promising evidence but also contradictory trials, therefore effectiveness uncertain		
• Glucosamine sulfate	OA	No safety signals
• Chondroitin	OA	No safety signals
• Avocado and soybean unsaponifiables	OA	No safety signals
• Devil's claw	OA	Uncommon serious adverse effects include bleeding, abnormal heart rhythm; also less serious gastrointestinal adverse effects
• Green-lipped mussel	OA	No safety signals
• Ginger	OA	No safety signals
• Gamma linoleic acid	RA	No safety signals
2: Minimal evidence of efficacy (single studies)		
• Willow bark	OA	Interactions with anticoagulants, NSAIDs and antihypertensives
• Methylsulfonylmethane	OA	No safety signals
• Antioxidants (vitamins A, C and E)	OA	No safety signals
• Boswellia resin	OA	No safety signals
1: Overall, no evidence to suggest efficacy, or minimal evidence outweighed by stronger negative evidence		
• Glucosamine hydrochloride	OA	No safety signals
• Homeopathy	OA, RA	No safety signals
• Green-lipped mussel	RA	No safety signals

ABBREVIATIONS: OA = osteoarthritis; RA = rheumatoid arthritis.

nutritional supplements and are available over the counter in numerous different doses and combinations. In keeping with available evidence, it is reasonable to recommend a trial of glucosamine sulfate 1500 mg/day, with or without chondroitin sulfate, for a period of at least three months for symptomatic relief of OA of the knee. The evidence for structure modification is not compelling enough to mandate routine glucosamine for joint protection.

Omega-3 fatty acids

Fish oil supplementation is almost *de rigueur* for the treatment of arthritis these days and is considered to be more a nutritional supplement than a complementary or alternative medicine. Omega-3 polyunsaturated fatty acids can be found in many available food oils including soybean, canola, flaxseed and walnut oils, but are in highest concentrations in fish oils.

Modern western diets contain a relatively low proportion of omega-3s, which have been shown to be protective against cardiovascular and inflammatory diseases. Basic scientific studies have suggested that omega-3s have anticatabolic and anti-inflammatory properties, with multiple effects on cartilage metabolism and the inflammatory cascade.

The most recent meta-analysis to be published on fish oil supplementation reviewed 17 randomised controlled trials

with the common outcome of pain relief in patients with rheumatoid arthritis (RA), arthritis related to inflammatory bowel disease or joint pain due to dysmenorrhoea.[5] Results showed that omega-3 fatty acids are moderately effective (effect size between 0.3 and 0.4) at reducing patient-reported joint pain, duration of morning stiffness and the number of tender and swollen joints. Their consumption also significantly reduced the amount of NSAID use over three to four months of therapy. There were no significant changes seen on x-ray over the study period.

New Zealand green-lipped mussels contain omega-3s, as well as vitamins associated with chondroitin sulfate, amino acids and minerals. It has been suggested that a diet rich in mussels has had a protective effect against arthritis in the coastal Maori population. A systematic review of the four randomised studies of green-lipped mussel consumption published to date showed consistent results of moderate pain relief in patients with mild to moderate OA of the knee across the studies, despite a number of methodological and reporting problems and small patient numbers.[6] There was no serious or significant toxicity reported.

Further studies are needed to better define the most appropriate dosage, delivery form and duration of therapy with fish oils and other sources of polyunsaturated fatty acids for any form of arthritis. Fish oil dosages between 2.6 and 7.1 g/day have an anti-inflammatory/analgesic action in RA. However, patients rarely take sufficiently high doses, as recently described in South Australia,[7] and dose-finding studies have not been performed in other inflammatory arthritides or in OA.

Avocado and soybean unsaponifiables

Avocado and soybean lipid extracts are used in combination for symptom control in OA. There are a number of proposed mechanisms for their effect, including *in vitro* increases in collagen synthesis and inhibition of collagenase activity, increased synthesis of aggrecans and decreased production of a number of proinflammatory cytokines. A Cochrane review of the use of herbal therapies for OA published in 2001 concluded that therapy with avocado and soybean unsaponifiables decreases pain, improves joint function and reduces the need for NSAIDs, with an overall improvement in the wellbeing of patients with OA.[8]

Since then, there have been two more studies published: one looked at avocado and soybean unsaponifiables for symptomatic treatment of patients with OA of the knee over three months,[9] and the second looked at avocado and soybean unsaponifiables for treatment over two years of structural change in patients with OA of the hip.[10] Results are consistent with the earlier conclusions. Some improvement was seen in patient-reported pain with avocado and soybean unsaponifiables 300 mg/day compared with placebo in patients with OA of the knee, but there was no evidence to support chondroprotection or structural improvement in patients with OA of the hip after two years of treatment with avocado and soybean unsaponifiables.

Gamma linoleic acid

Gamma linoleic acid is an omega-6 polyunsaturated fatty acid found in small amounts in green leafy vegetables and in nuts. It is an active component of evening primrose oil, borage seed oil and blackcurrant seed oil. Metabolism of gamma linoleic acid leads to an increased production of prostaglandin E2, which then decreases the production of inflammatory mediators such as interleukin (IL) 1, IL-2, tumour necrosis factor (TNF)-alpha and interferon (IFN)-gamma in autoimmune disorders including RA and psoriasis.

Ingestion of gamma linoleic acid has been shown to improve symptoms in patients with RA;[11] however, there has been little new evidence published. Studies of gamma linoleic acid use in patients with primary Sjögren's syndrome have been conflicting, with a suggestion that symptoms of eye discomfort and dryness were improved with treatment with gamma linoleic acid, but that it had no effect on fatigue. As an omega-6 fatty acid, gamma linoleic acid acts in opposition to the omega-3 fatty acids in some metabolic pathways; it is not clear if co-administration of fish oils and gamma linoleic acid might diminish any clinical response that either may confer.

Devil's claw – *Harpagophytum procumbens*

Devil's claw, *Harpagophytum procumbens*, is a plant native to southern regions of Africa that is commonly used alone or in combination with other complementary or alternative medicines in herbal treatments for arthritis. It contains the active ingredient harpagoside, of which a dosage of 50 mg/day or more has been shown to be effective for pain relief in patients with OA of the knee or non-specific low back pain in four studies of between 100 and 200 patients.[12] In head to head studies, devil's claw was significantly more effective than placebo, reducing pain levels by a mean of 80%, and was not inferior to diacerein (not available in Australia) or rofecoxib.

Different dosages and preparations have not been directly compared, and no serious adverse events have been described. The most common side effects are mild gastrointestinal problems and a small reduction in blood pressure. There are no studies looking at structure modification or progression of OA with devil's claw therapy.

Methylsulfonylmethane

Methylsulfonylmethane is the oxidised form of dimethyl sulfoxide, and is present in very low amounts in some fruits, vegetables and milk. Despite its popularity in arthritis remedies, particularly in combination with glucosamine and chondroitin, there is little convincing evidence of its benefit in the treatment of arthritis.

Two randomised controlled studies

have been published, one comparing methylsulfonylmethane and glucosamine hydrochloride with methylsulfonylmethane alone or placebo,[13] the other comparing methylsulfonylmethane alone with placebo.[14] Both reported improved patient-reported pain with methylsulfonylmethane alone compared with placebo, but patient numbers were small. The absence of published studies showing no effect is not sufficient to conclude that methylsulfonylmethane is effective; it is difficult to know how much publication bias is present, with bias being generally well recognised against the publication of negative studies.

S-Adenosylmethionine

S-Adenosylmethionine is a physiological compound found in normal tissues and body fluids and acts as a methyl group donor in numerous normal enzymatic reactions, including the biosynthesis of phospholipids and proteoglycan synthesis. As a dietary supplement, it is claimed to be effective as an anti-inflammatory and an antidepressant.

Clinical studies have suggested S-adenosylmethionine can improve pain levels in patients with OA.[15,16] One recent trial showed that S-adenosylmethionine had a similar effect to celecoxib, although there was no placebo arm to assess the placebo response. The mechanism of action for analgesia in OA is not clear, and it may be a central effect rather than a true antiarthritic one.

Boswellia serrata

Boswellia resin, extracted from the bark of *Boswellia serrata*, is commonly used in Ayurvedic herbal preparations in Indian traditional medicine for its anti-inflammatory properties. Three small trials showed improvement in pain, flexibility, walking distance and swelling in patients with knees affected by OA.[17] There are, however, methodological issues with these studies, which make it difficult to draw solid conclusions about the true effect of boswellia in patients with OA.

Ginger – *Zingiber officinale*

Ginger has been popular in many cultures over the centuries as an anti-inflammatory remedy for numerous diseases. In musculoskeletal disease, there have been surprisingly few studies of its clinical effects. Small but significant pain reductions have been shown in patients with OA of the knee treated with 255 mg of ginger extract over a six-week period compared with placebo;[18] however, joint function and quality of life did not show significant changes.

More recently, 250 mg of ginger extract taken four times a day was shown to reduce pain in patients with OA of the knee after six months; however, there was no significant benefit at three months.[19] These results are not particularly convincing of an over-riding benefit from ginger

supplementation, particularly as higher doses can be related to an increase in gastrointestinal side effects.

Turmeric – *Curcuma longa*

Another traditional phytotherapy, turmeric has been used for centuries in Ayurvedic medicine for its anti-inflammatory properties. The active ingredient is curcumin (diferuloylmethane). *In vitro* studies have shown that curcumin can suppress IL-1-induced activation of nuclear factor (NF) kB, leading ultimately to inhibition of COX-2 and matrix metalloproteinase 9 in human articular chondrocytes. It is difficult to extrapolate these findings into the clinical setting. Despite years of use for the treatment of arthritis, standardised clinical trials in OA or RA are lacking. There is a good basic science argument for curcumin use as an anti-inflammatory agent in arthritis; however, there are no convincing clinical studies to guide dosage or safety recommendations.

Vitamin supplementation

Antioxidant vitamins, including vitamins A, C and E, have been linked to improved outcomes in 640 patients from the Framingham Osteoarthritis Cohort Study.[20] Higher doses of vitamin C were associated with a reduced rate of progression in patients who had established disease and with a lower risk of developing knee pain. However, no effect of vitamin C was seen on the incidence of OA over the 10-year study period, and no association was seen between OA measures and nonoxidative vitamin supplements. More recent studies have also been disappointing, failing to show any benefit of vitamin C, vitamin A or selenium on symptoms in patients with either OA or RA.

Studies of vitamin E in patients with OA have been conflicting. Two short trials showed a benefit of daily vitamin E on pain in patients with OA of the knee at 10 days and at six weeks. However, two recent good-quality trials using of vitamin E 500 IU showed no symptomatic improvement over placebo at six months or two years and no evidence of structural modification or benefit at two years as measured by magnetic resonance imaging (MRI).[21,22] Vitamin supplementation cannot be recommended as a treatment for arthritis at this time.

Willow bark extract

The bark of the willow tree (*Salix* species) contains salicin, which inhibits both COX-1 and COX-2 isoforms of the COX enzyme. It would seem, therefore, that there would be a significant analgesic effect from the use of willow bark extract in patients with painful conditions such as OA and RA. The initial small two-week study that showed symptomatic benefit in patients with OA of the knee has not, however, been replicated,[23] and subsequent studies have failed to show any improvement of pain or function in patients with OA treated with willow bark extract.

Homeopathy

Homeopathy involves a patient-directed, individualised approach to symptom complexes rather than the disease entities we are comfortable with in conventional medicine. To that end, it is difficult to study the effect of homeopathic treatments in patients with OA or RA, because different patients with the same diseases will receive different therapy depending on their individual complaints both from arthritis and other comorbidities. Studies of individual homeopathic components often have negative results because the components are not intended for therapy in isolation.

To date, there have been no trials in patients with RA or OA to show a convincing clinical benefit from homeopathic treatment. However, the design of the trials did not reflect clinical practice and it is therefore not possible to make conclusions about its role in the treatment of arthritis based on the 'evidence'.

Physical treatment modalities

Alongside herbal and alternative medicines, physical interventions are also popular among patients with arthritis. There is an increasing body of literature available regarding acupuncture in patients with OA. Sham needle techniques are improving, so it is possible to perform good-quality randomised, placebo-controlled, double-blind studies of the effect of acupuncture. Although the research quality is improving, the emerging results are not as encouraging.

Three recent trials of acupuncture in patients with OA of the knee have shown varying results attributable to acupuncture. In one trial looking at acupuncture as an adjunct to exercise-based physiotherapy, 352 adult patients were randomised to receive one of: advice and exercise; advice, exercise and true acupuncture; or advice, exercise and nonpenetrating acupuncture.[24] At six months, all groups showed improvements in the WOMAC pain subscale from baseline, but there were no clinically important differences between the groups. Both the real and sham acupuncture groups showed small, statistically significant improvements in pain intensity, suggesting a strong placebo effect rather than a true effect from true acupuncture.

Another study compared periosteal stimulation therapy with control sham periosteal stimulation (needles are inserted into the periosteum but not stimulated) weekly for six weeks in 88 older adults with at least moderate knee pain and radiographic OA of the knee (at least grade 2).[25] Both groups showed reductions in pain, but the active intervention group improved significantly more than the control group. Measures of stiffness, function and NSAID use were no different between the two groups. However, by two months after completion of therapy, any improvements had been lost.

A third study looked at 181 patients with severe OA of the knee awaiting knee replacement, and randomised them to a six-week course of acupuncture, physiotherapy or standardised advice alone.[26] The study authors claimed a short-term benefit from acupuncture for pain relief compared with control (no therapy), which, although statistically significant, was small and did not persist to 12 weeks. The patients were not blinded to treatment, introducing the likelihood of significant placebo effect in the two treatment arms of the study. It is, therefore, not possible to say, in light of the most recent evidence, if acupuncture gives a clinically important symptomatic effect in patients with OA of the knee.

Two extensive systematic reviews have been published recently looking at studies of acupuncture for pain relief in patients with RA.[27,28] Both concluded that, at best, there is conflicting evidence as to whether there is any effect of either penetrating acupuncture or sham acupuncture on pain levels due to RA, and that further rigorous studies are warranted.

Static magnets are also popular among individuals keen to manage their own arthritis. However, a recent systematic review of 29 trials concluded that there is no convincing evidence for a benefit of magnets for pain relief or for the treatment of patients with OA.[29]

Perhaps a less popular strategy is the use of leeches for symptom relief in patients with OA. A randomised, placebo-controlled study of the effect of leech therapy in 113 patients with OA used an 'artificial leech' treatment as the control group.[30] All study groups showed a clinical improvement in pain and joint stiffness after 26 weeks, although the study authors comment that there was little difference between the groups.

Conclusion

There are many natural therapies that seem promising for the treatment of patients with arthritis. However, evidence-based medicine fails to provide absolute answers about what to take and how much it influences pain, function and disease progression in patients with the rheumatic diseases.

There are numerous systematic reviews of complementary and alternative medicines and therapies published in today's literature, seemingly more than there are definitive randomised controlled trials to be reviewed, but they nevertheless present similar conclusions. In most cases, larger, high-quality studies of complementary medicines are needed before their use can be confidently recommended.

More detailed information about the research evidence for other available complementary and alternative medicines for patients with OA, RA or fibromyalgia has been published recently by the British group, Arthritis Research Campaign.[31] MT

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A list of references is available on request to the editorial office.

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