

Original article

Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: a systematic review

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Abstract

Objectives. To critically evaluate the evidence regarding complementary and alternative medicine (CAM) taken orally or applied topically (excluding glucosamine and chondroitin) in the treatment of OA.

Methods. Randomized clinical trials of OA using CAMs, in comparison with other treatments or placebo, published in English up to January 2009, were eligible for inclusion. They were identified using systematic searches of bibliographic databases and manual searching of reference lists. Information was extracted on outcomes, and statistical significance, in comparison with alternative treatment of placebo, and side effects were reported. The methodological quality of the primary studies was determined.

Results. The present review found consistent evidence that capsaicin gel and S-adenosyl methionine were effective in the management of OA. There was also some consistency to the evidence that Indian Frankincense, methylsulphonylmethane and rose hip may be effective. For other substances with promising evidence, the evidence base was either insufficiently large or the evidence base was inconsistent. Most of the CAM compounds studied were free of major adverse effects.

Conclusion. The major limitation in reviewing the evidence is the paucity of randomized controlled trials in the area: widening the evidence base, particularly for those compounds for which there is promising evidence, should be a priority for both researchers and funders.

Key words: Complementary medicine, Systematic review, Osteoarthritis, Efficacy, Safety, Randomized controlled trials.

Introduction

OA is a degenerative and progressive disease mainly affecting the joint cartilage and the subchondral bone. Prevalence increases with age [1, 2], and it is estimated that 18% of females and 9.6% of males >60 years of age have symptomatic OA [3]. Almost 1 in 10 people aged

35–75 years in the UK and over 30 million people in the USA are diagnosed with this disease [4]. Knee and hip joints are the commonest sites affected among the US and Europe populations aged >45 years [5]. Economic costs associated with OA are high. In the USA, it was estimated as \$15.5 billion in 1994, with most of the cost due to work loss [6].

A large number of different therapies have been described in the medical literature in relation to the treatment of OA [7]. According to Osteoarthritis Research International (OARSI), 'treatment of OA is directed towards reducing joint pain and stiffness, maintaining and improving joint mobility, reducing physical disability and handicap, improving health related quality of life, limiting the progression of joint damage and educating patients about the nature of the disorder and its management' [8]. In 2005, an OARSI international committee of experts

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recommended using combinations of non-pharmacological and pharmacological modalities to achieve optimal management. Non-pharmacological modalities include education about the objectives of treatment and changes in lifestyle, such as exercise and weight reduction [8].

However, due to the chronic nature of the disease and its effects on quality of life, many patients with OA commonly try alternative methods of treatment [9]. These diverse treatment methods are commonly categorized as complementary and alternative medicines (CAMs). The World Health Organization has defined CAM as 'A broad set of healthcare practices that are not part of the country's own tradition and are not integrated into the dominant healthcare system' [10]. It has been reported that 46% of people in the UK use CAM during their lifetime and ~10% of the population will visit a complementary medical practitioner each year, and it is estimated that >£450 million is spent on CAM in each year in England [11, 12]. Further, a study of 1119 persons living in the community in the UK with chronic hip or knee pain (much of which would be related to OA) enquired about health-seeking behaviour in the past 12 months: 9% had seen an alternative therapy provider. Predictors of seeking help from an alternative therapy provider were: female gender, being overweight, reporting comorbidities, high social class, not living in an urban area and lower levels of depression/anxiety and pain severity and a lack of mobility problems [13]. Rheumatological problems are among the commonest disease conditions encountered by CAM practitioners with around four in five of their consultations related to rheumatological conditions [14].

Given the popularity of CAMs, it is important that patients and practitioners have accessible and clear evaluation of the efficacy and safety of these treatments. The purpose of the review is to produce such evidence regarding CAMs taken orally or applied locally for the treatment of OA. It produces the detailed scientific methods behind the patient- and practitioner-centred leaflet recently published by the Arthritis Research Campaign (www.arthritisresearchuk.org). We excluded consideration of glucosamine and chondroitin since these have been extensively reviewed in other publications [15]. We have ensured, where possible, that we report the conduct and results of the review according to the recently published guidelines on Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA) (<http://www.prisma-statement.org/>).

Methods

Eligibility criteria

The following criteria were used to select the articles: (i) the study was a randomized clinical trial involving a CAM other than glucosamine or chondroitin; (ii) route of administration was oral or topical; (iii) comparison was made with placebo or other treatment; (iv) the complementary medicine was available in the UK; (v) involved human subjects with OA; and (vi) the study was published

in English. Publications up until the end of January 2009 were included in the review.

Information sources

Publications included in the present review were retrieved using a computerized searches of the following databases: Allied and Complementary Medicine (1985 to January 2009); EMBASE (1980 to January 2009); Ovid MEDLINE (1950 to January 2009); EBM Reviews – ACP Journal Club (1991 to January 2009); EBM Reviews – Cochrane Central Register of Controlled Trials (fourth quarter, 2008); EBM Reviews – Cochrane Database of Systematic Reviews (fourth quarter, 2008); and EBM Reviews – Database of Abstracts of Reviews of Effects (fourth quarter, 2008).

Search

Search terms used were 218 names of CAMs that are commonly used in OA, and key words such as 'alternative medicine', 'complementary medicine', 'osteoarthritis', 'randomized controlled trials', 'systematic reviews' and 'meta-analysis'.

Study selection

Two reviewers independently screened the titles of the selected articles and excluded duplicates and those obviously irrelevant. Abstracts of the selected articles were examined independently by two reviewers who applied the selection criteria. If the information in the abstracts was insufficient to make a decision, full papers were retrieved and used for this purpose. The references of all selected relevant articles including systematic reviews and meta-analysis were manually searched to obtain additional relevant publications. During consensus meetings, disagreements of selections were resolved. For the purposes of this review, manuscripts involving glucosamine or chondroitin were only excluded at the final stage.

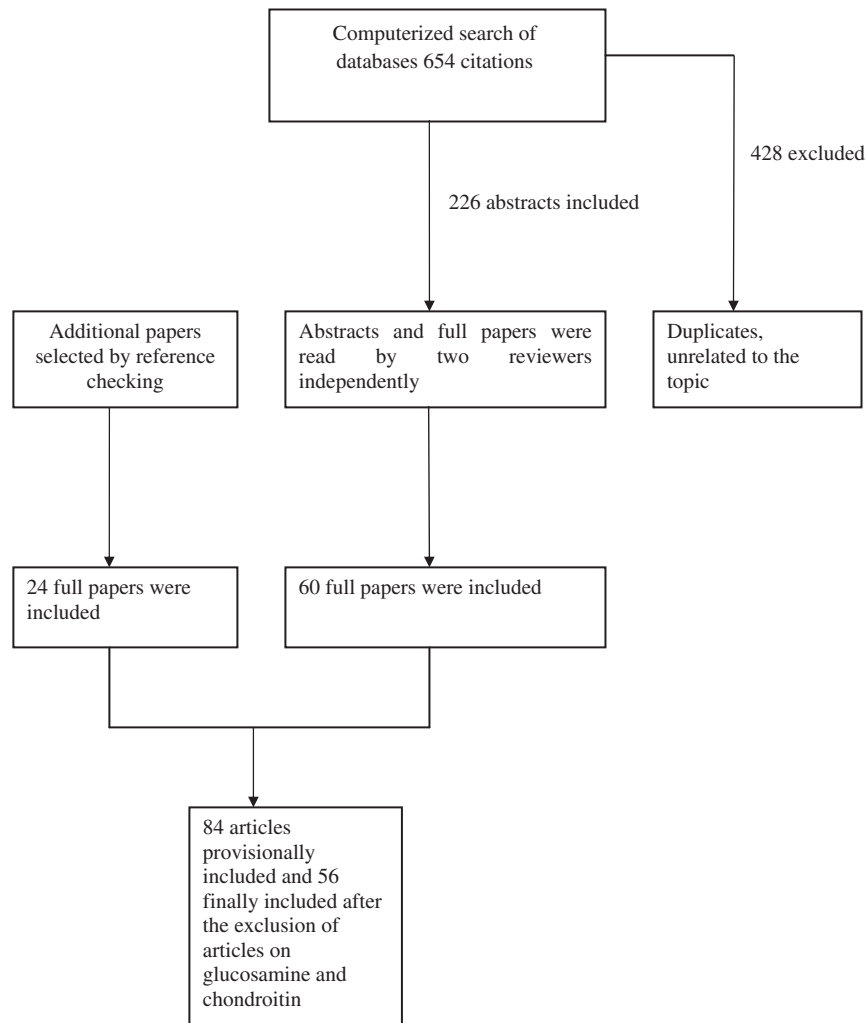
Data extraction and items

Data were extracted by a single reviewer and checked by a second reviewer. The data items extracted were: CAM(s) under investigation; number of persons recruited to the trial; length of follow-up; outcome measures studies; and data on statistical significance of change of outcome measure in CAM group in relation to the comparator and side effects reported. The five-point Jadad scoring system was used to assess the methodological quality of the selected trials with increasing score indicating a higher quality [16]. Some of the trials compared the effectiveness of the complementary medicine with a placebo (superiority trials) and others compared the complementary medicinal compound with another treatment (equivalence trials).

Results

Study selection

A total of 654 articles were identified by computerized search of databases, and, from these, 428 were excluded

Fig. 1 Process of selecting articles for inclusion in the review.

by examination of their titles. Excluded studies were mainly duplicates, studies on rheumatic diseases other than OA, study designs other than randomized controlled trials, studies on fractures, studies of other forms of complementary medicines such as acupuncture and massage, studies on animals and studies published in languages other than English. Abstracts of the remaining 226 studies and those identified by the screening of references of relevant original and review articles were scrutinized by the two reviewers. From this process, a total of 84 articles were potentially eligible and 56 remained after excluding those concerned exclusively with glucosamine and/or chondroitin. Identification of relevant studies is detailed in Fig. 1.

Study characteristics and results

We identified 25 substances with at least one eligible trial. There were nine compounds tested in single randomized controlled trials (RCTs), seven tested in two trials and nine tested in more than two trials.

Compounds tested in a single clinical trial

Articulin F. This ayurvedic herbal preparation was tested in a cross-over study among 42 patients with symptomatic OA plus radiological changes in any affected joints (Jadad score 4). After treatment, with 3 months of Articulin F or placebo two capsules/day allocated in random order, patients who received Articulin F had significantly better improvement in pain and function. However, there was no difference in joint structural changes according to radiological evaluation. No adverse effects necessitating discontinuation of Articulin F were reported [17].

Collagen. The ability of collagen hydrolysate to reduce pain in patients with knee OA was tested in a study of 389 patients across sites in the UK, USA and Germany (Jadad score 2). Patients were assigned to 10 g of collagen hydrolysate or placebo. Treatment was for 24 weeks and participants were followed for a further 8 weeks. There were no differences, overall, in pain, physical function or global assessment between the groups on intent-to-treat analysis but collagen hydrolysate was

superior when only German sites (which reported considerably lower drop-out) were analysed. There were approximately equal numbers of adverse events in both groups and most were mild-to-moderate gastrointestinal complaints [18].

Devil's claw. This herbal medicine (*Harpagophytum procumbens*), at a dose of six capsules/day (each containing 435 mg cryoground powder), was compared with diacerein 100 mg/day for a period of 4 months among 122 patients with hip and knee OA (Jadad score 4). Over the course of the study there was improvement in pain and disability, with no difference observed between treatments. Subjects taking devil's claw reported lower use of analgesic and non-steroidal anti-inflammatory medications. There were significantly fewer adverse event reports in the devil's claw group (16 vs 34%), with diarrhoea and flatulence most common [19].

Du Huo Ji sheng Wan. This Chinese herbal product was compared with diclofenac sodium among 200 patients with knee OA (Jadad score 4). The doses were six capsules (3 g each) and 25 mg, respectively, three times daily. After 4 weeks of treatment, patients in both study arms had similar improvements in pain and function scores. However, the improvements with *Du Huo Ji sheng Wan* (DJW) were slower to develop. The most common adverse events reported in the DJW group were high blood pressure (16%), dizziness, drowsiness (16%) nausea/vomiting and diarrhoea/constipation (12%), but were not significantly different to those reported in the diclofenac sodium group [20].

Eazmov capsules. This ayurvedic herbal preparation (*Cyperus rotundus*, *Tiospora cordifolia*, *Saussurea lappa*, *Picorrhiza kurroa* and *Zingiber officinale*) was compared with diclofenac sodium, each 50 mg three times daily, among 31 patients (Jadad score 3). After 6 months of treatment, patients who received Eazmov had less improvement in pain ($P < 0.001$) and disability ($P < 0.05$). However, significantly fewer adverse effects were reported by the patients allocated to Eazmov [21].

Fish liver oil, Reumalax, vitamin K and hyaluronic acid. None of these compounds was significantly more effective than placebo in single trials of treatment of OA (Jadad scores 3, 5, 4 and 5, respectively) [22–25].

Compounds tested in two clinical trials

Cetyl myristoleate. Cetyl myristoleate (CMO) is the cetyl ester of myristolic acid. It has been identified as an anti-inflammatory agent and as an immune system modulator. In the first RCT, oral CMO capsules were compared with placebo capsules (six capsules/day over 68 days of treatment) among 64 patients with chronic knee OA over 68 days of treatment (Jadad score 4). Patients treated with CMO capsules had significantly increased knee flexion (10.1°) compared with the placebo group (1.1°) and function, but there was no difference in knee extension [26]. In the second trial, CMO topical application was compared with placebo topical application among 40 patients with knee OA (Jadad score 5). Patients applied a

standardized amount of cream over a 10–12-cm area two times daily for 30 days. Patients applying CMO cream demonstrated greater improvements in the range of movement and function and no major adverse effects were reported [27].

Green-lipped mussel. In the first trial of 80 patients who had knee OA, all patients stopped NSAIDs and were transferred to paracetamol 2 g/day (with a further 2 g/day available for breakthrough pain) and then randomized to Lyprinol or placebo for treatment over 6 months. Lyprinol was at a dose of four capsules/day for 2 months and then two capsules/day for 4 months. Crude analysis revealed no significant difference in pain or patient global assessment between groups, although after adjustment for paracetamol consumption, Lyprinol was associated with greater reductions at some but not all time periods (Jadad score 5) [28]. In the second trial of 38 patients with knee or hip OA (Jadad score 4), patients received either 1150 mg/day of mussel powder or 210 mg/day of lipid extract over a 3-month period. Pain improved significantly more in the mussel extract group (visual analogue scale improvement 40 vs 13%) [29]. No major adverse effects were reported in these trials.

Pine bark. This herbal extract has been tested in the treatment of knee OA. In the first trial of 100 patients, after 3 months treatment with Pycnogenol (150 mg/day), patients reported reduced pain ($P < 0.04$) and an improvement in function ($P < 0.05$), whereas those on placebo demonstrated no change (Jadad score 5) [30]. In the second trial of 156 subjects, patients who received 50 mg Pycnogenol twice daily similarly demonstrated significant improvements in function whereas there were no changes in the placebo group. They also demonstrated decreased use of NSAIDs (58% reduction vs 1%) and gastrointestinal complications (63% reduction vs 3%) [31]. No serious adverse effects were noted on Pycnogenol in either trial.

SKI 306X. This oriental herbal mixture (*Clematis mandshurica*, *Trichosanthes kirilowii* and *Prunella vulgaris*) has been tested in patients with knee OA. In the first trial of 96 patients, SKI 306X was administered 200, 400 or 600 mg three times daily over 4 weeks compared with placebo (Jadad score 4). At all doses, SKI 306X demonstrated significantly lower levels of pain and better function after treatment, whereas there was no change for the placebo group [32]. In the second study of 249 patients, 200 mg three times daily over 4 weeks was equally as effective as 100 mg diclofenac-sustained release in reducing pain but was less effective in reducing disability [33] (Jadad score 3). In this latter study, discontinued treatment was similar in the SKI 306X and diclofenac sodium groups (16 vs 12%). The most common reasons for those on SKI 306X withdrawing were digestive symptoms (22 vs 26%) and respiratory symptoms (5 vs 2%). In the former study, there was no difference in the numbers reporting adverse events between placebo and any of the SKI 306X doses.

Stinging nettle. The first trial involving 27 patients with OA at the base of thumb was a cross-over design, using white deadnettle (which is non-stinging) as a control leaf. Patients applied the leaf for 30 s over the base of thumb once daily for a week (with a 5-week washout period). Treatment with stinging nettle was associated with greater reductions in pain and disability ($P < 0.03$ and $P < 0.01$, respectively) [34] (Jadad score 4). The second trial with 42 chronic knee pain patients who had a presumptive diagnosis of OA, failed to demonstrate any significant pain reduction for those applying stinging vs non-stinging nettle for 10 s at three knee sites daily over 1 week [35] (Jadad score 4). A single person in the former trial discontinued stinging nettle because of a hand rash and in the latter trial one person reported extreme pain after application.

Vitamin B complex. This was tested among patients with hand OA in a trial of 26 patients who had been prescribed NSAIDs. Subjects were randomly allocated for a 2-month period, daily 6400 µg folate with or without 20 µg cobalamin or lactose placebo. Tender hand joints were less and grip strength greater in those receiving the folate-cobalamin combination [36] (Jadad score 5). In the second trial of niacinamide, 72 patients took one tablet six times daily (total 3000 mg) or identical placebo for 12 weeks. Pain levels did not change on placebo but significantly reduced for those on niacinamide, whereas the measurement of global arthritis impact improved on those on niacinamide [-29% (95% CI $-6, -46$)] and significantly worsened for those on placebo [37] (Jadad score 4). In the latter trial, significantly more subjects on the niacinamide reported a side effect (40 vs 27%; $P = 0.03$), principally due to higher levels of heartburn and nausea.

Willow bark. In the first trial, willow bark extract (dose equivalent to 240 mg salicin/day) was compared with placebo over a 2-week treatment period in 78 patients with hip or knee OA. There was a statistically significant difference in change in pain using the Western Ontario MacMaster Questionnaire (willow bark 14% reduction vs placebo 2% increase; $P < 0.05$) [38] (Jadad score 4). In the second trial of 127 patients with knee or hip OA, willow bark at the same daily dose as the first trial was compared with both placebo and diclofenac sodium 100 mg/day over a 6-week period. Assessing pain by the WOMAC, willow bark was more efficacious at reducing pain than placebo (47 vs 17%) and no different from diclofenac sodium (10%) [39] (Jadad score 4). Adverse effects such as increased blood pressure, stomach upset and allergic reactions were reported. In the first and second trials, the proportion of patients reporting adverse events was similar on willow bark and placebo (41 vs 41% and 44 vs 49%, respectively), while a greater proportion of the diclofenac group reported such an event (70%).

Compounds tested in more than two clinical trials

Antioxidants. Two studies examined vitamin E in the treatment of knee OA involving 77 patients in a study of 500 IU/day for 6 months and 136 patients taking a similar

dose for 2 years. In neither study was vitamin E efficacious (compared with placebo) for any of the outcomes measured [40, 41]. A small trial of selenium and vitamins A, C and E involving 30 patients with OA of knee or hip found no difference in outcomes at 3 and 6 months [42]. Only the last trial mentioned adverse events—all five reported were in the placebo group. The median Jadad scores for these studies was 3.

Avocado-soybean unsaponifiables. Avocado-soybean unsaponifiables (ASUs) in the treatment of knee and/or hip OA has been tested in four similarly sized trials ($n = 163$ –260) with treatment between 3 and 12 months and which have a median Jadad score of 5 [43–46]. In all trials, treatment with this dietary supplement (300 mg/day and, in addition, in a single trial 600 mg/day) was compared with placebo. In two trials, ASU was found to be significantly more effective in improving pain and in three trials for improving function. There was no difference between the 300 and 600 mg in the trial that included both doses [45]. Adverse events were similar across ASU and placebo groups in all trials.

Capsaicin gel. The efficacy of capsaicin gel in the treatment of hand or knee OA has been tested in five RCTs, with sample sizes ranging between 14 and 200 and a median Jadad score of 4 [47–51]. In four trials, efficacy has been assessed compared with placebo, and in the fifth trial with both placebo and glyceryl trinitrate gel. In three trials, patients applied 0.025% capsaicin four times daily with the duration of treatment between 4 and 12 weeks. In the remaining studies, 0.015% capsaicin was applied once daily for 6 weeks and 0.075% capsaicin four times daily for 4 weeks. In all trials, capsaicin gel was found to be significantly more effective in improving pain than placebo, and similarly effective compared with glyceryl trinitrate gel in the single trial. In the 12-week study at the end of treatment, there was a 53% reduction in pain severity compared with 27% on placebo [47], whereas in the 4-week study the comparable reductions were 33 and 20% [48]. Trials also reported significant improvement (compared with placebo) in pain on movement and patient global assessment. Redness and burning sensation were reported as adverse effects. In two trials, 44 and 46% of capsaicin-treated patients reported such effects [47, 48].

Ginger. Efficacy of this herbal medicine in the treatment of knee or hip OA has been tested in three RCTs that have a median Jadad score of 3 [52–54]. In the first trial, using a cross-over design, EV.ext-33 170 mg ginger extract was compared with ibuprofen 400 mg and placebo three times daily amongst 67 patients with hip or knee OA who were given each treatment for 3 weeks. Overall, the study showed a significant reduction in pain and function for patients on ibuprofen but not for either ginger or placebo. In the second trial, EV.ext-77 255 mg ginger extract two times daily over a 6-week period in 29 patients with knee OA was compared with placebo. Improvement of pain across the trial was greater in the group taking ginger extract ($P < 0.05$). In the final study, 250 mg of ginger

extract and placebo were administered in a cross-over trial of 261 patients with each treatment lasting 12 weeks. Patients receiving ginger extract reported significantly lower pain and handicap. All trials acknowledge the difficulty in blinding subjects because of the pungent taste of the ginger extract. The most comprehensive reporting of adverse events [53] reported these by 59% of patients receiving ginger extract compared with 37% of those receiving placebo. Only one group of events differed between the groups: gastrointestinal events (45% patients vs 16%) particularly relating to eructation, dyspepsia and nausea; however, 70% of them were evaluated as mild. None of the other trials reported any excess overall adverse events, although bad taste was exclusively reported in those taking ginger extract.

Homeopathy. Homeopathic remedies in the treatment of OA were tested in three RCTs with a median Jadad score of 3 [55–57]. The efficacy of the homeopathic preparation (*Rhus toxicodendron* 12 \times , *Causticum* 12 \times and *Lac Vaccinum* 12 \times) in relieving knee pain associated with OA was assessed compared with paracetamol 2.6 g/day. In the first trial of 65 patients, no difference in outcome was found. The efficacy of *R. toxicodendron* 6 \times in relieving hip or knee pain associated with OA was assessed compared with placebo or fenopropfen 600 mg three times daily for a period of 2 weeks in a study of 36 patients. It was less effective than fenopropfen at reducing pain on movement and pain at rest and there was no difference from placebo. In the third trial of 184 patients, local application of a homeopathic remedy (Spiroflor), which contains *Symphytum officinale*, *R. toxicodendron* and *Ledum palustre* or piroxicam gel (0.5%) was applied as 1 g gel three times daily for 4 weeks. Overall, there was no difference in the level of pain reduction between the two groups. Only minor adverse symptoms were reported among persons taking the homeopathic remedies.

Indian Frankincense. This is a plant extract derived from *Boswellia serrata* tree. Its efficacy in knee OA has been tested in three RCTs with a median Jadad score of 4 [58–60]. The first trial was placebo controlled and of cross-over design involving 30 patients: when receiving *B. serrata*, patients demonstrated significantly greater reduction in pain, swelling and improvement in function over the 8 weeks of treatment with 333 mg three times daily. The second trial tested 5-Loxin, which is an extract of *B. serrata* enriched with 30% 3-O-acetyl-11-keto-beta-boswellic acid. Seventy-five subjects received 100 or 250 mg 5-Loxin, or placebo, for 90 days. Both doses of 5-Loxin conferred significantly improved pain and function compared with placebo ($P < 0.0001$ for both doses). In the final trial, *B. serrata* at 333 mg three times daily was tested against valecoxib 10 mg once daily for 6 months. At the end of the intervention, both *B. serrata* and valdecovib demonstrated a significant reduction in pain from baseline and the latter also for function (all $P < 0.001$). One month after stopping treatment, *B. serrata* demonstrated maintained improvement for pain and function ($P < 0.001$). There were no serious

adverse events reported in any study nor were adverse events of any sort significantly more common in the groups taking *B. serrata*.

Methylsulphonylmethane. Efficacy of methylsulphonylmethane (MSM), an organic sulphur compound in the treatment of knee OA, has been tested in three trials with sample sizes ranging between 50 and 118 and with a median Jadad score of 4 [61–63]. In all trials, MSM (at doses of 1.5, 3.375 and 6 g/day for 12 weeks) was found to be significantly more effective in improving pain compared with placebo. It was also more effective in improving function in two trials [61, 62] and in the third when combined with glucosamine [63]. Adverse events were either similar between MSM and placebo groups [61, 62] or no adverse events were reported [63].

Rose hip. The efficacy of this herbal medicine has been tested against placebo in three studies of patients with OA with sample sizes ranging between 94 and 112 and with a median Jadad score of 3 [64–66]. The doses tested were 1 g for 4 months, 5 g of Hyben Vital (a standardized powder) for 3 months and the same preparation for 4 months. In all three trials, there were some positive results in relation to rose hip. In a cross-over trial that included patients with OA of several sites, there was a highly statistically significant difference for just the first treatment period, an effect that the authors interpreted as signalling a strong carry-over effect [64]. The second trial of patients with hip or knee OA reported at the end of the 3-month period a significant improvement in those taking rose hip for activities of daily living, stiffness, patient global assessment, although there was no significant difference for pain [65]. In the final trial including patients with knee or hip OA, both pain and hip movement (but not knee movement) had improved more in the rose hip group [66]. In none of the trials was there any difference in adverse events between the groups.

S-adenosyl methionine. The efficacy of S-adenosyl methionine (S-AMe) in treating OA of knee, hip or spine has been tested in six trials with sample sizes ranging between 36 and 493 and a median Jadad score of 4 [67–72]. In all trials, the dose tested was 1200 mg/day and the comparisons were celecoxib 200 mg/day (16 weeks of treatment), piroxicam 20 mg/day (12 weeks), indomethacin 150 mg/day (28 days), ibuprofen 1200 mg/day (two trials both 30 days), and one trial compared against naproxen 750 mg/day and placebo (30 days). In all the trials, S-AMe was found to be equally effective as the NSAID and more effective than placebo for pain and function where this was measured separately or for a global score of which pain and function were a major part where they were not [71, 72]. In a meta-analysis of efficacy and safety and that included trials of i.v. administration, there was no significant difference between the likelihood of patients taking S-AMe and placebo reporting adverse effect but patients taking S-AMe were less likely to report an adverse event than those taking an NSAID [odds ratio (OR) 0.42 (95% CI 0.29, 0.61)]. The drop-out rate in trials was highest for those receiving

an NSAID (6.9%) followed by placebo (5%) and lowest for SAME (2.6%) [73].

Discussion

The present review found consistent evidence that capsaicin gel and SAME were effective in the management of OA. There was also some consistency to the evidence that Indian Frankincense, MSM and rose hip may be effective. For other substances, although there was some promising evidence, the evidence base was either insufficiently large or the evidence base was inconsistent. This applied to ASU, CMO, green-lipped mussel, pine bark extracts, SKI 306XI, vitamin B complex, ginger and homeopathy. Several compounds were the subject of very few trials (mostly single trials), but those that had been published were positive. Because of the low quality of the primary data and the possibility of publication bias, no robust conclusions can be drawn about these. This relates to Articulon F, devil's claw and DJW. No positive evidence was found regarding collagen, eazmov, fish liver oil, sruemalax, vitamin K, hyaluronic acid, stinging nettle, willow bark, or anti-oxidants such as vitamin E.

Most of these CAM compounds were free of major adverse effects and usually associated with minor adverse effects such as heartburn, diarrhoea and stomach upsets. However, willow bark and DJW were associated with increased blood pressure and dizziness. In most trials, patients who received CAM products had similar amounts of adverse effects compared with placebo, and relatively low levels compared with NSAIDs.

Interpretation and utilization of the above evidence into practice must be carried out with caution. The evidence regarding most CAM compounds for the management of OA is based on a single or small number of trials. In addition, many of these trials include only a small number of patients and had other methodological weaknesses. The major concern is publication bias since researchers and editors of journals are more likely, respectively, to submit and publish trials with positive results. Further, manuscripts in languages other than English were excluded from the current review. We found publications in other languages such as Chinese, German and French. All the articles found on phytodolor were in languages other than English and therefore have not been included in this review. However, one systematic review on phytodolor, which included articles published in other languages found good evidence to suggest that it was effective in the treatment of OA [74].

Soeken *et al.* [73] reviewed 11 eligible trials on SAME and meta-analysis revealed that it had similar efficacy in improving pain and functional limitation compared with NSAIDs and concluded that SAME was a useful therapy for OA considering its ability to relieve symptoms without the adverse effects often associated with NSAIDs. Trials of vitamins A, C, E and selenium in the treatment of OA were reviewed by Canter *et al.* [75], who found no evidence to suggest their efficacy either alone or in combination. Zhang *et al.* [76] in a review of capsaicin gel in the treatment of OA found three eligible articles and

meta-analysis revealed highly significant benefits in improving pain compared with placebo. All three articles used in this review and the five articles identified in the present review, individually had positive effects. Christensen *et al.* [77] in a meta-analysis of ASU in the treatment of OA, using the same articles as the current review, found a significantly better response from ASU compared with placebo (OR 2.19) and recommended a trial of ASU for ~3 months. Long and Ernst [78] reviewed trials on homeopathic remedies and found, that although promising, the evidence was inconclusive because of the paucity of evidence. The conclusions of these previous reviews of individual compounds are in keeping with those of the present review.

OA is a chronic disease that impairs quality of life and often this is associated with unsatisfactory control of symptoms. This systematic review provides evidence on efficacy of a number of CAM therapies that were used in OA. The major limitation in reviewing the evidence is the paucity of RCTs in the area: widening the evidence base, particularly for those compounds for which there is promising evidence, should be a priority for both researchers and funders.

Rheumatology key messages

- Only for a few compounds is there evidence of efficacy of CAMs in the treatment of OA.
- Most compounds' lack of trials means that it is not possible to draw any firm conclusions.
- For several compounds, there is no evidence of efficacy in the trial(s) conducted.

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