Alternative therapies for musculoskeletal conditions

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The use of complementary and alternative medicine is complex and nuanced. Patterns of use of
complementary and alternative medicine differ among racially and ethnically different groups.
Multivariate models of utilization indicate that ethnicity plays an independent role in the imple-
mentation of these modalities, in seeking practitioners and in health problems for which assis-
tance is required. Moreover, there are many reasons why people use complementary and
alternative medicine: conventional treatment may not be working as well as they would like;
they want greater relief of symptoms and/or disability; they have issues with side-effects of phar-
maceutical treatment; they wish to reduce some of the stress that comes from living with
a chronic illness and want to cope better; they believe that complementary and alternative ther-
apies are safer and ‘natural’; and they are influenced by the widespread advertising and attractive
claims that are made for many natural products. Although there are more than 150 different
kinds of syndromes and conditions associated with arthritis, this review will focus on currently
available evidence-based medicine for the two most common conditions diagnosed in Western
countries – osteoarthritis and rheumatoid arthritis – for which people seek and then implement
complementary and alternative medicine modalities.

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Although diseases with the greatest consequent mortality (e.g. cardiovascular disease, cancer) attract much of the public’s attention, musculoskeletal or rheumatic diseases are the major cause of morbidity throughout the world, having a substantial influence on health and quality of life, and inflicting a vast burden of cost on health systems. Musculoskeletal disease is a major cause of disability and handicap, and arthritis is the most prevalent form of musculoskeletal disease.\(^1\) Rheumatic diseases include more than 150 different conditions and syndromes, the common denominators being pain and inflammation. Five of these account for 90% of the cases – osteoarthritis (OA), rheumatoid arthritis (RA), fibromyalgia, systemic lupus erythematosus (SLE) and gout.\(^1–^4\)

Arthritis is a chronic disease affecting an estimated 43 million (20.8%) adults in the USA, and is the leading cause of disability in that country\(^3\), while OA is reported to be the most common joint disorder in the world.\(^4\) In Western populations it is one of the most frequent causes of pain, loss of function and disability in adults. Radiographic evidence of OA occurs in the majority of people by 65 years of age and in about 80% of those aged over 75 years. In Australia in 2004, there were 3.4 million people (~17% of the population) suffering from some form of arthritis, with ~60% of these being females. Of this total, 1.39 million had OA and more than 438,000 had RA.\(^5\)

The associated worldwide trend in morbidity is significant because it often leads to a reduction in quality of life and related conditions such as fatigue, depression and insomnia. Attendant costs to the health-care system are vast, and current medications, while often effective, are frequently associated with significant side-effects.

In the early 1990s an upsurge in the use of complementary and alternative medicine (CAM) was seen from reports that recognized the extensive use of treatments outside the realm of conventional medicine.\(^6,^7\)

A recent review reported that patients with musculoskeletal conditions often employ CAM modalities\(^8\) in one form or another. Collectively the evidence demonstrates that some CAM modalities show significant promise: for example herbal medicines, nutritional supplements, acupuncture, and mind–body medicine.

**HERBAL MEDICINES**

A number of herbal supplements have been investigated for their efficacy in patients with OA and RA (Table 1).\(^9–^13\)

**Camilla sinensis (green tea)**

The anti-inflammatory and pharmacological properties of green-tea extracts have been attributed to the high *content of polyphenols/catechins*, of which epigallocatechin-3-gallate (EGCG) predominates.\(^11,^14\) The emerging molecular evidence thus far gives strong biological plausability supporting the in-vitro observations that *catechins* extracted from green tea can exhibit both anti-inflammatory and chondroprotective effects and hence may be beneficial to arthritis sufferers.\(^14\)
Table 1. Botanicals with demonstrated therapeutic anti-inflammatory, analgesic and anti-rheumatic activity.

<table>
<thead>
<tr>
<th>Herbals/botanicals</th>
<th>Actions</th>
<th>Indications</th>
<th>Dosages</th>
<th>Contraindications and cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boswellia/</td>
<td>Anti-inflammatory</td>
<td>OA</td>
<td>600–1200 mg/day extract</td>
<td>Occasional mild diarrhoea or urticaria</td>
</tr>
<tr>
<td>frankincense</td>
<td>Anti-arthritis</td>
<td>RA</td>
<td>standardized to 60% boswellic acids</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt; &lt; 2 g/kg</td>
</tr>
<tr>
<td>(Boswellia serrata)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chilli/cayenne</td>
<td>Topical analgesic</td>
<td>OA</td>
<td>0.025–0.075% in a cream base or plaster</td>
<td>Local adverse effects include rash, swelling</td>
</tr>
<tr>
<td>Devil's claw</td>
<td>Anti-inflammatory</td>
<td>OA</td>
<td>Liquid extract (1:2) 6–12 mL/day</td>
<td>High doses may increase effects of warfarin</td>
</tr>
<tr>
<td>(Harpogophytum</td>
<td>Analgesic</td>
<td>RA</td>
<td>Trials indicate a need to use extracts with &gt;50 mg harpagoside for pain relief</td>
<td>Theoretical interaction with anti-arrhythmic drugs — monitor use</td>
</tr>
<tr>
<td>procumbens)</td>
<td>Chondro-protective</td>
<td>Lower-back pain</td>
<td></td>
<td>Not recommended in pregnancy</td>
</tr>
<tr>
<td></td>
<td>Anti-rheumatic</td>
<td></td>
<td></td>
<td>May cause gastrointestinal irritation, use with caution in patients with gastric and duodenal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ulcers, gallstones and acute diarrhoea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Suspend use 1 week before surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LD&lt;sub&gt;50&lt;/sub&gt; &lt; 13.5 g/kg</td>
</tr>
<tr>
<td>Ginger</td>
<td>Anti-inflammatory</td>
<td>RA</td>
<td>250 mg QID</td>
<td>Theoretically may increase bleeding when high doses taken with anticoagulants and antiplatelet</td>
</tr>
<tr>
<td></td>
<td>Analgesic</td>
<td>OA</td>
<td></td>
<td>agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Caution advised in patients with gastric ulcers, reflux</td>
</tr>
<tr>
<td>Phytodolor</td>
<td>Anti-inflammatory</td>
<td>OA</td>
<td>20 drops TID</td>
<td>None reported</td>
</tr>
<tr>
<td></td>
<td>Analgesic</td>
<td>RA</td>
<td>1200 mg/day in divided doses</td>
<td></td>
</tr>
<tr>
<td>rose hip</td>
<td>Anti-inflammatory</td>
<td>OA</td>
<td>5 g/day of powder orally administered</td>
<td>Side-effects reported include vomiting, hair loss, diarrhoea, headaches, dryness, abdominal</td>
</tr>
<tr>
<td>Tripterygium</td>
<td>Anti-inflammatory</td>
<td>RA</td>
<td>Moderate efficacy reported</td>
<td>pain and vaginal spotting</td>
</tr>
<tr>
<td>wilfordii Hook F</td>
<td></td>
<td></td>
<td>570 mg/day extract effective</td>
<td>Amenorrhoea reversible in women &lt;40 years of age with short-term use; irreversible in postmenopausal women</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Herbals/botanicals</th>
<th>Actions</th>
<th>Indications</th>
<th>Dosages</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Willow bark</td>
<td>Anti-inflammatory</td>
<td>OA</td>
<td>Tincture (1:1) 1–2 mL TID</td>
<td>High doses may theoretically increase effect of anticoagulants</td>
</tr>
<tr>
<td>(Salix alba)</td>
<td>Analgesic</td>
<td>RA</td>
<td>Trials for OA and lower-back pain</td>
<td>Salicylate sensitivity</td>
</tr>
<tr>
<td></td>
<td>Anti-rheumatic</td>
<td>Lower-back pain</td>
<td>used preparations standardized to 240 mg/day salicin in divided doses</td>
<td>LD$_{50}$ 28 mL/kg&lt;br&gt;Requires thorough evaluation for renal, hematological, and hepatic function</td>
</tr>
</tbody>
</table>

OA, osteoarthritis; RA, rheumatoid arthritis.
**Uncaria tomentosa, Uncaria guianensis (cat’s claw)**

Extracts of cat’s claw (Figure 1) have been shown to possess antioxidant, anti-inflammatory and immunomodulatory properties. The most investigated of the active constituents in *Uncaria tomentosa* extract for immunomodulatory and anti-inflammatory effects are pentacyclic oxindole alkaloids, which are reported to induce an immune regulating factor. Pain associated with activities of daily living was significantly reduced; however, pain at rest or at night was not reduced during the 4-week trial period. In a further study designed to test the use of an extract of cat’s claw from the part of the vine that is rich in pentacyclic alkaloids (roots) versus placebo showed a reduction in the number of painful joints in patients with RA (53.2% versus 24.1%; \( P < 0.044 \)). As no adverse effects were reported, this small preliminary study showed the relative safety and modest benefit to the tender joint count of a highly purified extract from the pentacyclic chemotype of *Uncaria tomentosa* in patients with active RA taking sulphasalazine or hydroxychloroquine. Other research groups have documented the safety and pharmacological profile of cat’s claw, which is considered non-toxic, and there are no known contraindications or drug interactions. However, there is a need for rigorous testing of the effectiveness of the recommended doses. Until a full pharmacokinetic profile is investigated it would be prudent to avoid its use in women attempting pregnancy, during pregnancy and lactation, and for children below 3 years of age.

Figure 1. Uncaria tomentosa, Uncaria guianensis (cat’s claw).
**Harpogophytum procumbens (devil’s claw)**

Harpogophytum procumbens (Figure 2) has been shown to be effective for arthritis in two reviews. 17,18 There is little evidence for efficacy of extracts containing <30 mg/day of the active constituent, harpagoside, and that a correct dose is >50 mg/day for OA of the knee and hip. Devil’s claw exhibits cellular signalling modulating activities that down-regulate inflammatory markers. 19–21 Five randomized clinical trials (RCTs) have reported on the effects of devil’s claw in the treatment of OA. 22 Of these, three were placebo-controlled and two were compared with common pharmaceuticals (diclofenac and phenylbutazone). Three trials demonstrated significant positive results, while two studies that employed <30 mg harpagoside recorded results that were less significant. An aqueous extract of devil’s claw (consisting of 60 mg harpagoside) was found to be as effective as 12.5 mg of rofecoxib for the treatment of acute non-specific lower-back pain in a double-blind pilot RCT. 22 Three other trials have also demonstrated efficacy in lower back pain, with 100 mg of harpagoside considered superior when neurological deficits are present. 18,23

**Tripterygium wilfordii Hook F**

Extracts from the roots of Tripterygium wilfordii Hook F (TwHF) (Figure 3) have been used for the treatment of various autoimmune and inflammatory diseases, including RA, SLE, nephritis, psoriasis and asthma. 24 An ethanol/ethyl acetate extract has

*Figure 2. Harpogophytum procumbens (devil’s claw).*
demonstrated therapeutic benefit in patients with treatment-refractory RA.\textsuperscript{25} At the doses of 180 mg/day and 360 mg/day, T\textit{w}HF extract was of benefit and well tolerated by most patients. A prospective double-blind RCT of T\textit{w}HF ethanol/ethyl acetate extracts in RA patients has also been reported.\textsuperscript{25} With a two-dose regimen for 20 weeks, patients at the higher dose achieved a rapid ACR-20 response, with 50\% of patients improving during the first 4 weeks of treatment. Both treatment groups showed a significant decrease in the number of tender and swollen joints and improvement in the physician’s global assessment. In a further phase-I study, eight out of nine patients treated with T\textit{w}HF extract (>360 mg per day) showed improvements in both clinical manifestations and laboratory findings.\textsuperscript{26} It was concluded that the extract of T\textit{w}HF at dosages up to 570 mg/day appeared to be safe, and doses >360 mg/day were associated with clinical benefit in patients with RA. In both of these studies, no toxic or adverse effects other than diarrhoea were observed in patients receiving the highest dose. An RCT of a topical application of T\textit{w}HF in 61 patients with RA demonstrated efficacy in improving ACR-20 score.\textsuperscript{27}

\textbf{Curcuma longa (turmeric)}

Turmeric (Figure 4) has been used for centuries in Ayurvedic medicine as a treatment for inflammatory disorders, including arthritis.\textsuperscript{28,29} The major chemical constituent of turmeric is curcumin (diferuloylmethane), which constitutes up to about 90\% of the total curcuminoid content, with the remaining 10\% consisting of demethoxycurcumin and bis-demethoxycurcumin.\textsuperscript{28} Animal studies have demonstrated that oral administration of curcumin to rats decreased the levels of inflammatory glycoprotein, GpA-72, with a concomitant reduction in paw inflammation.\textsuperscript{30} Curcumin has also been shown to inhibit the carrageenin-induced paw oedema in mice and rats, with an ED\textsubscript{50} dose of 48 and 100.2 mg/kg, respectively.\textsuperscript{30,31} In a double-blind cross-over

\textbf{Figure 3.} Tripterygium wilfordii Hook F.
clinical trial of 18 patients with RA given curcumin (1200 mg/day) for 2 weeks followed by 300 mg/day of phenylbutazone for another 2 weeks, respondents showed a significant improvement in morning stiffness, walking time, and reduction in joint swelling.\textsuperscript{32}

\textit{Zingiber officinale} (ginger)

The fresh/dried roots of \textit{Zingiber officinale} (Figure 5) is reported to possess anti-inflammatory, antiseptic and carminative properties and has been used to treat inflammatory and rheumatic diseases.\textsuperscript{33} The pungent phenolic constituent of ginger, 6-gingerol, has been shown to inhibit lipopolysaccharide- (LPS-) induced nitric oxide synthase (iNOS) expression and production of NO in macrophages and to block peroxynitrite-induced oxidation and nitration reactions in vitro.\textsuperscript{33–35} Cumulative laboratory animal data suggest that 6-gingerol is a potent inhibitor of NO synthesis and effective in inhibiting production of prostaglandin E2 (PGE2) and tumour necrosis factor \(\alpha\) (TNF-\(\alpha\)) and cyclo-oxygenase 2 (COX-2) expression in human synoviocytes by regulating nuclear factor \(\kappa\)B (NF\(\kappa\)B) activation and degradation of its inhibitor IkBa subunit.\textsuperscript{33}

A recent RCT employing \textit{Zingiber officinale} and \textit{Alpinia galanga} (Eurovita Holding, Denmark) comprising 255 mg extracted from 2500–4000 mg ginger and 500–1500 mg galanga rhizome, demonstrated a positive effect on knee OA. Clinical trial participants in the ginger-extract group experienced a 63% reduction in knee pain on standing versus 50% in the placebo group.\textsuperscript{36} A highly purified and standardized ginger extract had a statistically significant effect on reducing symptoms of OA of the knee with a high safety profile and mild adverse gastrointestinal events in the ginger-extract group. In a further cross-over RCT, in patients with OA the ginger extract showed statistically significant efficacy in the first period of treatment before cross-over; however, a significant

\textbf{Figure 4.} Curcuma longa (turmeric).
difference was not observed in the study overall. In a limited study with RA patients, ginger was effective in relieving pain and swelling in the joints of seven RA patients. Based on this limited information, recommendation for its use is difficult and limited in treating OA or RA.

**Capsicum spp (chilli/cayenne)**

*Capsicum* spp (Figure 6) are commonly used topically in a cream base for the relief of lower-back pain. A recent systematic review included four studies on cayenne and concluded that there is evidence that it reduces lower-back pain more than placebo.

An early review analysed three RCTs and reported that cayenne had poor to moderate efficacy for the treatment of chronic musculoskeletal or neurological pain. Cayenne was responsible for a higher rate of side-effects than was placebo; given that the action of chilli is to increase blood circulation, it is prudent to enquire whether it is the heat generated that alleviates the pain.

**Gaultheria yunnanensis (wintergreen)**

Topical natural products containing wintergreen (Figure 7) include liniments, balms, creams, gels, oils, lotions, patches, ointments and other products that are applied to the skin, and these are often sought with the intention of providing relief of mild arthritis pain that affects only a few joints, as well as to ease sore muscles, back pain and OA. No clinical trials evaluating these effects are currently available. However,
in-vivo studies have shown that a salicylate fraction isolated from wintergreen has analgesic and anti-inflammatory properties.\textsuperscript{42} Caution, even with topical products, is required in patients receiving warfarin, as adverse interactions and bleeding have been reported to be a risk with its use.\textsuperscript{43}
Phytodolor

Phytodolor (Steigerwald Arzneimittelwerk GmbH, Germany) is a herbal proprietary product that includes aspen (*Populus tremula*), golden rod (*Solidago virgaurea*) and golden ash (*Fraxinus excelsior*). Although most of the available literature is German, a recent systematic review of six RCTs concluded that Phytodolor reduced the pain associated with rheumatic disorders. The dose administered was 30 drops three times a day for three of the trials and 40 drops three times a day for the remainder, with duration ranging from 2 to 4 weeks.

*Boswellia serrata* (boswellia/frankincense)

*Boswellia serrata* (Figure 8) is a popular Ayurvedic herb that is purported to exhibit effective analgesic, anti-inflammatory and anti-arthritic activity. Pilot studies indicate that boswellia may be an effective intervention for rheumatoid arthritis because of its anti-inflammatory properties. A recent RCT assessed its efficacy, safety and tolerability in 30 patients with OA of knee over a 16-week period. Patients receiving 333 mg of boswellia extract containing 40% BA three times a day reported a significant decrease in knee pain and swelling, and an associated increase in movement. A further RCT compared the same extract with valdecoxib in 66 patients with knee OA over 6 months. This study has a slower

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*Figure 8. Boswellia serrata (boswellia/frankincense).*
onset of action with pain relief persisting for 1 month after ceasing treatment, while valdecoxib acted faster but lasted only for the duration of therapy.47

**Willow bark**

There is a resurgence of interest in willow bark (Figure 9) as a treatment for chronic pain syndromes that include RA and OA. While white willow (*Salix alba*) is the willow species most commonly used for medicinal purposes; crack willow (*Salix fragilis*), purple willow (*Salix purpurea*), and violet willow (*Salix daphnoides*) are all salicin-rich species and are available under the label of willow bark. Randomized clinical trials of short duration have provided evidence of efficacy.48

**Rose hip (rose haw)**

Recent systematic searches of the literatures49,50 have demonstrated that rosehip powder or the seeds of the *Rosa canina* subspecies (Figure 10) had a moderate effect in patients with osteoarthritis. In a study that enrolled 94 patients with osteoarthritis of the hip or knee in a double-blind placebo-controlled cross-over trial51 reported that the 47 patients that were given 5 g/day of the herbal remedy for a period of 3 months resulted in a significant reduction in WOMAC (Western Ontario and McMaster Universities) pain (P < 0.014) as compared to placebo when tested after 3 weeks of treatment. Furthermore, the clinical data suggested that the herbal remedy not only alleviated symptoms but also reduced the consumption of ‘rescue medication’.

![Figure 9. Willow (Salix spp).](image)
NUTRITIONAL MEDICINE

Supplements

Various nutritional products are commonly used for pain control for rheumatic problems (Table 2). Most reduce pain via their anti-inflammatory effects. Nutrition is increasingly linked to a range of degenerative and developmental disorders. Nutritional deficiencies and imbalances can result in metabolic and systemic disturbances that may increase susceptibility to joint disease.

Glucosamine

The therapeutic effectiveness of glucosamine treatment on OA has been demonstrated by improved mobility and relief of pain in animal models as well as in RCTs. A recent meta-analysis concluded that the evidence for efficacy in improving symptoms in OA was conflicting, and that glucosamine hydrochloride was not effective.

A Cochrane review concluded that a specific type of glucosamine supplement (from Dona, Rotta Pharmaceuticals Inc) was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic OA. Results for the non-Rotta preparation were not statistically significant. The review analysed data from 20 RCTs involving 2570 participants, of which ten RCTs used the Rotta preparation. A second systematic review reviewed RCTs of at least 1 year’s duration. It was reported that glucosamine sulphate may be effective and safe in delaying the progression and improving the symptoms of knee OA. A previous Cochrane review of 16 RCTs had found that glucosamine was effective; however, these included smaller trials with less methodological rigor.
Table 2. Supplements with demonstrated therapeutic anti-inflammatory, analgesic and anti-rheumatic activity.

<table>
<thead>
<tr>
<th>Supplements</th>
<th>Actions</th>
<th>Indications</th>
<th>Dosages</th>
<th>Contraindications and cautions</th>
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</thead>
<tbody>
<tr>
<td>Glucosamine sulphate</td>
<td>Anti-inflammatory</td>
<td>OA</td>
<td>1500 mg/day usually in divided doses</td>
<td>Occasional mild digestive problems, headache, drowsiness and skin reactions</td>
</tr>
<tr>
<td>Glucosamine hydrochloride</td>
<td>Chondro-protective</td>
<td>OA</td>
<td>Most research has been conducted on glucosamine sulphate</td>
<td>Shellfish allergy — glucosamine is not extracted from the protein component of shellfish, however caution advised</td>
</tr>
<tr>
<td>Chondroitin</td>
<td>Chondro-protective</td>
<td>OA</td>
<td>1200 mg/day usually in divided doses</td>
<td></td>
</tr>
<tr>
<td>Collagen hydroly</td>
<td>Chondro-protective</td>
<td>OA</td>
<td>10 g/day</td>
<td></td>
</tr>
<tr>
<td>Lipids (avocado/soybean unsaponifiables)</td>
<td>Chondro-protective</td>
<td>OA</td>
<td>300–600 mg/day</td>
<td></td>
</tr>
<tr>
<td>Methylsulphonylmethane</td>
<td>Chondro-protective</td>
<td>OA</td>
<td>500 mg TID alone or in combination with glucosamine</td>
<td></td>
</tr>
<tr>
<td>New Zealand green-lipped mussel</td>
<td>Anti-inflammatory</td>
<td>OA</td>
<td>1050–1150 mg/day of freeze-dried powder</td>
<td>Gastrointestinal discomfort, gout, skin rashes and one case of granulomatous hepatitis have been reported in trials Contraindicated in people with shellfish allergies Theoretical caution with hypertension due to sodium content</td>
</tr>
<tr>
<td>SAMe</td>
<td>Anti-inflammatory</td>
<td>OA</td>
<td>A lower dose of 400 mg/day may be used as a maintenance dose once a response occurs</td>
<td>Tricyclic and SSRI antidepressants as serotonin syndrome theoretically possible Thyroxine — monitor Betaine — monitor Extreme caution in bipolar disorder, schizophrenia, schizoaffective disorder and Parkinson’s disease</td>
</tr>
</tbody>
</table>

OA, osteoarthritis; RA, rheumatoid arthritis; SSRI, selective serotonin reuptake inhibitor.
A concern with most trials of glucosamine sulphate, glucosamine hydrochloride and chondroitin sulphate in the treatment of OA is weak research design. The Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) was designed to address these inconsistencies and provide some clarity on the effectiveness of glucosamine (1500 g/day) and chondroitin (1200 mg/day) for the treatment of knee pain in OA by employing a rigorous research design. The GAIT found that glucosamine and chondroitin sulphate, alone or in combination, did not significantly reduce OA knee pain more than did placebo. A combination of glucosamine and chondroitin sulphate was found to be effective in a subgroup of patients with moderate to severe knee pain (79.2% versus 54.3% for placebo). The combined emerging data suggests that glucosamine has a structure-modifying effect. However, debate remains regarding this, largely in relation to methodological issues surrounding outcome measures used in the positive studies.

**Chondroitin**

An RCT employing galactosaminoglucuronoglycan sulphate (GS) on 40 patients with tibiofibular OA of the knee were allocated to receive 50 intramuscular injections (one injection twice weekly) for 25 weeks. GS had a significant therapeutic effect on all symptoms evaluated. No important local or systemic side-effects were noted. Favourable effects have been reported in pain reduction and improvement in mobility when GS was given either intra-articularly or orally to elderly patients with joint degeneration.

A double-blind RCT with 104 patients receiving oral chondroitin 4-sulphate and chondroitin 6-sulphate (CS4 and CS6) at a dose of 800 mg/day or placebo for 1 year showed that CS4 and CS6 had a beneficial effect in terms of both clinical manifestations and anatomical progression in patients with OA of the knee. The main efficacy criterion was the Lequesne functional score. Functional impairment was reduced by approximately 50%, with a significant improvement over placebo for all clinical criteria. Tolerance was excellent or good in more than 90% of cases. This study suggests that CS acts as a structure modulator as illustrated by improvement in the inter-articular space visualized on x-rays of patients treated with CS4 and CS6.

A double-blind RCT of 46 patients with symptomatic OA of the knee examined the effect of 400 mg chondroitin sulphate twice a day for 1 year. After 3 months, joint pain was significantly reduced in the chondroitin sulphate group compared to the placebo group. This difference became more pronounced after 12 months. The increase in overall mobility capacity was significantly greater at 6 and 12 months in the CS group than in the placebo group. After 1 year, the mean width of the medial femorotibial joint was unchanged from baseline in the CS group, but had decreased significantly in the placebo group. Although no statistical comparison was presented for the change in joint-space width between the two groups, the finding suggests the possibility that CS treatment may slow the progression of OA. A proprietary CS was studied in a double-blind RCT of 85 patients with OA of the knee. Participants received Condrosulf at a dose of 400 mg TID or placebo for 6 months. Lequesne's index, spontaneous joint pain, and walking time all decreased progressively in the CS group, with a significant difference in favour of the CS group for each of these parameters. In a double-blind RCT parallel-group study using either CS 1 g/day or placebo on 130 patients for 3 months, followed by a 3-month post-treatment period, the CS group experienced greater but non-significant improvement than the placebo group at the treatment
endpoint, as measured by the Lequesne index. Improvement became significant in the completer population. In the intention-to-treat population, all variables tended toward greater improvement in the CS group than the placebo group. One month after treatment, CS had a significantly higher persistent effect than placebo on the Lequesne index, pain with activity, and other efficacy criteria. Adverse event rates did not differ significantly.

To assess the clinical efficacy of CS in comparison with the non-steroidal anti-inflammatory drug (NSAID) diclofenac sodium, a multicentre double-blind RCT double-dummy study of 146 patients for 6 months was conducted. Patients treated with diclofenac showed prompt reduction of clinical symptoms that reappeared, however, after the end of treatment. In the CS group, the therapeutic response appeared later but lasted up to 3 months after the end of treatment. It was concluded that CS has slow but gradually increasing clinical activity in OA, and that these benefits last for a long period after the end of treatment. Shortcomings in these studies were that only a relatively small number of patients were involved, and that no dose-finding investigations for CS could be found.

A double-blind prospective RCT study of 300 patients given Condrosulf® 800 mg daily or placebo for 2 years investigated the structure-modulating properties of CS in gonarthrosis by measuring the modifications in minimum joint space width, mean thickness, and mean surface of the cartilage in internal femorotibial function. There was a significant difference, with worsening of the affection, in the placebo group compared to the CS group. In the group treated with CS, there were no significant variations in any radiological parameters, which remained remarkably stable. The statistical analysis revealed a significant difference in the CS group compared to the placebo group with regard to maintenance of the cartilage analysed, in both the intention-to-treat analysis (the accepted manner of analysis of clinical trials, where subjects are analysed whether or not they complete the study protocol) and also in the per protocol analysis (when only subjects who completed the study protocol are examined). It was shown that CS was superior to placebo with regard to stabilization of minimum joint space width of the internal femorotibial articular space, the mean thickness, and the surface.

Hence there are sufficient controlled trial data to support the use of CS in symptomatic OA, CS having fewer side-effects than currently used NSAIDs.

Chondroitin sulphates appear to have a role in prevention of disease progression. The requisite is that CS be further evaluated in studies of longer treatment duration, with larger numbers of patients, and using well-established measures of function and progression.

A recent meta-analysis of a set of poor- to moderate-quality trials that were largely heterogeneous in methodology, making interpretation of the data difficult, concluded that the results were unreliable. Furthermore, the authors concluded that – since large-scale and methodologically sound trials indicate that the symptomatic benefit of chondroitin is minimal or non-existent – chondroitin cannot be recommended.

Collagen hydrolysate

Four open-label and three double-blind trials have been reported. In a 24-week multinational double-blind RCT on knee OA, 10 g/day did not improve the WOMAC index. Post-study analysis suggested that the hydrolysate could be more efficient in severe OA. A 60-day cross-over double-blind RCT on knee and hip OA compared 10 g/day of collagen hydrolysate, gelatin, gelatin + glycine + calcium phosphate, or egg
The gelatin preparations were not significantly different from each other and were superior to egg albumin in reducing pain as assessed by a patient questionnaire. According to the best-evidence synthesis, evidence of efficacy for collagen hydrolysate is equivocal. However, a growing body of evidence provides a rationale for the use of collagen hydrolysate for patients with OA.

**Methylsulphonylmethane (MSM)**

In a 12-week double-blind RCT on knee OA, 500 mg of MSM three times a day – used alone or in combination with 500 mg of glucosamine hydrochloride three times a day – significantly improved a Likert scale of pain and Lequesne’s functional index (LFI). The combination of both ingredients was not more efficacious than each ingredient used alone. A further 12-week double-blind RCT on knee OA, 3 g of MSM given twice a day was more efficient than placebo in decreasing WOMAC pain and functional scores. According to the best-evidence synthesis, MSM provides moderate evidence of efficacy for knee OA.

**S-Adenosyl methionine (SAMe)**

A practical amount of research evidence exists to support the use of SAMe for the treatment of pain associated with OA. A meta-analysis of 11 RCTs comprising 1442 participants with an average age of 60.3 years from 2002 demonstrated that SAMe is as effective as NSAIDs in reducing the pain of OA, with significantly fewer side-effects.

**New Zealand green-lipped mussel**

The reported incidence of arthritis in coastal-dwelling Maoris is low, and it has been suggested that this is possibly due to their high consumption of green-lipped mussels. However, results from clinical trials have been inconsistent, with a recent review concluding that ‘there is little consistent and compelling evidence, to date, in the therapeutic use of freeze-dried green-lipped mussel powder products for RA and OA treatment’ but that further investigations are warranted.

**Lipids (avocado/soybean unsaponifiables, ASUs)**

Four double-blind RCTs and one systematic review have evaluated ASUs on knee and hip OA. In two 3-month RCTs, one on knee and hip OA and one on knee OA only, 300 mg once a day decreased NSAID intake. No statistical differences in any primary or secondary endpoints were detected at 300–600 mg once a day. In a 6-month RCT on knee and hip OA, 300 mg once a day resulted in an improved LFI compared with placebo. ASUs had a 2-month delayed onset of action as well as residual symptomatic effects 2 months after the end of treatment. In a 2-year RCT on hip OA, 300 mg once a day did not slow down narrowing of joint-space width. In addition, none of the secondary endpoints – LFI, visual analogue scale (VAS) of pain, NSAID intake, and patients’ and investigators’ global assessments – was statistically different from placebo after 1 year. However, a post-hoc analysis suggested that ASUs might decrease narrowing of joint space width in patients with the most severe hip OA.
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Actions</th>
<th>Indications</th>
<th>Outcome measures</th>
<th>Pain effect sizes/quality grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relaxation</td>
<td>PMR + imagery versus usual care — 10 sessions</td>
<td>RA</td>
<td>AIMS 2 mobility arm function (SS); AIMS 2 pain</td>
<td>Low</td>
</tr>
<tr>
<td>Meditation</td>
<td>MBSR programme versus waiting-list control — 8 sessions</td>
<td>Chronic low-back pain</td>
<td>CPAQ; SF–36 physical function</td>
<td>Moderate</td>
</tr>
<tr>
<td>Guided imagery</td>
<td>Guided imagery + PMR versus usual care — 12 sessions</td>
<td>OA</td>
<td>AIMS 2 pain; Self-reported mobility</td>
<td>Low</td>
</tr>
<tr>
<td>Hypnosis</td>
<td>PMR versus hypnosis versus usual care — 8 sessions</td>
<td>OA</td>
<td>Pain medication (for hypnosis and relaxation groups compared with usual care)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Tai chi</td>
<td>Tai chi versus meeting and telephone control — brief contact: — 5 weeks contact; — 12 weeks contact</td>
<td>OA</td>
<td>Satisfaction with health; Arthritis self-efficacy</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Yoga + exercise OR Yoga + relaxation + education versus self care or waiting-list — 8 sessions; — 12 sessions</td>
<td>Lower-extremity</td>
<td>Pain and functional measures; Joint pain and stiffness; physical function (KWOMAC); Joint tenderness, swollen joint count; 50-foot walk; Grip strength</td>
<td>6–50% attrition rate in both groups</td>
</tr>
<tr>
<td></td>
<td>Yoga + relaxation + education versus self care or waiting-list — 8 sessions; — 12 sessions</td>
<td>Lower-extremity</td>
<td>Pain and physical function (WOMAC)</td>
<td>Moderate overall</td>
</tr>
</tbody>
</table>

PMR, progressive muscle relaxation; AIMS 2, Arthritis Impact Measurement Scales – 2; SS, statistically significant; CPAQ, Chronic Pain Acceptance Questionnaire; SF-36, Short Form 36-item Health Survey; VAS, Visual Analogue Scale.
Although ASUs might display medium-term symptom-modifying effects on knee and hip OA, their symptom-modifying effects in the long term (>1 year) have not been confirmed. Based on the best-evidence synthesis, ASUs are good for symptom-modifying effects in knee and hip OA with some evidence of absence of structure-modifying effects. A recent systematic review on ASUs recommended further investigation because three of the four rigorous RCTs suggest that ASUs are effective symptomatic treatment, but the long-term study was largely negative.81,82

**ACUPUNCTURE**

Non-pharmacological treatments such as acupuncture are attractive because of their safety profiles and lack of the adverse events that have been well documented with the use of pharmaceuticals, especially when considering elderly populations.
A recent meta-analysis and systematic review concluded that acupuncture procedures that meet criteria for adequate treatment were significantly better than sham acupuncture or no additional intervention in improving pain and function in patients with chronic knee pain due to OA. These recent studies confirm an earlier systematic review and meta-analysis which concluded that: (1) acupuncture is often used for treating and relieving chronic pain due to OA; (2) the meta-analysis of three trials showed a significant effect of manual acupuncture compared to a sham acupuncture procedure; and that (3) there were confirmed beneficial effects for ameliorating pain for peripheral-joint OA. However, due to the nature of the heterogeneity in the results, there is a need for further research to confirm these findings and provide more information on long-term effects.

MIND–BODY MEDICINE

Multimodal cognitive-behavioural/mind–body therapies (Table 3), in combination with educational/information components (such as patient education/self-management programmes), may be appropriate adjunctive treatments in the management of rheumatoid arthritis and osteoarthritis.

SUMMARY (TABLE 4: LEVELS OF EVIDENCE)

Patients expect – and should obtain – advice from their general practitioners regarding dietary/supplement therapies for which there is a high level of evidence, as conclusions about efficacy should fit into clinical practice. There is a strong scientific rationale for the use of an integrative approach to the management of OA and RA (see Practice points).

<table>
<thead>
<tr>
<th>Practice points</th>
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<tbody>
<tr>
<td>For the management of OA and RA pain and attendant psychological distress:</td>
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<tr>
<td>• stress management techniques (e.g. meditation, relaxation therapies)</td>
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<tr>
<td>• acupuncture</td>
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<tr>
<td>For improved mobility and relief of pain of OA:</td>
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<tr>
<td>• glucosamine sulphate</td>
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<tr>
<td>To maintain viscosity in joints and stimulate cartilage repair in OA:</td>
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<tr>
<td>• chondroitin sulphate</td>
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<tr>
<td>• collagen hydrolysate</td>
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<tr>
<td>• lipids (avocado/soybean unsaponifiables)</td>
</tr>
<tr>
<td>To alleviate OA- and RA-associated inflammation and pain:</td>
</tr>
<tr>
<td>• various herbal medicines (Table 1)</td>
</tr>
</tbody>
</table>
Research agenda

- link the patient's viewpoint unequivocally with evidence-based medicine
- elucidate functions and mechanisms of activity of herbal medicines/nutraceuticals, as the available in-vitro and in-vivo animal and human data suggest that herbal medicines and nutraceuticals may influence the course of OA and RA through a wide variety of mechanisms. Safety of use may be significantly enhanced by increasing the knowledge base of herbal medicines/nutraceuticals and their interactions with pharmaceuticals
- focus on empirical evidence for dosages to be employed and associated cost-effectiveness

REFERENCES


