

Original article

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

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Abstract

Objective. To critically evaluate the evidence regarding complementary and alternative medicine (CAM) taken orally or applied topically (excluding fish oil) in the treatment of RA.

Methods. Randomized controlled trials (RCTs) of RA using CAMs, in comparison with other treatments or placebo, published in English up to August 2010, 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 treatments, and reported side effects. The methodological quality of the primary studies was determined using the Jadad scoring system.

Results. Reported RCTs were available for 18 CAMs in the management of RA. There was no consistent evidence available for any of the reviewed substances to suggest that they were efficacious as complementary medicines to standard treatment. Nevertheless, the studies conducted on borage seed oil ($n=2$) and thunder god vine ($n=3$) have been positive and may warrant further investigation. Not all CAM compounds studied were free of major adverse effects.

Conclusion. The major limitation in reviewing the evidence for CAMs is the paucity of RCTs in the area. The available evidence does not support their current use in the management of RA.

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

Introduction

Over recent years, the management of RA has changed dramatically with considerable improvements in outcomes [1]. Understanding the importance of treating this condition early and dynamically with appropriate medication,

and the development of highly effective biologic agents, has led to a paradigm shift towards the goal of disease remission. Nevertheless, due to the chronic nature of the disease and its effects on quality of life, patients commonly try complementary methods of treatment for RA [2]. Complementary and alternative medicines (CAMs) are defined by the World Health Organization as 'a broad set of health care practices that are not part of the country's own tradition and are not integrated into the dominant healthcare system' [3]. Recently published data from the Health Survey for England 2005 showed that the lifetime and 12-month prevalence figures for CAM use by arthritis sufferers were 38 and 17%, respectively [4]. It is estimated that >£450 million is spent on CAM in each year in England alone [5, 6]. CAM is most popular among patients who are suffering from diseases for which conventional therapies have failed to offer a cure or

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satisfactory control [7]. A systematic review of the expectations of CAM users showed that the three most significant expectations are the hopes to influence the natural history of the disease, to prevent illness and to receive treatments free of adverse effects [8]. Rheumatological problems are among the commonest disease conditions encountered by CAM practitioners with around four in five of their consultations related to rheumatological conditions [9].

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 this review is to produce such evidence regarding CAMs (and for RA these are likely to be complementary rather than alternative) taken orally or applied topically for the treatment of RA utilizing, where possible, the recently published guidelines on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (<http://www.prisma-statement.org/>). It provides additional information to the National Institute for Health and Clinical Excellence (NICE) guidelines, which focused on dietary interventions and only a limited number of CAMs, and included non-randomized controlled trial (non-RCT) data [10]. We excluded ω -3 polyunsaturated fatty acid supplementation (i.e. fish oil) since it has been the subject of previous, authoritative reviews and meta-analysis [11,12]. The data from this review formed the basis for a patient and practitioner centred leaflet published by Arthritis Research UK (www.arthritisresearchuk.org).

Methods

Eligibility criteria

The following criteria were used to select articles: (i) the study was an RCT involving a CAM; (ii) the route of administration was oral or topical; (iii) comparison was made with placebo or a treatment of established efficacy; (iv) the CAM was available in the UK; (v) the study involved human subjects with RA; and (vi) was published in English. Publications up until the end of August 2010 were eligible for inclusion in the review.

Information sources

Publications included in the present review were retrieved using computerized searches of the following databases: Allied and Complementary Medicine (1985 to August 2010), EMBASE (1980 to August 2010), Ovid MEDLINE (1950 to August 2010), EBM Reviews – ACP Journal Club (1991 to August 2010), EBM Reviews – Cochrane Central Register of Controlled Trials (2nd Quarter 2010), EBM Reviews – Cochrane Database of Systematic Reviews (2nd Quarter 2010) and EBM Reviews – Database of Abstracts of Reviews of Effects (2nd Quarter 2010).

Search

Two hundred and eighteen names of CAMs that are commonly used in rheumatic diseases and key words

such as ‘alternative medicine’, ‘complementary medicine’, ‘rheumatoid arthritis’, ‘randomized controlled trials’, ‘systematic reviews’ and ‘meta-analysis’ were used in the search.

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 positive decision, full papers were retrieved and used for this purpose. The references of all selected relevant articles including systematic reviews and meta-analyses were manually searched to obtain additional relevant publications. During consensus meetings, disagreements of selections were resolved.

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 studied, 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 score was used to assess the methodological quality of the selected trials with increasing score indicating a higher quality [13]. Trials could have compared the effectiveness of the CAM with a placebo (superiority trials) or with a treatment of established efficacy (equivalence trials).

The results are summarized in text and tables into three categories: compounds with one trial (Table 1), two trials (Table 2) and more than two trials (Table 3). Trials are included in the tables if they involved a placebo comparison and data from individual trials are included if the report involved a direct comparison between the intervention and placebo arms of the trial.

Results

Study selection

A total of 871 articles were identified by the computerized search of databases and from them 769 were excluded by examination of their titles. Excluded studies were mainly duplicates, studies on rheumatic diseases other than RA, study designs other than RCTs, studies on fractures, studies of complementary medicines that are not applied topically or taken orally such as acupuncture and massage, studies on animals and studies published in languages other than English. Abstracts of the remaining 102 studies and those identified by the screening of references of relevant original and review articles were examined by the two reviewers. From this process, a total of 46 articles were considered eligible, of which 34 were on compounds other than ω -3 polyunsaturated fatty acid (i.e. fish oil): identification of relevant studies is detailed in Fig. 1.

TABLE 1 Complementary medicines for RA tested in single trials

Compound	Country of study	Subjects (n)	Outcomes ^a	Duration of treatment, months	Jadad score	Reference
Cannabis spray (oral)	UK	58	Difference (+): pain on movement, pain at rest, sleep quality, DAS-28, SF-MPQ (pain at present) No difference: morning stiffness, SF-MPQ (total pain intensity, present intensity)	1.25	5	[14]
Cat's claw	Austria	40	Difference (+): number of painful joints No difference: number of swollen joints, morning stiffness, disease activity, pain, ESR, CRP	6	5	[15]
Feverfew	UK	41	Difference (+): grip strength No difference: early morning stiffness, inactivity stiffness, Ritchie articular index, patient and physician global assessment, ESR, CRP and other laboratory parameters	1.5	4	[16]
Flaxseed oil	Finland	22	No direct comparison between intervention and placebo group	3	4	[17]
Rose hip	Germany	89	Difference (+): HAQ-DI, HAQ physician's global scale, RAQoL, SF-12 (physical) No difference: HAQ pain, HAQ patient's global scale, DAS-28, SF-12 (mental)	6	4	[19]
Vitamin B ₆	Taiwan	43	Difference (+): plasma pyridoxal 5'-phosphate, plasma IL-6, plasma TNF- α No difference: serum folate, high-sensitivity CRP, ESR, white blood cell, total lymphocyte, neutrophil, T cell (CD3), B cell (CD19), Th cell (CD4), T-suppressor cell (CD8), Th/suppressor ratio (CD4/CD8)	3	1	[22]
Willow bark extract	Germany	26	Difference (+): None No difference: pain, tender joint count, swollen joint count, HAQ-DI, morning stiffness, patient and physician assessment of efficacy, ESR, CRP, ACR-20 responders, SF-36 (physical and mental)	1.5	4	[23]

^aDifferences (+): intervention is significantly better than placebo in outcome measure; no difference: where no statistical difference in outcome measure; difference (-): placebo is significantly better than intervention for outcome measure. SF-MPQ: short form-McGill pain questionnaire; HAQ-DI: Health Assessment Questionnaire-Disability Index; RAQoL: RA quality of life; SF-12: short form 12.

TABLE 2 Complementary medicines for RA tested in two trials

Compound	Country of study	Subjects (n)	Outcomes ^a	Duration of intervention, months	Jadad score	Reference
Antler velvet	Canada	168	Difference (+): none No difference: pain (AIMS2 and HAQ), tender joint count, swollen joint count, patients and physician global assessment of disease activity, CRP, function (AIMS2 and HAQ), quality of life (AIMS2 and HAQ) Difference (+): none	6	5	[24]
Blackcurrant seed oil	Canada	40	No difference: arthritis impact measurement scales (AIMS2: symptoms, affect, function), patient global assessment Difference (+): joint tenderness count and score	1	3	[25]
Borage seed oil	USA	34	No difference: patient and clinician global assessment, pain, activities, swollen joint count and score, morning stiffness, grip strength, ESR, RF titre, platelet count No direct comparison between intervention and placebo group	6	4	[26]
	UK	30	Difference (+): tenderness count and score, swollen joint count and score, physician global assessment, pain, grip strength (left)	1.5	4	[27]
	USA	37	No difference: patient global assessment, vocational activity, morning stiffness, grip strength (right), ESR, RF titre, platelet count Difference (+): swollen joint count, tender joint count, HAQ score	6	4	[28]
	USA	56	No difference: swollen joint score, morning stiffness, physician and patient global assessment, pain	6	5	[29]
Evening primrose oil	UK	40	No direct comparison between intervention and placebo group	6	4	[30]
	UK	49	No direct comparison between intervention and placebo group	12	4	[31]
Green-lipped mussel	UK	30	Difference (+): none No difference: pain, morning stiffness (min), articular index, PIP circumference, joint size, analgesic use	1	2	[32]
	UK	35	No difference: ESR, haemoglobin, platelets Ritchie articular index, grip strength, pain (present, morning), RF, IgG, limbering up time	4	4	[33]
Homeopathy	UK	58	Difference (-): subjective impression of symptoms Differences (+): none	3	3	[34]
	Brazil	44	No difference: articular index, ESR, duration of morning stiffness Differences (-): pain Differences (+): none	6	3	[35]
	UK	42	No difference: morning stiffness, 15-m walking time, Ritchie articular index, grip strength, functional class, other medications, ESR, seronucoids, physician assessment Difference (+): pain, apolipoprotein A-I	3	4	[36]
Vitamin E	Iran	102	No difference: oxidative modification of lipids and proteins, haematological and biochemical assessments of inflammatory activity, Ritchie articular index, early morning stiffness duration, number of swollen joints No direct comparison between intervention and placebo group	3	4	[37]

^aDifferences (+): intervention is significantly better than placebo in outcome measure; no difference: where no statistical difference in outcome measure; difference (-): placebo is significantly better than intervention for outcome measure. IgG: Immunoglobulin G.

TABLE 3 Complementary medicines for RA tested in more than two trials

Compound	Countries of study	No. Subjects (range)	Significant differences in outcome ^a	Duration of treatment (range), months	Median Jadad score	References
Collagen	USA (2), Italy, Germany	60–190	Differences (+): no. of swollen joints, no. of painful joints, joint swelling index, joint tenderness/pain index, 15-min walk time, overall status, analgesic use, physician assessment of efficacy Differences (–): pain, physician global assessment, patient global assessment	3–6	4	[39–42]
Selenium	Denmark, Belgium (2)	15–55	Differences (+): arm movement, health perception	3–6	4	[43–45] ^b
Thunder god vine	Canada, USA	35–61	Differences (+): modified ACR20 response (2 studies), tender joint count (2), swollen joint count (2), grip strength, morning stiffness, ACR functional class, ESR (2), CRP (2), RF, pain, physician and patient global assessment (2)	1.5–5	4	[46, 47]

^aDifferences are noted in a single study unless otherwise indicated. ^bStudy did not directly compare the intervention and placebo groups.

Study characteristics and results

We identified 18 substances of CAM with at least one eligible trial. There were eight compounds tested in a single RCT, seven tested in two trials and only three tested in more than two trials.

Compounds tested in single trials

Cannabis oral spray. The oral spray is a blend of the whole-plant *Cannabis sativa*, and this herbal medication was tested for a period of 5 weeks among 58 patients with RA (Jadad score 5) [14]. After treatment, patients who received the oral spray had significantly better improvement in pain on movement, pain at rest and quality of sleep compared with patients who received placebo. There was also a significant improvement in the 28-joint DAS (DAS-28) and the short-form McGill pain questionnaire (pain at present subscale) compared with placebo. Dizziness and nausea (26 vs 4%), light headedness (10 vs 4%) and dry mouth (13 vs 0%) were adverse effects more common in the cannabis oral spray group.

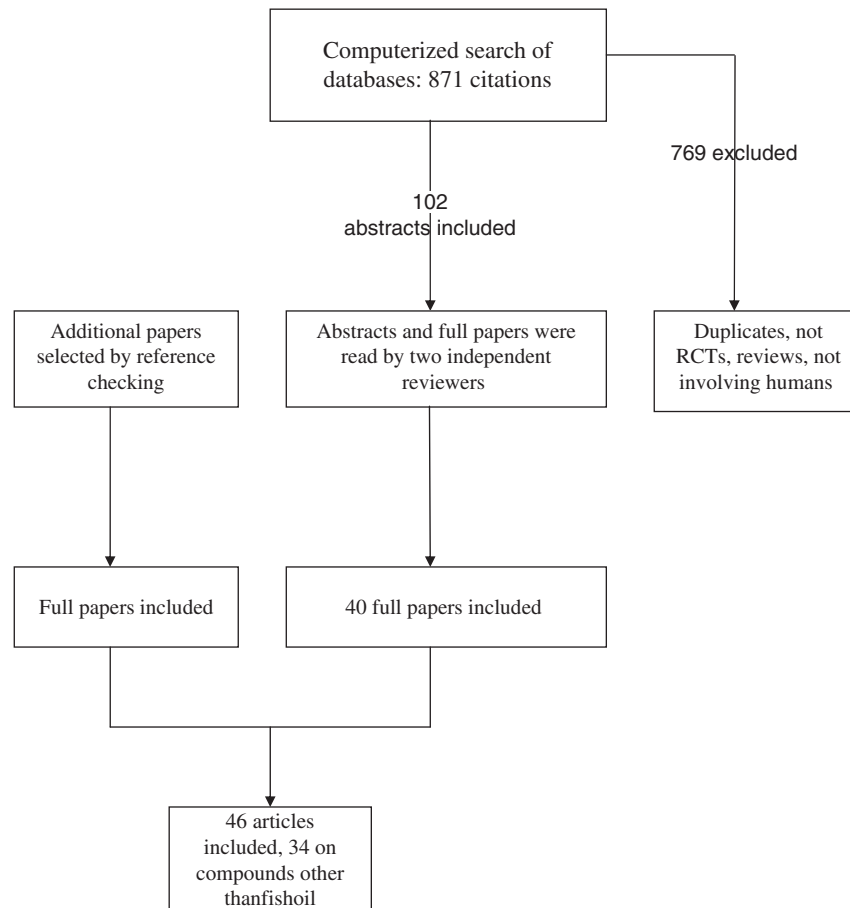
Cat's claw (Uncaria tomentosa). This South American herb was tested for a period of 24 weeks among 40 patients with established RA (Jadad score 5) [15]. All patients had been treated with SSZ or HCQ for a period of at least 6 months. Patients who received 20 mg dry extract of *Radix U. tomentosae* had a greater reduction in the number of tender joints compared with patients who received placebo (53 vs 24%; $P=0.044$). However, there was no significant difference in any of seven other outcome variables studied. There were no differences in adverse events reported between the groups.

Feverfew (Tanacetum parthenium). Feverfew is a perennial plant of the sunflower family and medicinal preparations are from the leaves. Dried chopped feverfew (mean dose 76 mg daily) was tested for a period of 6 weeks among 41 female patients with RA who had inadequately controlled inflammatory joint symptoms (Jadad score 4) [16]. Patients who received feverfew had significantly better improvement in grip strength compared with patients who received placebo at 6 weeks, but there was no difference on any other measure. There were no individual adverse events reported in more than a single patient and no difference between groups.

Flaxseed oil. Oil extracted from the seeds of the flax plant *Linum usitatissimum* (30 g/day—31% alpha-linolenic acid) was tested for a period of 3 months among 22 patients with RA satisfying 1987 ARA criteria (Jadad score 4) [17, 18]. At the end of the treatment period, in comparison with a group receiving 30 g safflower oil (33% linoleic acid), no significant difference was observed in any of the clinical or laboratory parameters. However, as a measure of adherence, those in the intervention group did show an increase in alpha-linolenic acid. No details were given of the relative frequency of adverse events in the study groups.

Rose hip. This herbal medicine powder made from the fruit of *Rosa canina* (5 g/day vs placebo powder) was

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



tested for 6 months in a group of 89 patients who met the revised ARA criteria for RA (Jadad score 4) [18, 19]. Measures of disease activity, quality of life, physical function and physician global assessment all improved to a greater extent in the intervention group. There were more drop-outs (14 vs 11) and adverse effects (26 vs 14) in the placebo group. There was one serious event (vasculitis allergica) in the intervention group, but it was unclear whether this was related to Rose hip as the patient was on several concurrent medications.

SKI306X. This is a mixture of three herbal medications prepared from *Clematis mandshurica*, *Trichosanthes kirilowii* and *Prunella vulgaris*. After a washout period of 14 days when NSAIDs were discontinued and patients were required to have demonstrated an increase in their pain, 183 patients with RA according to revised ARA criteria [18] were randomly assigned to receive either SKI306X 200 mg three times per day or celecoxib 200 mg twice per day for a 6-week period (Jadad score 4) [20]. During treatment, patients in both groups reported similar improvements in pain and an identical proportion (1/3) had achieved a 20% improvement in ACR criteria (ACR20) response rate. Drug-related adverse events were reported by 30% of the SKI306X and 24% of the

celecoxib groups. The most frequent adverse event in the SKI306X group was epigastric pain (9.9%), but overall there were no significant differences observed in the occurrence of drug-related adverse events.

Vitamin B₆. Efficacy of this supplement has been tested in a 12-week trial of 43 patients who met the ACR 1991 revised criteria for RA (Jadad score 1) [21]. Subjects were allocated to 5 mg/day folic acid with or without 100 mg/day vitamin B₆ [22]. There was no significant difference in clinical measures of disease activity between the groups (disease activity score or number of painful or swollen joints). The active intervention group did, however, demonstrate significantly greater reductions in levels of inflammatory and immune response as evidenced by lower levels of plasma pyridoxal 5'-phosphate, IL-6 and TNF- α . No mention was made of any adverse events.

Willow bark extract. This extract of the bark of *Salix daphnoides* was tested for a period of 6 weeks among 26 patients with RA (Jadad score 4) [23]. Patients received either an extract containing 240 mg/day salicin, or placebo. Patients who received willow bark achieved a -8 mm change in pain [15% reduction on a 100 mm visual analogue scale (VAS)] compared with a -2 mm

change in pain (4% reduction) among those who received placebo. However, this difference was not statistically significant. There were seven adverse events reported in the trial overall and none was assessed as serious. Only one event in the willow bark groups was classified as possibly causal: mild itching of the arms.

Compounds tested in two trials

Antler velvet. This is a dietary supplement made from deer or elk ground antlers. In the first trial, 168 patients with stable RA but with pain of at least 25 mm on a 100 mm VAS, recruited by physician referral or from public advertisement, were randomly assigned to receive either elk velvet antler (EVA: 1 g whole beam/day) or placebo for 6 months. There were no significant differences observed in respect of change of pain, disease activity or overall health status between the groups (Jadad score 5) [24]. In the second trial, 40 patients with stable RA who were taking prescription or over-the-counter medications were randomly assigned to receive, in addition, one of the following four treatments: placebo capsules, EVA capsules 430 mg/day, 860 mg/day or 1290 mg/day (Jadad score 3) [25]. There were similar effects on pain, affect, function and global assessment across all treatment and placebo groups. There were no significant differences in adverse event frequency observed across the placebo or treatment groups in either study.

Blackcurrant seed oil. Blackcurrant seed oil (BCSO) is a rich source of γ -linolenic acid and, in the first trial, 34 patients with RA satisfying the revised ARA criteria [18] were randomly assigned to receive either BCSO 10.5 g/day or placebo capsules for 24 weeks. There were no differences in response, overall, between patients in the two groups; however, patients who received BCSO did have significantly greater improvement in tenderness count ($P=0.01$) and tenderness score ($P=0.03$) (Jadad score 4) [26]. In the second trial, 30 patients with RA (receiving only NSAIDs) were randomly assigned to BCSO 3 g/day or placebo (sunflower seed oil) for 6 weeks (Jadad score 4) [27]. Patients were assessed at baseline, 6 and 12 weeks. After the 6-week treatment period, patients on placebo demonstrated no significant difference on any of the clinical parameters, while those who received BCSO had significant improvement only in morning stiffness ($P < 0.05$). This improvement was not maintained at 12 weeks (i.e. a further 6 weeks with no treatment). At 6 weeks (but not 12 weeks), the patients receiving BCSO demonstrated a significant reduction in IL-1 β , Prostaglandin E (PGE)₂ and IL-6 but not TNF- α , while there were no such differences in the placebo group. In relation to the former study, it was reported only that no patients taking BCSO withdrew because of adverse events. There was a high rate of withdrawal (seven patients in BCSO and placebo groups) due to the number of large capsules ($n=15$) requiring to be consumed per day.

Borage seed oil. In the first trial, 37 patients with RA according to revised ARA criteria and treated only with aspirin, NSAIDs and/or CSs [18] were randomly assigned to receive either 1.4 g/day γ -linolenic acid in borage seed oil

or placebo for 24 weeks (Jadad score 4) [28]. Patients who received borage seed oil had significant improvement in tender joints count, tender joint score, swollen joint count, swollen joint score and pain compared with patients who received placebo. In the second trial, 56 patients with RA according to revised ARA criteria [18] and on stable therapy were randomly assigned to borage seed oil 2.8 g/day or placebo for 6 months (Jadad score 5) [29]. Patients who received borage seed oil had significant improvement in tender joints count, tender joint score, swollen joint count, pain (measured by VAS) and HAQ score compared with patients who received placebo. Only the former study reported adverse events: there were no differences between the groups. Belching and soft stools were reported in those taking borage seed oil.

Evening primrose oil. In the first trial, 40 patients with RA who had upper gastrointestinal lesions due to NSAID use were randomly assigned to receive either evening primrose oil 6 g/day (which contain 540 mg of γ -linolenic acid) or olive oil 6 g/day as the placebo for 6 months (Jadad score 4) [30]. Patients who received evening primrose and placebo both had a significant improvement in articular index at 6 months, while patients in the placebo arm had, in addition, a significant improvement in pain. In the second trial, 49 patients meeting ARA criteria for RA [18] were randomly assigned to receive one of three treatments for 12 months: evening primrose oil (12 capsules/day equivalent to 540 mg γ -linolenic acid), evening primrose oil and fish oil (12 capsules per day equivalent to 450 mg γ -linolenic acid and 240 mg eicosapentaenoic acid), or placebo (Jadad score 4) [31]. All groups consumed significantly less NSAIDs, but there were no significant changes in clinical or laboratory parameters. In this latter study, of those who received evening primrose oil with or without fish oil ($n=31$), two withdrew because of gastrointestinal upset and three because of increasing RA symptoms. Of the 18 placebo patients, 10 withdrew because of increasing RA symptoms. Four patients in the evening primrose oil groups reported adverse effects, but none in the placebo group: the effects were nausea, diarrhoea and headache.

Green-lipped mussel. This is a dietary supplement containing large amounts of omega-3 fatty acids. It is extracted from the bivalve mollusc *Perna canaliculus*. The first trial was a cross-over trial of 30 patients using 300 mg seatone (green-lipped mussel extract) three times daily, in addition to existing drug regimens, for 4 weeks (Jadad score 2) [32]; the second a trial of 35 patients using 230 mg/day seatone for 4 months (Jadad score 4) [33]. In neither trial was there a significant improvement in any clinical or biochemical parameters in comparison with placebo. In the latter trial, there were significantly more patients on green-lipped mussel who felt their symptoms had worsened. In the former trial, three patients taking green-lipped mussel had stopped treatment because of headache, abdominal pain, diarrhoea and constipation.

Homeopathy. Efficacy of various homeopathic remedies in RA has been tested in two RCTs. The first trial was of cross-over design of 112 patients with seropositive RA on stable treatment (Jadad score 3): patients received either homeopathic medicines used for treating RA in 6cH (10^{-12}) or 30cH (10^{-30}) dilutions or identical placebo for 6 months [34]. The most commonly used prescriptions were *Rhus toxicodendron* and sulphur, and seven other homeopathic medicines accounted for 80% of the prescriptions. The only significant difference was that patients had lower pain scores after placebo therapy. Only 58 patients completed the trial, but none withdrew because of adverse events. The second study of individual homeopathic remedies (or placebo) used in 44 patients with RA according to ARA criteria [18] for a period of 6 months showed no difference in the physician assessment of treatment effectiveness and showed generally similar profiles of clinical and biochemical parameters [35]. The homeopathic group improved in four out of nine measures and the placebo group in three (Jadad score 3). There was no formal reporting of adverse events in these studies.

Vitamin E. Efficacy of this supplement was tested for a period of 12 weeks among 42 patients with RA who met the revised ARA criteria (Jadad score 4) [18]. They required to be receiving stable NSAID treatment and second-line medication. Patients were randomly assigned to receive either Vitamin E 600 mg twice per day or placebo for 12 weeks. At the end of treatment, patients who received vitamin E had significant improvements in morning and evening pain and pain after activity compared with patients who received placebo ($P < 0.05$). No change was observed in the laboratory measures of inflammatory activity. There were no significant differences in adverse events reported between the two groups (vitamin E: five events in 20 patients; placebo: seven events in 22 patients) [36]. In the second study, vitamin E 400 mg/day was tested in a factorial design with conjugated linoleic acids (CLAs) in 102 subjects over 3 months (Jadad score 4) [37]. The trial has not been analysed in a way that allows the main effects of vitamin E and CLAs to be determined. Physician global assessment and pain (morning, night and post-activity), morning stiffness, number of swollen and tender joints and disease activity improved in all treated groups but not placebo. The greatest improvements were seen in groups taking CLAs alone or in combination with vitamin E. There were no serious adverse events reported in any group.

Compounds tested in more than two trials

Collagen. Efficacy of this dietary supplement in RA has been tested in four, placebo-controlled trials (median Jadad score 4) and in one trial in comparison with MTX (Jadad score 3). Five hundred and three patients were randomly assigned either to 0.1 mg/day of chicken type II collagen or 10 mg MTX once per week for 24 weeks [38]. Both groups improved over the course of the study, but achieving an ACR20 was significantly more common in those taking MTX (58 vs 42%) as was improvement in pain, disability, patient global assessment as well as

ESR and CRP. Adverse events were significantly less common in the collagen group (6 vs 10%)—the most common in the collagen group (17 out of 43) being abdominal pain or epigastric discomfort. Among the placebo-controlled trials, 60 patients with severe, active RA tested 0.5 mg chicken type II collagen for 90 days [39]. Those allocated collagen demonstrated a greater reduction in number of swollen joints, joint tenderness and demonstrated less of an increase in 15-min walk time. It was reported that no side effects were evident. The remaining placebo-controlled trials involved 60 patients testing chicken type II collagen at 0.25 mg/day for 6 months [40], 90 patients testing bovine type II collagen 1 mg or 10 mg/day for 12 weeks [41] and 190 patients testing bovine type II collagen at 0.1 mg then 0.5 mg/day for 6 months [42]. None of these latter trials demonstrated a significantly better outcome for patients on active treatment. Although there was no evidence of an excess of adverse events in any trials, 3/29, 10/95 and 7/60 patients randomly assigned to collagen withdrew from the studies, respectively, due to lack of efficacy.

Selenium. Efficacy of this dietary supplement in RA has been tested in three placebo-controlled trials, with a median Jadad score of 4. The trials were conducted among 40 patients treated with 256 µg/day for 6 months [43], and two trials of 55 and 15 patients treated with 200 µg/day for 3 months [44,45]. Only in the smallest trial, which was published in the form of a 'Letter to the Editor', was selenium found to be more effective in improving pain and morning stiffness than placebo [45]. In the other two trials no significant improvement was seen in any of the measured clinical parameters such as pain, morning stiffness or grip strength. In the first trial, 7/20 and 3/20 patients in the selenium and placebo groups, respectively, reported mild gastrointestinal side effects [43]. The second trial reported mild to moderate adverse events, but that there were no differences between the groups [44].

Thunder god vine. This is a traditional Chinese herbal medicine derived from root pulp of the plant *Tripterygium wilfordii*, which has been tested in three trials with a median Jadad score of 4. In the first trial, 61 patients with RA meeting revised ARA criteria [18], with at least 3 tender and swollen joints, and stable doses of drugs were randomly assigned to receive either thunder god vine cream or placebo cream for a period of 6 weeks. After the treatment, patients who received thunder god vine cream had 8.1-fold odds with 95% CI (1.9, 35) of achieving an ACR20 response ($P = 0.002$) compared with patients who received placebo [46]. In the second trial, 35 patients with RA were randomly assigned to receive thunder god vine 180 mg/day, 360 mg/day or placebo [47]. After the 20-week treatment period, patients who received thunder god vine had significant improvement in tender joints, swollen joints, pain assessment, physical function (high dose), patient global assessment (high dose), morning stiffness (high dose), ESR (high dose) and CRP (high dose). In the final study of 24 weeks duration, 121 patients with established RA of at least 6 months duration were

randomly assigned to thunder god vine 180 mg/day or 2 g/day SSZ [48]. The primary outcome was ACR20 at 24 weeks: significantly more patients on thunder god vine than SSZ (65 vs 33%) achieved this. In the second study, 4 (from 12) patients on placebo, 6 (from 12) on low-dose thunder god vine and 5 (from 12) on high-dose thunder god vine reported an adverse event. The most common adverse event in the low- and high-dose group (3 and 4, respectively) was diarrhoea. Combining both low- and high-dose groups, three patients reported nausea and hair loss. In the third study, only 62 of 121 patients completed the study. Incomplete information was available on patients who withdrew: of those who completed, 57 and 61% of those on thunder god vine and SSZ, respectively, reported an adverse event related to the study drug, while 5 and 12% reported a serious adverse event. The most common adverse events in the thunder god vine group were diarrhoea (25%), nausea (22%), dyspepsia (22%), abdominal pain (18%) and upper respiratory tract infection (18%).

Discussion

This systematic review of CAMs taken orally or applied topically for RA (and excluding fish oil) has found that 18 have been tested for efficacy in RCTs. Only for three of those do more than two trials exist. We concluded that there was not good evidence for efficacy for any of the reviewed compounds. The low number of trials conducted for most CAMs means that although we cannot conclude that they are efficacious, neither is the evidence strong enough for any one compound to be sure that it is not efficacious. However, collagen and selenium, which have been tested in four and three trials, respectively, only showed a positive effect for any of the outcome measures in at the most a single trial. In contrast, despite being based on only two and three trials, respectively, borage seed oil and thunder god vine have demonstrated efficacy in the studies conducted and may warrant further investigation. The CAM compounds examined were generally free of major adverse effects in the reported trials and had similar profiles to the comparison interventions. However, some, such as thunder god vine, reported important or high levels of adverse events and frequent withdrawal from trials.

Most of the trials reported scored relatively highly on quality (at least 4 out of 5) on the Jadad score. Many have examined multiple outcomes across clinical, functional and biochemical domains. Few specify which is the primary outcome the study has been designed to test and thus although a positive outcome may be reported in a trial, this needs to be considered in the context of how many outcomes were examined. In summarizing the results we have reported all positive outcomes. However, even if a compound is not effective, the probability of an outcome (among several) being significantly different from placebo is greater than the traditional 5% significance level. Therefore, if the compound examined has the same efficacy as the placebo, large numbers of

outcomes increase the likelihood of statistically significant differences between the groups.

A major issue in undertaking reviews in the field of complementary medicine is the possibility of publication bias. Many of the studies conducted are small and the concern is that those with positive results are more likely to be published than those which are not positive. This concern was raised in our reviews of FM (particularly in relation to homeopathy) [49] and OA [50]. It is less of a concern in this review of RA since we conclude that there is not good evidence of efficacy for any of the compounds reviewed. If there is publication bias, then its effects are not strong.

Only RCTs published in English were considered in this review, due to available resources, and this is a limitation. We found some publications available in other languages such as French, Chinese, Japanese and German, including on green-lipped mussel and collagen.

Within this review, we have extracted information on adverse events and their frequency within the included trials. Generally, these events have been at a similar level to placebo comparison groups and have not been serious. However, in our companion report for the Arthritis Research UK (see 'Additional resources' section), we did highlight a single complementary medicine as having, more generally, safety concerns: thunder god vine. The herb can be extremely poisonous if not extracted properly. In addition to the effects noted in the trials included in this review, other types of study have noted an effect of male fertility in both animals and humans [51,52], dysmenorrhoea and adverse effects on renal function [53] and embryotoxicity in mouse [54]. The study of both theoretical and observed interactions with conventional medicines is outwith the scope of this review, but some details are available for each compound in the accompanying Arthritis Research UK report. Finally, another important issue to be considered in interpreting the trials of complementary medicines is potential variability in the products used: differences could occur, for example, in the extraction or purification process.

We did not review fish oil—since this has been the subject of other reviews. A recent meta-analysis identified 17 articles investigating the role of fish oil in patients with RA [12]. This demonstrated the benefits of fish oil in significantly reducing pain, duration of morning stiffness and number of tender or swollen joints in patients. In addition, fish oil significantly reduced the consumption of NSAIDs. This CAM, therefore, seems more promising than any of the CAMs reviewed in the current article.

The conclusions of this review are consistent with NICE guidelines on management of RA published in February 2009. Some of the substances considered in this report were considered under the heading diet and others under CAM. Both categories also included interventions that were not eligible for this review. The report concluded that clinicians should 'inform people with RA who wish to experiment with their diet that there is no strong evidence that their arthritis will benefit' and that 'although

[complementary therapies] may provide short-term symptomatic benefit, there is little or no evidence for their long-term efficacy' [10].

In conclusion, RA is a chronic disease associated with disability and potentially premature mortality. Despite the proven clinical efficacy of conventional pharmacological treatment, many patients try complementary medicines, often from fear of toxicity from other drugs. While most of the CAMs have few trials evaluating efficacy in RA, this systematic review of oral and topical CAMs (excluding fish oil) did not find good evidence that any of them were efficacious. However, those compounds that have shown efficacy in the small number of trials conducted (e.g. borage seed oil and thunder god vine) are worthy of further investigation in terms of both efficacy and safety.

Additional resources

An accompanying Arthritis Research UK booklet provides additional details on each of the compounds listed here including: potential active ingredients, hypothesized mechanisms and possible interactions. It is available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_11012010154331.pdf.

Rheumatology key messages

- Complementary medicines are popular amongst patients with rheumatic diseases and are perceived as natural and safe.
- There are relatively few complementary medicines that have been tested in RCTs.
- For RA, OA and FM, no complementary medicine taken orally or topically has demonstrated efficacy.

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