

Herbal medicines for the treatment of rheumatoid arthritis: a systematic review

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Objective. With the growing interest in herbal therapies among persons with rheumatoid arthritis, there exists a need for investigation into their safety and efficacy. The purpose of this study was to conduct a systematic review to examine the evidence for the use of herbal medicines for RA based on randomized clinical trials (RCTs).

Methods. A computerized search of eight electronic databases and the bibliographies of identified articles resulted in 14 studies meeting the inclusion criteria. Two raters independently extracted data and rated the trials for quality.

Results. There is moderate support for γ -linolenic acid (GLA), which is found in some herbal medicines, for reducing pain, tender joint count and stiffness. For other herbal medicines there was only a single RCT available, resulting in weak evidence. In general, herbal preparations were relatively safe to use.

Conclusions. Given the number of herbal medicines promoted for RA, further research is needed to examine their efficacy, safety and potential drug interactions.

KEY WORDS: Herbal medicine, Complementary and alternative medicine, Rheumatoid arthritis.

Rheumatoid arthritis (RA) is a chronic disease of unknown cause affecting over 2 million adults in the USA [1]. An inflammatory disease of the synovium, it results in pain, stiffness, swelling, deformity and, eventually, loss of function in the joints. Because there is currently no known cure or means of preventing RA, the American College of Rheumatology recommends the earliest possible diagnosis and treatment with disease-modifying anti-rheumatic agents to limit the degree of irreversible joint damage [1]. Despite early detection, current treatment medications are limited in their efficacy and are frequently toxic.

Many patients look for complementary and alternative medicine (CAM) options in coping with this debilitating disease. Research has indicated that people suffering from chronic pain, as in RA, and those dissatisfied with current treatment are very likely to seek alternative treatments, and an estimated 60–90% of persons with arthritis use CAM [2]. Among the most widely used treatments are chiropractic and herbal therapies [2]. This growing interest in alternative medical practices clearly indicates the need for more thorough investigation into the safety and efficacy of CAM. An

earlier review [3] conducted in 2000 was limited in that it excluded trials of herbal preparations against active comparators. Therefore, the purpose of this systematic review was to examine the current clinical evidence for (or against) the use of herbal medicines for RA based on randomized clinical trials (RCTs) of herbal preparations against all control treatments.

Methods

Inclusion and exclusion criteria

We sought to identify clinical trials of herbal preparations administered orally or topically for RA in which patients were randomly assigned to receive either herbal medicines or control treatments, i.e. placebo or active therapy. Additional inclusion criterion were that (i) the dosage of the herbal was described, (ii) both baseline and endpoint clinical data were included, and (iii) if the sample included patients with other forms of arthritis, results could be determined separately for the RA patients. Animal studies were excluded from the review, as were studies of semisynthetic plant-based drugs. One mixed herbal remedy (Phytodolor[®]) was excluded from this systematic review because it has recently been submitted to a separate review [4].

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Search strategy

The following electronic databases were searched for publications dated between 1966 and 2001: MEDLINE, EMBASE, CINAHL, Cochrane Controlled Trials Register (CCTR), Science Citation Index, BIDS ISI and Cochrane Complementary Medicine Field Specialized Registry. Thesaurus and free-text searches were performed across each database to combine the terms 'arthritis' and 'herbal medicine'. The general structure of the search strategy was 'arthritis (or synonyms) and herbal (or synonym)'. No methodological filter was applied and the search was not limited by language. We used the following keywords: 'arthritis', 'rheumatoid arthritis', 'reactive arthritis', 'adjuvant arthritis', 'infective arthritis', 'osteoarthritis', 'gouty arthritis', 'juvenile rheumatoid arthritis', 'psoriatic arthritis' and 'peri-arthritis'. The free-text search terms included '(arthritis*)' and the combined terms '(hip, knee, joint, musculoskeletal-skeletal)' and '(pain, inflammation, movement, stiffness)'. Herbal keywords included 'medicine herbal', 'medicines herbal', 'herbal medicine', 'drugs Chinese herbal', 'plants medicinal', 'phytomedicine' and 'phytotherapy'; free-text search terms included 'herb*' and 'plant*'. Additionally, we searched the bibliographies of articles obtained for further trials.

Data extraction

Two raters (KLS and SAM) independently assessed whether the identified studies met the inclusion criteria and extracted information regarding the sample, treatment duration and dosage, adverse effects and results. In addition, both raters assessed the methodological quality using the Jadad scale [5], which assesses randomization, double-blinding and drop-outs. Where possible, we computed effect sizes (ESs) comparing treatment and control conditions for the change from baseline. Any differences between raters in extraction and rating were resolved through discussion.

Results

Fourteen studies met the inclusion criteria [6–19] (Table 1). On the basis of Jadad's recommended cut-off score, all were rated to be of high quality (score ≥ 3). Sample sizes ranged from 18 to 182 with an average of 47.

Five additional randomized trials were identified but subsequently excluded. Three failed to include clinical baseline and/or endpoint data [20–22], one used a semisynthetic herb [23], and one did not present data in such a way that separate results for RA patients could be determined [24].

ESs were computed to reflect the magnitude of the effect; that is, the standardized difference in the change from baseline to endpoint between the treatment and control groups. However, this was not possible for seven of the 14 studies [6, 7, 10, 11, 15, 17, 18], in which authors reported medians and ranges, displayed the results graphically or failed to include sufficient statistical data to calculate the ES for the change.

γ -Linolenic acid (GLA)

Borage seed oil, *Borago officinalis*. Two studies examined the efficacy of borage seed oil for RA. The first [12] compared 1.4 g/day of GLA, administered as borage seed oil, with placebo capsules containing cottonseed oil. At the end of 6 months of treatment,

patients treated with borage seed oil had significant improvement, compared with those in the placebo group, in joint tenderness counts and scores, joint swelling scores, physician global assessment, and pain. No patient in the treatment group went into remission, although seven (36.8%) had meaningful improvement and seven (36.8%) showed no improvement; in the placebo group, one (5.6%) improved and 12 (63.2%) did not.

In the second study, 56 patients received either 2.8 g/day of GLA produced from borage seed oil or placebo (sunflower seed oil) [19]. At the end of 6 months, patients treated with borage seed oil showed significant improvement compared with placebo patients in tender joint count, swollen joint count, tender joint score, pain as measured on a visual analogue scale (VAS), and the Health Assessment Questionnaire score. Overall, a greater percentage of the treatment group (64%) compared with the placebo group (21%) demonstrated meaningful improvement, defined as improvement of at least 25% in at least four measures. This difference indicates that the borage seed oil group was 6.5 times more likely than the placebo group to experience meaningful improvement.

Evening primrose oil, *Oenothera biennis*. In a 6-month trial of evening primrose oil (EPO), 40 patients were randomly assigned to receive 6 g/day of EPO (540 mg GLA/day) or placebo (olive oil, 6 g/day) [7]. Thirteen patients receiving EPO and 17 in the placebo group completed the trial. Reasons for withdrawal from the EPO group included nausea ($n=2$), joint surgery ($n=2$), deteriorating condition ($n=1$) and flu-like symptoms ($n=1$). Three withdrew from the control group because of nausea and the other moved from the area. Between-group comparisons were not reported. However, within-group comparisons showed a significant reduction in morning stiffness in the EPO group, with no change in the Ritchie articular index (AI) or pain. In contrast, olive oil produced a significant reduction in AI and pain but no change in morning stiffness. Neither group demonstrated a change in well-being or Health Assessment Questionnaire scores.

Another study of EPO [6] involved 49 patients with mild RA, who were randomly assigned to receive EPO, EPO/fish oil combination or placebo (liquid paraffin). EPO capsules provided 540 mg GLA and EPO/fish oil capsules provided 450 mg GLA and 240 mg essential fatty acids. Using intent-to-treat analysis at the end of 12 months, researchers found no significant change for any of the groups in the clinical measurements. However, a significantly greater percentage of patients in the treatment groups reported subjective improvement compared with the placebo patients (94 vs 30%) and 73% of EPO and 80% of EPO/fish oil patients had reduced or stopped their non-steroidal anti-inflammatory drugs (NSAIDs) compared with only 33% of placebo patients ($P < 0.05$).

Eighteen patients participated in a 3-month trial [11] in which EPO (20 ml/day) was compared with olive oil (20 ml/day). Patients were permitted to continue on

TABLE 1. Randomized controlled trials for herbal medicines in the treatment of rheumatoid arthritis

First author	Jadad score	Sample size	Intervention/control	Outcome variables	Results	Adverse effects
Belch [6]	4	49	540 mg/day GLA in EPO; 450 mg GLA as EPO plus fish oil/liquid paraffin for 12 months	Morning stiffness, grip strength, Ritchie AI, pain	No significant changes	Treatment group: nausea and diarrhoea ($n=4$) Placebo group: none
Brzeski [7]	4	40	540 mg/day GLA in EPO/olive oil for 6 months	Ritchie AI, pain, morning stiffness, well-being, health assessment	Treatment groups improved significantly in morning stiffness; control group improved in pain scores	None reported
Chopra [8]	5	182	444 mg RA-1/placebo for 16 weeks	Joint count pain and swelling, health assessment, global assessment	No significant difference between groups	Treatment group: epigastric pain/burning or retrosternal burning (18%), pruritus generalized (20%), anorexia (11%), nausea (14%) Placebo group: epigastric pain/burning or retrosternal burning (26%), pruritus generalized (20%), anorexia (17%), nausea (14%)
Deal [9]	3	31	0.025% capsaicin cream/vehicle cream for 4 weeks	Pain, pain relief, global evaluation compared with control group	Significant reduction in pain for treatment group	Treatment group: mild burning (44%) Control group: migraine, cramps, back pain, rhinitis (percentages not reported)
Deodar [10]	4	18	1200 mg/day curcumin/300 mg/day phenylbutazone for 2 weeks	Morning stiffness, walking time, grip strength, articular index, swelling, global assessment	Each group improved significantly in morning stiffness, walking time, joint swelling	No side-effects
Jäntti [11]	4	18	20 ml/day EPO/olive oil for 12 weeks	Joint score index, pain, morning stiffness, grip strength	No significant changes	None indicated
Leventhal [12]	4	37	1.4 g/day GLA from borage seed oil/cottonseed oil for 6 months	Joint tenderness count and score, joint swelling count and score, global assessment, pain, morning stiffness, grip strength	Significant improvement in joint tenderness count and tenderness score, joint swelling score, MD global assessment and pain for treatment group compared with placebo	Treatment group: soft stool ($n=2$), flatulence ($n=1$), belching ($n=1$) Placebo group: soft stool ($n=1$), constipation ($n=1$)
Leventhal [13]	5	24	2.0 g/day GLA in BCSO/placebo tablets containing soyabean oil for 6 months	Joint tenderness count and score, joint swelling count and score, pain, morning stiffness, grip strength, global assessment	Significant improvement in joint tenderness and tenderness score for treatment group compared with control group	Treatment group: none Placebo group: nausea ($n=2$)
Mills [14]	4	20	Reumalex/calcium phosphate for 2 months	Pain, modified Ritchie score	Significant improvement in modified Ritchie score for treatment group compared with placebo	Not reported separately for RA patients
Nordström [15]	3	22	30 g/day flaxseed oil/safflower oil for 12 weeks	Global assessment, functional class, joint score index pain	No significant change within either group	'Some experienced loose stools'
Patrick [16]	4	41	70–86 mm/day feverfew/cabbage leaf for 6 weeks	Morning stiffness, pain, grip strength, Ritchie AI	Significant improvement in grip strength for treatment compared with placebo group	Treatment group: minor ulceration and soreness of tongue ($n=1$)

TABLE 1. Continued

First author	Jadad score	Sample size	Intervention/control	Outcome variables	Results	Adverse effects
Sander [17]	4	37	1200 mg/day H15 the first week and 3600 or 2400 mg/day for next 11 weeks/placebo tablets for 12 weeks	Ritchie AI for pain and swelling, overall health, pain, NSAID dose	No significant difference in improvement between groups	Control group: lightheadedness (<i>n</i> = 1) Treatment group: stomatitis (<i>n</i> = 1) Control group: exanthem, nausea, increased joint complaints (<i>n</i> = 1 each)
Tao [18]	3	70	60 mg/day TWH/placebo tablets for 12 weeks	Tenderness score, swelling count, morning stiffness, mean grip strength, 15m walking time	Significant improvement in treatment group in tenderness score, swelling count, morning stiffness, and grip strength compared with placebo	Treatment group: skin rash and cheilosis (<i>n</i> = 15), diarrhoea (<i>n</i> = 6), anorexia (<i>n</i> = 2), abdominal pain (<i>n</i> = 2) Placebo group: skin rash and cheilosis (<i>n</i> = 1), abdominal pain (<i>n</i> = 1)
Zurier [19]	4	56	2.8 g/day GLA from borage seed oil/sunflower seed oil for 6 months	Swollen joint count, tender joint count and score, pain, degree of disability, duration of morning stiffness, grip strength global assessment	Significant improvement in tender joint count, swollen joint count, tender joint score, pain and Health Assessment, Questionnaire score for treatment group compared with placebo	Treatment group: diarrhoea (<i>n</i> = 5), belching (<i>n</i> = 3) Placebo group: belching (<i>n</i> = 2), diarrhoea, constipation, rash (<i>n</i> = 1 each)

All were double-blind placebo-controlled designs except Deodar [10], which was a double-blind crossover design, and Tao [18], which was a double-blind crossover placebo-controlled design.

long-term anti-rheumatic drugs throughout the study and to use paracetamol for pain if necessary; NSAIDs were not allowed. At the end of the trial, no significant changes were observed in the clinical variables. In the treatment group, four patients were considered better, four the same, and one worse; in the control group, five patients were better and four were worse.

Blackcurrant seed oil, *Ribes nigrum*. In a 6-month study, 34 patients received either blackcurrant seed oil (BCSO) ($n=20$) or placebo ($n=14$) [13]. The daily dose of BCSO was 10.5 g (2.0 g GLA); identically appearing placebo capsules contained soyabean oil. Throughout the study, patients maintained their pretrial doses of NSAIDs and/or corticosteroids. Among those who completed the study, the treated group showed significant improvement in joint tenderness count [ES=1.73, 95% confidence interval (CI) 0.519, 2.93] and tenderness score (ES=1.51, 95% CI 0.339, 2.68) compared with the placebo group. Intent-to-treat analysis confirmed that these results were not due to bias from dropouts. One patient in the BCSO group experienced meaningful improvement while six had no meaningful change; in the placebo group none of the seven had meaningful change.

Meta-analysis of GLA effect sizes

Table 2 includes information about both individual and pooled or combined ESs related to the effectiveness of GLA. The pooled ES is the mean ES weighted for sample size. ESs for physician global assessment were not homogeneous and therefore not combined. Pooled ESs ranged from 0.225 for stiffness to 0.925 for tender joint count. Interpreting the pooled ES in terms of the binomial effect size display [25], the difference in the 'success rates' of GLA compared with placebo was 68 vs 32% for pain, 71 vs 29% for tender joint count, 60 vs 40% for swollen joint count and 61 vs 39% for stiffness. Only

the ES for swollen joint count failed to reach statistical significance.

Other herbal preparations

Capsaicin. Patients with moderate to very severe knee pain and meeting at least three of the criteria for definite or probable RA were randomly assigned to apply capsaicin (0.025%) or the vehicle cream four times per day for 4 weeks [9]. During the trial, 94% of treatment and all placebo patients took oral arthritis medications that had been stabilized before the study; 88 and 80% respectively were on NSAIDs. However, intra-articular corticosteroid injections to the knees were not permitted. Two of the 16 patients in the treatment group withdrew because of adverse experience and/or failure to comply with protocol; none in the control group withdrew. At the end of the 4 weeks, the mean physician global assessment scores did not differ between groups (ES=0.5693, 95% CI -0.17, 1.31), but there was a significant difference in the reduction in patient VAS pain scores between treatment and control groups (57 vs 32% reduction from baseline; ES=0.9269, 95% CI 0.163, 1.69). Mild burning at the site of the capsaicin application was reported by 44% of those in the treatment group, raising questions about whether patients could be considered blinded.

Curcumin (*diferuloyl methane*). Eighteen patients participated in a crossover study of 1200 mg/day of curcumin vs 300 mg/day of phenylbutazone [10]. Curcumin is a constituent of the rhizome of turmeric (*Curcuma longa* Linn.) with anti-inflammatory activity. Patients in each group showed significant improvement from baseline in morning stiffness, walking time and joint swelling. Although the authors indicate 'convincing evidence of the anti-rheumatic activity of curcumin', no comparisons were reported between the curcumin and phenylbutazone groups.

Feverfew (*Tanacetum parthenium*). In a study of 41 women with symptomatic RA, half received 70–86 mg/day of dried, powdered feverfew and half received identically treated cabbage [16]. Subjects maintained their current NSAID and analgesic treatment throughout. At the end of 6 weeks, treatment and placebo groups showed a significant difference in the change in grip strength (ES=0.915, 95% CI 0.265, 1.57). Other clinical assessments demonstrated no significant change. The authors concluded that, perhaps at larger doses or over a longer period of time, feverfew might have some benefit for RA.

Flaxseed oil. Twenty-two patients received 30 g/day of either flaxseed oil or safflower oil for a 3-month period [15]. All patients also took NSAIDs. On the basis of within-group comparisons, none of the clinical parameters changed in either group.

H15 (extract of *Boswellia serrata*, *olibanum*). Resinous extracts of *Boswellia serrata* are a traditional Ayurvedic medicine. H15 also contains terpene, arabinose, galactose, sylose, β -sistotrine and phlobaphene. Patients in the treatment group ($n=18$) received 1200 mg in the first week and either 3600 mg/day or 2400 mg/day for

TABLE 2. Meta-analysis of effect sizes for GLA by outcome

Outcome	First author	Effect size	95% CI
VAS pain	Leventhal [12]	0.756	(-0.045, 1.515)
	Leventhal [13]	0.734	(-0.384, 1.772)
	Zurier [19]	0.557	(-0.080, 1.171)
	Weighted mean	0.760	(0.373, 1.147)
Tender joint count	Leventhal [12]	1.069	(0.235, 1.843)
	Leventhal [13]	1.726	(0.425, 2.838)
	Zurier [19]	0.674	(0.032, 1.292)
	Weighted mean	0.925	(0.466, 1.384)
Swollen joint count	Leventhal [12]	0.634	(-0.156, 1.390)
	Leventhal [13]	-0.063	(-1.108, 0.988)
	Zurier [19]	0.430	(-0.199, 1.043)
	Weighted mean	0.400	(-0.039, 0.840)
Stiffness	Leventhal [12]	0.424	(-0.355, 1.179)
	Leventhal [13]	0.361	(-0.714, 1.396)
	Zurier [19]	0.540	(-0.695, 1.154)
	Weighted mean	0.225	(0.018, 0.898)

Effect size is the standardized difference between groups in the change from baseline with a positive value favouring GLA with the weighted mean weighted for sample size. Q-statistics for homogeneity of effect size were not significant ($P > 0.20$).

the next 11 weeks; those in the control group ($n=19$) received identically appearing but unnamed placebo pills [17]. Throughout the study, concomitant medications were permitted if they had been used for 3 months before the study. In addition, two patients in the treatment group continued to receive oral steroids while one patient in the treatment group and three placebo patients needed corticosteroid injections after 6 weeks. At the end of the 12 weeks, researchers found no significant or clinically relevant change from baseline or any difference between groups in pain and swelling. However, use of NSAIDs did decrease by an average of 5.8% for those in the treatment group compared with 3.1% in the control group. The authors concluded that adjuvant therapy with H15 in patients with chronic polyarthritis cannot be supported by these results.

RA-1 (standardized Ayurvedic formulation). RA-1 is a standardized formulation prepared from purified plant extracts of *Withania somnifera* (ashwagandha), *Boswellia serrata* (guggula), *Zingiber officinale* (adarak or ginger) and *Circuma longa* (haldi or curcumin). RA-1 tablets or identical placebo tablets were distributed randomly to 182 patients with active-on-chronic RA; 80 active and 85 placebo patients completed the 4-month trial [8]. These patients were recruited from free 'diagnosis and therapy guidance arthritis camps', which were part of a community-based campaign to increase public awareness of RA. The total daily dose of extract was 444 mg, but during the trial the chief investigator was permitted to increase dosage in the event of clinical worsening. Twenty-eight of 80 in the RA-1 group (35%) and 44 of 85 in the placebo group (52%) did have their dosage increased. Although NSAIDs were prohibited during the trial, oral paracetamol in 500 mg tablets was permitted as rescue analgesic as needed. At the end of the trial, researchers found no statistically significant difference between RA-1 and placebo groups in the change in clinical efficacy or laboratory efficacy variables. A greater proportion of patients in the treatment group, however, did demonstrate over 50% reduction in joint swelling compared with the placebo patients ($P < 0.5$).

Reumalex. Reumalex[®] is a herbal mixture containing 100 mg Pulv White Willow Bark BHP, 40 mg Pulv guaiacum resin BHP, 35 mg Pulv Black Cohosh BHP, 25 mg Pulv Ext Sarsaparilla 4:1 and 17 mg Pulv Ext Poplar Bark 7:1. Fifty-two patients with osteoarthritis and 20 with RA received two tablets/day of Reumalex or placebo (calcium phosphate) for a period of 2 months [14]. Subjects were permitted to maintain previous levels of self-prescribed medications, including analgesics, with no difference found between groups at the end of the treatment. Four patients in each group withdrew from the study, but the authors do not indicate whether these were osteoarthritis or RA patients. Among the RA patients (10 treatment and 10 control), there was a significant difference in the change in modified Ritchie AI ($ES=1.99$, 95% CI 0.93, 3.04), but no difference in the change in pain as measured by the revised Arthritis Impact Measurement Scale (AIMS2) ($ES=0.17$,

95% CI -0.71 , 1.05). Results suggest the possibility of an anti-inflammatory effect for the herbal mixture.

***Tripterygium wilfordii* Hook F.** *Tripterygium wilfordii* Hook F (TWH), a herbal plant growing mainly in South China, was described in ancient Chinese medical texts and has been used widely in China for treatment of joint pain. Seventy patients with active symptoms who had not responded to NSAIDs for at least 2 months were randomly assigned to 60 mg/day of TWH or identically appearing placebo tablets for 3 months [18]. At the end of treatment, patients receiving TWH showed significant improvement in all parameters compared with placebo: tenderness score, swelling count, morning stiffness and grip strength. Also, the percentage of patients experiencing improvement was significantly higher for the TWH group, with an overall effective rate of over 90%. These clinical improvements appeared within the first 4 weeks of treatment.

Discussion

The positive results from three RCTs included in this review provide moderate support for GLA as having a medium to strong effect in reducing pain and tender joint count and a small effect in reducing stiffness in RA for those with active disease. GLA produces anti-inflammatory hormone-like substances, including prostaglandin E_1 , that in turn help to reduce clinical symptoms. It is found in blackcurrant oil (6% GLA), borage seed oil (9% GLA) and evening primrose oil (2% GLA). As a result of taking such supplements, patients may be able to reduce their use of NSAIDs. Three other trials [6, 7, 11] tested the efficacy of evening primrose oil and found inconsistent results. Two of these trials [7, 11] used olive oil as the placebo. In one trial [7], changes within the treatment group showed a decrease only in stiffness while within the control group there was a decrease in pain. In the second trial [11], no significant changes were observed. However, most patients had only mild inflammatory activity so there may not have been sufficient statistical power to detect significant changes. Also, other research findings [26] have indicated that 18 g/day of olive oil used as a placebo reduced morning stiffness and pain score, which may account for the lack of significant findings in these studies. In the third study [6] no significant changes were noted. Again, patients in this trial all had mild RA compared with the studies of borage seed oil and BCSO where patients had active disease; it is conceivable that this accounts for the discrepant results.

For all the other herbal preparations, only a single trial is available. This lack of independent replication seriously weakens the evidence (i.e. a single RCT with significant results) for *Tripterygium wilfordii* Hook F (TWH), Reumalex[®], RA-1, feverfew and capsaicin. Those who received TWH demonstrated significant improvement on several measures compared with placebo: tenderness score, swelling count, morning stiffness, and grip strength. Other herbal preparations

showed significant results for a single outcome measure: Reumalex reduced the modified Ritchie AI, a greater proportion of those receiving RA-1 demonstrated over 50% reduction in joint swelling compared with placebo, those receiving feverfew showed a significant change in grip strength, which is not one of the core set of outcome measures recommended for RA [27], and capsaicin reduced pain scores. Capsaicin works by depleting substance P, which is found at nerve endings and is involved in transmitting the pain signal. On the basis of single trials, there is no support for the efficacy of flaxseed oil, curcumin and H15 for RA.

All trials were rated of high quality using the Jadad scale. Some reports, however, failed to specifically state inclusion [10, 15] or exclusion [6, 9, 11, 15, 16] criteria and some [9–11, 16–18] failed to indicate whether compliance was assessed. Still others reported only within-group analyses [7, 10, 15] and only two [18, 19] reported performing a power calculation to determine sample size, suggesting that some studies may have suffered from low statistical power.

The incidence of adverse effects reported across these trials of herbal preparations for RA is low and most adverse effects were minor. Patients receiving capsaicin reported the highest incidence of adverse effects, 44% experiencing mild burning at the site of application. The incidence was relatively high also for RA-1, the Ayurvedic plant-derived formulation, with over 10% of patients reporting epigastric or retrosternal burning, pruritus generalized, anorexia or nausea. Potential adverse effects have been noted for TWH, with substantial risk of gastrointestinal disturbances, skin rashes, amenorrhoea, leucopenia and thrombocytopenia [28]. In addition, the immunosuppressive properties of extracts from the root of TWH may promote the development of infectious diseases. Long-term safety data are largely missing for any of the included herbal medicines.

Given the number of herbal preparations that are promoted for RA and the number of trials located, further research is needed to examine not only the efficacy of these treatments but also the safety and potential drug interactions of the herbal preparations. Outcome measures should include disability, joint pain and swelling, pain, and both patient and physician global assessment.

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