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Cameron M, Gagnier JJ, Chrubasik S

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[Intervention Review]

Herbal therapy for treating rheumatoid arthritis

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ABSTRACT

Background

Herbal medicine interventions have been identified as having potential benefit in the treatment of rheumatoid arthritis (RA).

Objectives

To update an existing systematic (Cochrane) review of herbal therapies in RA.

Search methods

We searched electronic databases Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE, EMBASE, AMED, CINAHL, Web of Science, Dissertation Abstracts (1996 to 2009), unrestricted by language, and the WHO International Clinical Trials Registry Platform in October 2010.

Selection criteria

Randomised controlled trials of herbal interventions compared with placebo or active controls in RA.

Data collection and analysis

Two authors selected trials for inclusion, assessed risk of bias and extracted data.

Main results

Twelve new studies were added to the update, a total of 22 studies were included.

Evidence from seven studies indicate potential benefits of gamma linolenic acid (GLA) from evening primrose oil, borage seed oil, or black-current seed oil, in terms of reduced pain intensity (mean difference (MD) -32.83 points, 95% confidence interval (CI) -56.25 to -9.42,100 point pain scale); improved disability (MD -15.75% 95% CI -27.06 to -4.44%); and an increase in adverse events (GLA 20% versus placebo 3%), that was not statistically different (relative risk 4.24, 95% CI 0.78 to 22.99).

Three studies compared *Tripterygium wilfordii* (thunder god vine) to placebo and one to sulfasalazine and indicated improvements in some outcomes, but data could not be pooled due to differing interventions, comparisons and outcomes. One study reported serious side effects with oral *Tripterygium wilfordii* Hook F. In the follow-up studies, all side effects were mild to moderate and resolved after the intervention ceased. Two studies compared Phytodolor® N to placebo but poor reporting limited data extraction. The remaining studies each considered differing herbal interventions.

Authors' conclusions

Several herbal interventions are inadequately justified by single studies or non-comparable studies in the treatment of rheumatoid arthritis. There is moderate evidence that oils containing GLA (evening primrose, borage, or blackcurrant seed oil) afford some benefit in relieving symptoms for RA, while evidence for Phytodolor® N is less convincing.*Tripterygium wilfordii* products may reduce some RA symptoms, however, oral use may be associated with several side effects. Many trials of herbal therapies are hampered by research design flaws and inadequate reporting. Further investigation of each herbal therapy is warranted, particularly via well designed, fully powered, confirmatory clinical trials that use American College of Rheumatology improvement criteria to measure outcomes and report results according to CONSORT guidelines.

PLAIN LANGUAGE SUMMARY

Herbal therapy for rheumatoid arthritis

This summary of a Cochrane review presents what we know from research about the effects of herbal therapy for rheumatoid arthritis (RA).

The review shows that in people with RA:

- Evening primrose oil, borage seed oil, or blackcurrent seed oil (containing gamma-linolenic acid (GLA)) probably improve pain; may improve function; and probably does not increase adverse events (unwanted side effects).

- *Tripterygium wilfordii* Hook F may improve some symptoms of rheumatoid arthritis, and higher doses (180 mg - 350 mg daily) may be more effective than lower doses (60 mg daily). There are some adverse events associated with Tripterygium wilfordii Hook F.

- We are uncertain of the effects of other herbal therapies because only single studies were available, or important features of RA, such as changes in the number of swollen and tender joints, were not reported.

Often we do not have precise information about side effects and complications, particularly for rare but serious side effects. Possible side effects associated with *Triperygium wilfordii* Hook F may include painful periods in women, decreased fertility in men, insufficient urine excretion, and increased rate of infections. Possible side effects associated with GLA sourced from evening primrose oil include headache, nausea, and diarrhoea, and rare complications include allergy and seizures.

What is rheumatoid arthritis and what is herbal therapy?

When you have RA, your immune system, which normally fights infection, attacks the lining of your joints. This makes your joints swollen, stiff and painful. The small joints of your hands and feet are usually affected first. There is no cure for rheumatoid arthritis at present, so treatments are used to relieve pain and stiffness and improve your ability to move.

Herbal interventions are defined as any plant preparation (whole, powder, extract, standardised mixture) used for medicinal purposes. Historically, many herbal therapies have been used to treat RA. Like conventional non-herbal drugs, many herbal therapies are believed to act by blocking the activity of these immune cells and substances and reducing inflammation in the joints, and some people believe they have fewer side effects.

Best estimate of what happens to people with rheumatoid arthritis:

Pain (higher scores mean worse or more severe pain):

-People who took eveing primrose oil, primrose oil, borage seed oil, or blackcurrent seed oil (wih the active ingredient GLA) rated their pain to be 33 points lower (9 to 56 points lower) on a scale of 0 to 100 after 6 months of treatment (33% absolute improvement).

-People who took placebo rated their pain to be 19 points lower after treatment.

Physical function (higher score means greater disability):

-People who took GLA rated their disability 16% better.

-People who placebo rated their disability 5% better.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Evening primrose oil, borage seed oil, blackcurrent seed oil (containing gamma-linolenic acid) for rheumatoid arthritis

Patient or population: patients with treating rheumatoid arthritis

Settings: community

Intervention: Evening primrose oil, borage seed oil, blackcurrent seed oil (with gamma-linolenic acid) versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	**Evening primrose oil, borage seed oil, blackcurrent seed oil (with gamma-linolenic acid) versus placebo**				
ACR 50% improvement - not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Pain Visual Analogue Scale. Scale from: 0 to 100. (follow-up: 6 months)	The mean pain in the control groups was **60.6 points**[1]	The mean Pain in the intervention groups was **32.83 lower** (56.25 to 9.42 lower)		82 (3)	⊕⊕⊕⊖ **moderate**[2]	Absolute risk difference 33 points lower (9 to 56 points lower); relative % change 54% (15 to 92%); NNTB 3 (2 to 12)[3]
Disability (HAQ score) percent change. Scale from: 0 to 100. (follow-up: 6 months)	The mean disability (haq score) in the control groups was **42.5** [4]	The mean Disability (HAQ score) in the intervention groups was **16 lower** (27 to 4 lower)		41 (1)	⊕⊕⊖⊖ **low**[2,5]	Absolute risk difference 16% lower (4 to 27% lower); relative % change 38% (9% to 64%); NNTB 3 (95% CI 2 to 11)
Participants (n) reported adverse events (follow-up: 6 months)	**Medium risk population**		**RR 4.24** (0.78 to 22.99)	61 (2)	⊕⊕⊕⊖ **moderate**[2]	Absolute risk difference 15% (0 to 30%); relative percent change 324% (-22% to 2199 %); NNT=n/a [3]
	39 per 1000	**165 per 1000** (30 to 897)				

Change in radiographic progression - not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Achievement of low disease state (DAS 28) - not measured	See comment	See comment	Not estimable	-	See comment	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidance
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] From Zurier 1996, mean (SD) pain at baseline in placebo = 60.6 (21.0)
[2] Unclear if randomisation was concealed or outcome assessor blinded
[3] NOTE: Number needed to treat (NNT)=n/a when result is not statistically significant. NNT for dichotomous outcomes calculated using Cates NNT calculator (http://www.nntonline.net/visualrx/). NNT for continuous outcomes calculated using Wells Calculator (CMSG editorial office).
[4] From Zurier 1996, mean (SD) HAQ score on 0-100 scale at baseline in placebo = 42.5 (11.25)
[5] Results based on one small trial nly

Summary of findings 2.

Triptrygium wilfordii Hook F 360 mg versus placebo for Rheumatoid arthritis

Patient or population: patients with Rheumatoid arthritis

Settings: Community

Intervention: Triptrygium wilfordii Hook F 360 mg versus placebo

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Triptrygium wilfordii Hook F 360**				

		mg versus placebo				
ACR 50% improvement (follow-up: 20 weeks)	**Medium risk population**[1]		**RR 11.92** (0.73 to 193.38)	23 (1)	⊕⊕⊖⊖ **low**[2,3]	Absolute risk difference = 45% (15% to 76%) increase; relative percent change = 1090% (-27% to 19238%); NNTB n/a[4]
	1 per 1000	**12 per 1000** (1 to 193)				
Change in pain - not measured	See comment	See comment	Not estimable	-	See comment	Not measured
HAQ disability score - not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Participants (n) reported adverse events (follow-up: 20 weeks)	**Medium risk population**		**RR 1.36** (0.49 to 3.82)	23 (1)	⊕⊕⊖⊖ **low**[2,3]	Absolute risk difference = 12% increase (-28% to 52%); relative percent change = 36% (-51% to 282%); NNTH = n/a [4]
	333 per 1000	**453 per 1000** (163 to 1272)				
Change in radiographic progression - not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Achievement of low disease state (DAS 28) - not measured	See comment	See comment	Not estimable	-	See comment	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidance
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Only one study available, with control event rate of 0%; thus assumed 1% control event rate for purposes of calculations; control event rates for 5 trials in review (different therapies) ranged from 0 to 35%
[2] Unclear if randomisation was concealed
[3] Results based on one small trial
[4] NOTE: Number needed to treat (NNT)=n/a when result is not statistically significant. NNT for dichotomous outcomes calculated using Cates NNT calculator (http://www.nntonline.net/visualrx/); or for single studies as 1/RD. NNT for continuous outcomes calculated using Wells Calculator (CMSG editorial office)

BACKGROUND

Rheumatoid arthritis (RA) is a common, immune-mediated disease characterized by chronically progressive inflammation and destruction of joints and associated structures as well as systemic symptoms. Early diagnosis and advances in molecular biology have led to improved therapy and better outcomes for patients, but the disease still causes a significant burden of illness. Current therapy has a goal of complete and long-lasting remission but, typically, only partial remission is achieved and frequent relapses or even non-response are common (Tarner 2008). Because many antirheumatic and immune-modulating drugs in current use are associated with severe, possibly life-threatening, adverse effects (Tarner 2008) it is understandable that many patients of rheumatologists use complementary or alternative medicines (CAM) including herbal medicines which they may believe to be safer (Boisset 1994; Buchbinder 2002; Cronan 1989).

Historically, there have been a variety of herbal medicines that have been used in the treatment of rheumatological conditions, including conditions resembling what we now know as RA. For example, in Chinese medicine 'Lei Gong Teng' (thunder god vine or 'three-wing nut') has been used for centuries to treat inflammatory tissue swelling (MacPherson 1994), preparations of Salix species (Vlachojannis 2009), devil's claw (*Harpagophytum procumbens*) (Chrubasik 2007a) and nettle (*Urtica dioica*) (Chrubasik 2007b) are popular antirheumatic remedies in Europe, and *Zingiber officinalis* (Chrubasik 2005), *Capsicum frutescens, Mentha piperita, Arnica montana, Curcuma longa, Tanacetum parthenium, and Zingiber officinalis* have been reported as treatments for various types of pain including joint pain (Chrubasik 2007a, ESCOP 2009).

Several novel therapeutic targets have been identified as involved in the pathogenesis of RA. These include molecules that regulate tumor necrosis factor (TNF) (eg: TNF-alpha converting enzyme), the complex cytokine network (eg: IL-6, IL-15, IL-17) and several adipokines. Strategies that aim at cellular targets of the disease include antibodies to CD20 or BLyS (also known as TNF ligand family member 13b), which deplete or inhibit B cells, and approaches that interfere with membrane-derived microparticles. Components of subcellular pathways, which are predominantly upstream of the central regulator of transcription nuclear factor kappaB, are also involved, such as mitogen-activated protein kinases, Janus kinases, signal transducer, activator of transcription proteins and suppressors of cytokine signalling proteins (Tarner 2007). Non-herbal traditional disease modifying anti-rheumatic drugs, such as methotrexate, may target several of the systems described above to reduce inflammation (Katchamart 2010). Similarly, several herbal medicinal products may act as multi-component drugs at the molecular level, acting on several therapeutic targets simultaneously. The newer biologic disease-modifying anti-rheumatic drugs target individual components of these systems (Singh 2009).

Most of the herbal medicinal products used orally have a broad mechanism of action, as shown by in vitro studies. We recently summarized the in vitro studies for most of these herbal medicinal products (Cameron 2009). Herbal medicinal products may be more or less involved in the inhibition of cyclo-oxygenase-1 or 2, lipoxygenase and enzymes that participate in cartilage destruction, such as elastase and hyaluronidase. The active principles may also inhibit the release of pro-inflammatory cytokines and stimulate the production of cytokines that inactivate enzymes, such as metalloproteinases (Cameron 2009). For most of the HMPs a radical scavenging effect was also demonstrated. Topical capsaicin has a different mechanism of action. It stimulates the vanilloid receptors (Dedov 2000), interferes with the synthesis, storage, transport and release of substance P (Buck 1986), inhibits the lipoxygenase (Flynn 1986) and reversibly destroys fine nerve endings (Nolano 1999). Also, *Uncaria tormentosa* (cat's claw) and *Tanacetum parthenium* are anti-inflammatory and antinociceptive as well as acting on 5-HT2 receptors (Jurgensen 2005; Mittra 2000). Therefore, it appears that herbal medicines have some mechanisms of action that have relevance to the pathogenesis and symptoms associated with rheumatoid arthritis.

OBJECTIVES

To update an existing Cochrane systematic review of the effectiveness of herbal therapies in the treatment of rheumatoid arthritis (RA) by adding data from relevant clinical trials published in the period from 2000 to 2009.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled (placebo or active control) parallel and crossover trials examining the effects of herbal interventions for treating RA.

Types of participants

All persons diagnosed with RA according to American College of Rheumatology (ACR) criteria (Arnett 1988). Studies with samples defined according to vague descriptions (eg: 'joint pain') were not considered.

Types of interventions

Any form of herbal intervention compared with an inert (placebo) or active control, via any route of administration, was included. Herbal therapy used in conjunction with other treatments or combined with a non-herbal substance were also included if the effect of the non-herbal intervention was (a) consistent among all groups, and (b) quantifiable. Herbal interventions included any plant preparation (whole, powder, extract, standardised mixture) but excluded homeopathy, aromatherapy or any preparation of synthetic origin.

Types of outcome measures

As far as possible, we extracted data for these main outcomes as recommended by the Cochrane Musculoskeletal Group: disease activity as measured by proportion with American College of Rheumatology 50% improvement (ACR50 responders), or ACR20 responders if reported; reduction in pain; physical function as measured by the Health Assessment Questionnaire (HAQ); achievement of low disease state as measured by the Disease Activity Score (DAS); change in radiographic progression; number of participants with any adverse event, or number of adverse events.

Other outcomes included: proportion of ACR20 responders, swollen joint count, tender joint count, measures of joint stiffness, grip strength, withdrawals due to adverse events.

Search methods for identification of studies

For this review update we searched the following electronic databases (from the date of the last search in the previously published version of the review to May 21st, 2009):

1. Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2009);
2. MEDLINE via Ovid (2000 to May Week 2 2009);
3. EMBASE via Ovid (2000 to May 2009);
4. AMED via Ovid (1985 to May 2009);
5. CINAHL via Ovid (2000 to Week 5 2008), via EBSCOHost (2008 to May 2009);
6. Dissertation Abstracts (May 2009);
7. Web of Science (May 2009).

Thesaurus and free text searches were performed, appropriate to each database, to combine terms describing RA and terms describing herbal medicine. No methodological filter was applied and the search was not limited by language.

The full search strategies for each database are outlined in Appendix 1.

We searched the WHO International Clinical Trials Registry Platform in October 2010 (http://www.who.int/ictrp/en/) for ongoing and unpublished trials.

Data collection and analysis

Selection of studies

Because of the large number of studies included in this update and the inclusion of studies in languages other than English, all review authors and some assistants (authors of the previous review, and a colleague from the German Cochrane Centre) contributed to eligibility decisions and data extraction. The contributions of authors and assistants are detailed at the end of this review. All titles and abstracts identified from the electronic databases and other searches were independently examined by at least two review authors. The full manuscript was retrieved for each record that had the possibility of meeting the review criteria. At least two authors independently assessed eligibility of each retrieved study for review according to the inclusion criteria. Data were extracted from each eligible study by two review authors or assistants acting independently.

Where a study was defined as a crossover trial, data were extracted only up to the point of crossover in order that these data could be compared with those derived from parallel group trials. Where an outcome was reported using two outcome measures (eg, pain on a continuous 100 point VAS scale and pain on a categorical scale of 0 to 4 points), data were displayed preferentially using the continuous scale. Results are reported for the categorical scale out of interest.

Assessment of risk of bias

Three review authors (MC, SC, JG) assessed the risk of bias of the included trials against key criteria: random sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias, in accordance with methods recommended by The Cochrane Collaboration (Higgins 2008). Each criterion was judged explicitly as: A = Yes, low risk of bias; B = No, high risk of bias; C = Unclear, either lack of information or uncertainty over the potential for bias. Potential disagreements were discussed and resolved by referring to the original protocol and, if necessary, arbitration by a member(s) of the steering group.

Analysis

Descriptive results were reported for all included studies. Studies with the same comparator were pooled in meta-analyses, and a random effects model applied. For dichotomous outcomes, odds ratios or relative risks were calculated. For continuous outcomes, a mean difference (MD) was calculated, and confidence intervals (CI) reported at 95%. The Chi^2 test and I^2 statistic of heterogeneity were conducted. Threshold values (P and I^2) for heterogeneity were not determined a priori; rather heterogeneity was reported using both Chi^2 and I^2 statistics, with I^2 of 30% to 60% considered to represent moderate heterogeneity, and I^2 of more than 60% as substantial heterogeneity. This categorical classification was consistent with the Chi^2 statistic analyses if P = 0.10 was accepted as the arbiter of significance. Reasons for heterogeneity were explored by reviewing study designs and results. $I^2 \geq 80\%$ was considered to represent unacceptable heterogeneity, indicating that the studies could not be rationally pooled. Studies that reported pooled data were analysed using the generic inverse variance method.

Summary of findings

Main results of the review are presented in the summary of findings tables, including an overall grading of the evidence using the GRADE approach (Schünemann 2008b) and a summary of the available data on the main outcomes, as described in the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2008a). We present a summary of findings table gamma linolenic acid 1400mg or greater versus placebo, and Triptrygium wilfordii Hook F 360 mg versus placebo (there were insufficient outocme data from single trials for the other interventions). We included the outcomes recommended as by the Cochrane Musculoskeletal Group for reviews of interventions for rheumatoid arthritis (disease activity as measured by proportion with ACR50 improvement; reduction in pain; physical function as measured by HAQ; achievment of low disease state as measured by DAS; change in radiographic progression; number of participants with any adverse event). The GRADE approach categorises the quality of evidence for as high, moderate, low or very low as an indication of confidence in the results of studies and meta-analyses. For example, high quality evidence is robust and further studies are very unlikely to change our confidence in the estimate of effect; conversely, low quality evidence is open to question and further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

We also determined the absolute risk difference and relative percent change and entered these into the comments column of the 'Summary of findings' table. For dichotomous data, the absolute risk difference is calculated by using RevMan to generate the Risk Difference analysis and then reporting the result as a percentage. The relative percent change is calculated by finding the relative risk (RR) from RevMan and then applying the formula RR-1 equals the relative percent change. The number needed to treat (NNT) was calculated for statistically significant outcomes from the control group event rate (unless the population event rate was known) and the relative risk using the Visual Rx NNT calculator (Cates 2004). For

continuous outcomes, absolute risk difference was derived from the mean difference (MD) generated in RevMan divided by scale of the instrument; relative percent change was derived from MD divided by the basline mean of the control group; and NNT was calculated for statistically significant outcomes using the Wells calculator at the CMSG editorial office (www.cochranemsk.org). The Wells calculator requires input of the minimally important clinical difference (MCID) for continuous outcomes: For pain we used an MCID of 15 out of 100 points, and for function, an MCID of 0.22 units on a 0 to 3 HAQ scale (or 7% on change scale) to estimate NNT.

RESULTS

Description of studies

See: tables 'Characteristics of included studies'.

From approximately 2500 citations, a total of 12 new studies, including four studies published prior to 2000, were identified for inclusion in the updated review (Biegert 2004; Chopra 2000; Cibere 2003; Eberl 1988; Goldbach-Mansky 2009; Li 2007; McCarthy 1992; Meier 1987; Mur 2002; Sandler 1998; Song 2007; Tao 2002). These studies were added to 10 of the 11 studies included in the original review (Belch 1988; Brzeski 1991; Deal 1991; Jantti 1989; Leventhal 1993; Leventhal 1994; Pattrick 1989; Tao 1989; Watson 1993; Zurier 1996). One trial was identified via the search of the WHO Clinical Trial Registry (Shamsi 2009), however we did not find any published results from this trial.

One study included in the original review recruited participants with any form of arthritic disease (Mills 1996). This study was excluded from this update because data for the subgroup of participants with RA could not be distinguished from the overall data reported. Other reasons for excluding studies were: (a) not a randomised controlled trial, (b) discussion paper, (c) full study details not available, (d) unable to identify the herbal components of the intervention, (e) case series, (f) review paper, (g) inappropriate statistical analysis, or (h) duplicate publication. See: tables 'Characteristics of excluded studies'.

Twenty of the studies were of parallel design (Belch 1988; Biegert 2004; Brzeski 1991; Chopra 2000; Cibere 2003; Deal 1991; Eberl 1988; Goldbach-Mansky 2009; Li 2007; Jantti 1989; Leventhal 1993; Leventhal 1994; McCarthy 1992; Meier 1987; Mur 2002; Pattrick 1989; Sandler 1998; Song 2007; Tao 2002; Watson 1993), one used a crossover design (Tao 1989) and one had a partial crossover design (Zurier 1996).

The 22 studies covered 13 herbal interventions, four being combination products. Herbal monopreparations included borage seed oil (two studies), blackcurrant seed oil (two studies) and evening primrose oil (three studies) as plant sources of gamma linolenic acid; *Tanacetum parthenium* (feverfew; one study); *Uncaria tomentosa* (cat's claw; one study); *Salix* cortex (willow bark); *Boswellia serrata; Tripterygium wilfordii* (thunder god vine) (two studies) in topical and oral preparations; and topical capsaicin (one study). Herbal mixtures included the Ayurvedic formula RA-1 (one study); SKI306X (one study); *Ganoderma lucidum*, a mushroom given together with San Miao San consisting of *Rhizoma atractylodis*, *Cotex phellodendri and Radix achyranthes bidentatae* (one study); and finally Phytodolor® N consisting of *Populus tremula, Fraxinus excelsior* and *Solidago virgaurea* (two studies).

One study (Belch 1988) included three parallel arms comparing evening primrose oil, a mixture of evening primrose oil and fish oil, and placebo, but only the evening primrose oil and placebo arms were considered in this review. Two studies included data on people with osteoarthritis (OA) as well as RA. These data were presented separately in one study (Deal 1991) but were not presented for the RA subgroup in the other (Mills 1996).

Seven of the studies investigated the effects of plant sourced gamma-linolenic acid (GLA) on a total of 286 participants. Sources of GLA were evening primrose oil (EPO) (Belch 1988; Brzeski 1991; Jantti 1989), blackcurrant seed oil (Leventhal 1994; Watson 1993) and borage seed oil (Leventhal 1993; Zurier 1996). Placebo oils used in the GLA studies included olive oil (Brzeski 1991; Jantti 1989), sunflower oil (Watson 1993; Zurier 1996), liquid paraffin (Belch 1988), cottonseed oil (Leventhal 1993) and soybean oil (Leventhal 1994). The remaining studies included in the review reported the effects of oral interventions of SKI306X on 183 participants (Song 2007), RA-1 on 182 participants (Chopra 2000), *Tripterygium wilfordii* Hook F on 226 participants (Goldbach-Mansky 2009; Tao 1989; Tao 2002), *Boswellia serrata* on 78 participants (Sandler 1998), Phytodolor® N on 47 participants (Eberl 1988; Meier 1987), feverfew on 41 participants (Pattrick 1989), cat's claw on 40 participants (Mur 2002), willow bark on 26 participants (Biegert 2004), *Ganoderma lucidum* together with San Miao San on 65 participants (Li 2007) and the effects of topical applications of *Tripterygium wilfordii* on 61 participants (Cibere 2003) and capsaicin on 38 participants (Deal 1991; McCarthy 1992).

Overall, the studies reported a wide variety of clinical outcomes with some studies also reporting biochemical outcomes (Belch 1988; Goldbach-Mansky 2009; Jantti 1989; Leventhal 1993; Leventhal 1994; Li 2007; Pattrick 1989; Sandler 1998; Tao 1989; Watson 1993). Only clinical outcomes were considered in this review.

Risk of bias in included studies

See: tables 'Risk of bias'.

The risk of bias of each study was assessed independently by two review authors according to the criteria described in the methods (Higgins 2008; Schünemann 2008a; Schünemann 2008b). Quality of the included studies was variable and should be taken into account when interpreting the results of this review. In general, methodological quality of the new studies was superior to that of the older studies, suggesting that quality of research design and reporting has improved since 2000 (Biegert 2004; Chopra 2000; Li 2007; Song 2007).

A total of three studies adequately met all six validity criteria and thus were at minimal risk of bias (Biegert 2004; Chopra 2000; Song 2007). In six studies the method of randomisation was not described (Belch 1988; Jantti 1989; Mur 2002; Pattrick 1989; Sandler 1998; Tao 2002), in two studies the method of blinding was not described (Goldbach-Mansky 2009; Meier 1987) and in one study numbers and reasons for withdrawals were not reported (Cibere 2003). In eight studies neither the method of randomisation nor the method of double blinding was described (Brzeski 1991; Deal 1991; Eberl 1988; Leventhal 1993; Leventhal 1994; Tao 1989; Watson 1993; Zurier 1996). One study of topical capsaicin was downgraded, despite reporting a complete description of the double-blinding method, because we considered that placebo validity and blinding may have been compromised by the burning side effect of this top-

ical intervention (McCarthy 1992). Another study did not address all incomplete outcome data in the report (Li 2007).

Allocation concealment was assessed according to the Cochrane format, as described in the methods (Higgins 2008). Allocation concealment was well described and considered adequate in five studies (Biegert 2004; Chopra 2000; Cibere 2003; Li 2007; Song 2007) but could not be clearly determined in any other study. Several studies suffered from other biases such as differences in baselines (eg: Goldbach-Mansky 2009; Li 2007).

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**

See: Characteristics of included studies; tables 'Summary of findings; Table 1, 'Details of the herbal medicinal products used for the treatment of RA'.

Twenty-two studies assessed products from 13 different plant species. Each herbal intervention was considered separately and consequently eight studies were discussed independently (Biegert 2004; Chopra 2000; Cibere 2003; Li 2007; Mur 2002; Pattrick 1989; Sandler 1998; Song 2007) and the remaining studies were grouped in some manner with studies of the same intervention. Results from the two crossover studies (Tao 1989; Zurier 1996) were reported on only up to the point of crossover. Data from a study with a mixed cohort (participants with either OA or RA) were separated (Deal 1991) and the data for participants with RA were reported in this review.

Gamma linolenic acid

Although there were seven studies of gamma linolenic acid (GLA), the studies were heterogeneous. Three plants oils were used as sources of GLA (borage seed, blackcurrant seed, evening primrose) and the approximate percentage of GLA varies among these oils such that the daily doses of GLA ranged from 525 mg (Watson 1993) to 2800 mg (Zurier 1996).

Small daily dose GLA (525 mg to 540 mg)

Three studies, each of daily doses of GLA between 525 mg and 540 mg, were incompletely reported and data could not be extracted (Belch 1988; Brzeski 1991; Watson 1993). Results of these three studies are summarised and reported descriptively. In two of these studies GLA was administered as evening primrose oil (Belch 1988; Brzeski 1991) and the third study used blackcurrent seed oil as the GLA source (Watson 1993).

No significant improvements in visual analogue pain scores were identified in any of the low dose studies. Morning stiffness, measured in minutes, was reported in all three studies and found to be statistically significantly reduced in two studies (Brzeski 1991; Watson 1993). Non-significant trends to improvement in Ritchie index were reported in two studies (Brzeski 1991; Watson 1993). Trends to reduced pain, improved grip strength and improved patient global assessment were also reported in one study (Watson 1993).

Participants' self-assessments generally favoured oils containing GLA over placebo oils. An improvement in well being was reported by almost all participants receiving blackcurrant seed oil compared with 20% of those receiving the placebo oil (Watson 1993). In another study 94% of patients receiving evening primrose oil (EPO) reported a subjective improvement compared to a little over 40% in the placebo group; after a three-month placebo phase, 80% of patients taking EPO, compared to 14% of those taking placebo, relapsed at least to their baseline parameters (Belch 1988).

In two of these studies, participants reported whether they reduced their routine dose of NSAIDs during the intervention period. The intervention periods differed: six months in one study (Brzeski 1991) and 12 months in the other (Belch 1988), and these data were reported as a dichotomous variable so that the actual amount of dose reduction was unknown in most cases. In one study, 11 out of 15 people receiving GLA reported reduced or ceased NSAID intake compared with five participants out of 15 receiving placebo (Belch 1988). In the other study, three participants in each group reported reduced NSAID intake, by 400 mg ibuprofen daily, and no participants ceased NSAID use (Brzeski 1991). Also in this study, one participant in each of the GLA and placebo groups reported increased NSAID use (Brzeski 1991). When these data were pooled, the relative risk of reducing NSAIDs was higher among participants using GLA than those using placebo oils (RR 1.89, 95% CI 0.96 to 3.76) (Analysis 1.10). This risk estimate is drawn from studies of small sample size with incomplete data reporting and is considered low quality evidence.

Only one study included dichotomous data for participants who reported adverse events: 2 out of 16 participants in the GLA and 0 out of 18 participants in the placebo group (Belch 1988). The relative risk of adverse events was higher among participants using GLA than among participants using the placebo oil (RR 5.59, 95% CI 0.29 to 108.38) (Analysis 1.11). The same study reported the number of participants who withdrew from the study due to worsening disease: 1 participant out of 16 who received GLA and 10 participants out of the 18 people who received the placebo oil. These withdrawal rates equate to a relative risk of worsening disease in favour of the placebo group over the GLA group (RR 0.11, 95% CI 0.02 to 0.78) (Analysis 1.12).

Large daily dose GLA (1400 mg or greater)

Four of studies investigated daily doses of GLA between 1400 mg and 2800 mg and were adequately reported to allow data extraction and some data pooling (Jantti 1989; Leventhal 1993; Leventhal 1994; Zurier 1996). Three of these studies reported outcomes for pain, global evaluation, morning stiffness and joint assessment using the same outcome measures, and these data were combined (Leventhal 1993; Leventhal 1994; Zurier 1996). The other study reported outcomes for pain and morning stiffness using different outcome measures and were reported in isolation (Jantti 1989).

Pain

Pain measured using a 100 mm visual analogue scale (VAS 0 to 100), and reported as percentage change from baseline (Leventhal 1993; Leventhal 1994; Zurier 1996). Using a random-effects model, pooled results showed significant improvement among people using GLA compared with people using placebo oils (MD -32.83, 95% CI -56.25 to -9.42, P = 0.006) (Analysis 1.1). Although these studies applied slightly different lengths of intervention: 24 weeks (Leventhal 1993; Leventhal 1994), six months (Zurier 1996), results displayed little heterogeneity (Chi^2 1.25, I^2 = 0%, P = 0.54) and were considered as pooled data only. These studies together provided moderate evidence that approximately six months of daily use of plant oil in a dose equivalent to at least 1400 mg GLA afforded statistically significant improvements in self-reported VAS pain scores in people with RA (Summary of findings table 1).

In another study (Jantti 1989), 100 mm VAS pain scores were reported as absolute pain scores at the end of the 12-week intervention period. These results favoured the placebo group with a non-significant MD of 6.00 (95% CI -16.36 to 28.36, P = 0.60) (Analysis 1.1). It is unclear why these results differed from those of the other three large dose studies, but possible explanations include a shorter intervention period (12 weeks), use of a non-inert oil (olive oil) in the placebo group and a small sample size that may have contributed to Type II error.

Pain measured using a categorical scale of 0 to 4 (none to very severe) and reported as percentage change from baseline (Leventhal 1993; Leventhal 1994; Zurier 1996) also showed near significant improvement among people using GLA compared with people using placebo oils (MD -34.19, 95% CI -71.57 to 3.18, P = 0.07; data not shown). These studies were moderately heterogeneous (Chi^2 4.95, I^2 = 59.6%, P = 0.08) but within acceptable thresholds for data pooling.

Morning stiffness

Duration of morning stiffness was measured in minutes. Absolute values of morning stiffness after 12 weeks of GLA intervention showed a non-significant improvement in the treatment group (MD -5.00, 95% CI -41.68 to 31.68, P = 0.79) (Jantti 1989). Measures of morning stiffness, adjusted to change scores from baseline, were pooled for the three studies with intervention periods of approximately six months (Leventhal 1993; Leventhal 1994; Zurier 1996). These results favoured GLA over placebo (MD -55.07, 95% CI -76.87 to -33.27, P < 0.01) (Analysis 1.2). These three studies together provided high quality evidence that approximately six months of daily use of plant oil in a dose equivalent to at least 1400 mg GLA afforded statistically significant improvements in self-reported duration of morning stiffness in people with RA. Given the previously mentioned caveats regarding the three-month study (Jantti 1989), there was bronze level evidence that shorter duration of treatment with GLA did not produce significant improvement.

Joint tenderness

Tender joint count out of 68, adjusted as a percentage change from baseline scores, reduced in favour of GLA in each of the three longer-term studies (Leventhal 1993; Leventhal 1994; Zurier 1996). Pooled results of the three studies, using a random-effects model, returned a MD of -53.80 (95% CI -95.61 to -12.00, P = 0.01) (Analysis 1.3). These studies were substantially hetergeneous (Chi^2 6.62, I^2 = 69.8%, P = 0.04) but each study returned results in favour of GLA with none of the 95% CIs extending to favour placebo, indicating that the findings were consistent but the overall effect (Z = 4.01) may be considered an estimate within a range.

Using the categorical scale of 0 to 3 (none to severe), improvement in joint tenderness as a percentage change from baseline was reported among particapnts using GLA in each of the longer-term studies (Leventhal 1993; Leventhal 1994; Zurier 1996). Pooling these data and applying a random-effects model returned a MD of -56.64 (95% CI -98.10 to -15.17, P < 0.01) (Analysis 1.5). Consistent with the 68 tender joint count scores, these studies displayed substantial heterogeneity (Chi^2 5.69, I^2 = 64.9%, P = 0.06) albeit within an acceptable threshold for data pooling. The overall effect (Z = 4.06) should be viewed as a broad estimate of effect size.

When considered together, these three studies provided high quality evidence that approximately six months daily use of at least 1400 mg GLA afforded statistically significant improvement in joint tenderness, measured either as 68 tender joint count or self-reported categorical grading of tenderness.

Joint swelling

Swollen joint count (out of 66), adjusted as a percentage change from baseline scores, reduced in favour of GLA in two of the three studies of approximately six months duration (Leventhal 1993; Zurier 1996). In the third study (Leventhal 1994) results slightly, non-significantly favoured placebo (MD 8.00, P = 0.62) but this study was hampered by small sample size (n = 14) and large variance in swollen joint count scores (95% CI -124.61 to 140.61). When these data were pooled, this small sample study had some influence: MD of -14.43 and the overall effect (Z = 1.66) was not statistically significant (95% CI -31.43 to 2.56, P = 0.10) (Analysis 1.4). In all three studies of approximately six-months duration, joint swelling was also scored on a scale of 0 to 3 (none to severe) and converted to a percentage change from baseline measures. Consistent with the 66 swollen joint count scores, results in one of the studies slighty favoured placebo over GLA and shifted the weighted mean to midline when data were pooled (Leventhal 1994). Applying a random-effects model returned a MD of -24.02 (95% CI -70.80 to 22.76) and a small, non-significant estimate of overall effect (Z = 1.01, P < 0.31) (Analysis 1.6).

Global evaluation

Six out of the seven GLA studies evaluated the global impression of the intervention. All but one of these (Brzeski 1991) reported that participants found GLA to be superior to placebo. Due to differences in scales and the detail of data reporting, data were available for extraction and pooling from three studies only (Leventhal 1993; Leventhal 1994; Zurier 1996). In these studies global evaluations of disease activity by physician and patient were measured using a 0 to 4 (none to very severe) scale and converted to percentage changes from baseline scores.

The mean difference for patient global evaluation was -20.87 (95% CI -39.43 to -2.31, P = 0.03) (Analysis 1.8). These three studies together provided high quality evidence that daily treatment with at least 1400 mg of GLA over approximately six months afforded statistically significant improvement in self-reported evaluation of disease severity over placebo intervention among people with RA.

Pooled data for physician global evaluation returned a non-significant MD of -21.28 (95% CI -70.52 to 27.95, P = 0.40) (Analysis 1.9). Global evaluation by physicians showed substantial and unacceptable heterogeneity between the studies (Chi^2 11.20, I^2 = 82.1%, P < 0.01). In only one of these three studies was the procedure for the physician fully described and made it clear that all assessments of disease activity in any individual were undertaken by the same physician throughout the trial (Zurier 1996). The other two studies may have been compromised by inter-rater variability (Leventhal 1993; Leventhal 1994).

Adverse events

Dichotomous data for participants who reported adverse events was reported in one low dose (Belch 1988) and one higher dose study (Leventhal 1993). The risk of adverse events tended to be higher among participants using GLA (any dose) than among participants using the placebo oil, but this did not reach statistical significance (RR 4.24, 95% CI 0.78 to 22.99; Analysis 1.11).

Tripterygium wilfordii Hook F - oral

Although undertaken by the same research team, data from three studies of oral administration of *Tripterygium wilfordii* Hook F (TwHF) could not be pooled because the interventions and measures differed between the trials (Goldbach-Mansky 2009; Tao 1989; Tao 2002).

A 60 mg daily dose of TwHF was compared with placebo in a crossover trial, the first arm of which lasted for 12 weeks. Clinical outcome measures were: joint tenderness (0 to 3, none to severe), joint swelling of 60 joints only, morning stiffness (in hours), grip strength (mm Hg), and 15-metre walking time (in seconds). Improvements in each of these measures were reported in favour of TwHF (Tao 1989). Statistically significant decreases were found in joint tenderness (MD -14.00, 95% CI -19.02 to -8.98, P < 0.01) (Analysis 2.1) and 60 swollen joint count (MD -3.10, 95% CI -5.53 to -0.67, P = 0.01) (Analysis 2.2). Non-significant decreases were reported in morning stiffness (MD -1.40, 95% CI -4.18 to 1.38, P = 0.32) (Analysis 2.3) and 15-metre walking time (MD -10.40, 95% CI -22.07 to 1.27, P = 0.08) (Analysis 2.5). An increase in grip strength was also demonstrated (MD 3.20, 95% CI -20.01 to 26.41) (Analysis 2.4) but this improvement was not large enough to be statistically significant (Z = 0.27, P = 0.79).

In the second study, larger doses of TwHF were used and compared to placebo in high (360 mg) and low (180 mg) daily doses. Clinical outcomes were assessed using the American College of Rheumatology (ACR) core set of measures at the 20%, 50% and 70% improvement levels (Tao 2002). Eight out of 10 participants in the high dose group and 4 out of 10 participants in the low dose TwHF group satisfied the ACR20 improvement criteria at the end of the intervention period. No participants in the placebo group satisfied these criteria. These dichotomous data converted to a risk ratio of 10.64 (95% CI 0.64 to 176.54) (Analysis 3.1) for satisfying ACR20 improvement criteria when taking 180 mg TwHF compared with placebo and a risk ratio (RR) of 20.09 (95% CI 1.30 to 310.16) (Analysis 4.1) for the same improvement when taking 360 mg TwHF rather than placebo. Graphic presentation of between group comparisons of each of the disease activity component measures (tender joint count, swollen joint count, pain, physical function, patient global, physician global, erythrocyte sedimentation rate, C-reactive protein) indicated that all outcomes were improved in the high dose group over both the low dose and placebo groups and, similarly, that improvements were observed on all measures in the low dose group over the placebo group. These data were not reported in a form that allowed extraction for re-analysis.

In the most recent study, 180 mg of TwHF (given as 60 mg three times per day) was compared with 2000 mg sulphasalazine (1000 mg twice per day) over 24 weeks with clinical (ACR20, ACR50, ACR70, and DAS28) and laboratory (ESR, serum C reactive protein, interleukin-6) outcome measures collected at baseline, week 2, week 4, and every 4 weeks thereafter (Goldbach-Mansky 2009). This study was hampered by large withdrawals from both treatment groups (TwHF: commenced n =60, withdrew n=23, completed n=37; sulfalazine: commenced n=61, withdrew n=36, completed n=25). Using an intention-to-treat analysis with mixed effects modeling, to account for all randomised participants, 65.0% of participants receiving TwHF (95% CI 51.6% to 76.9%) and 32.8% of participants receiving sulfalazine (95% CI 21.3% to 46.0%) were predicted to be ACR20 responders (P = 0.001). Re-analysis of response to treatment using ACR20 as a dichotomous variable supports this finding of a better response in the TwHF group compared with placebo (RR 1.98, 95% CI 1.32 to 2.97; Analysis 5.1). In both groups the ACR20 response occured as early as two weeks after commencing treatment, but at all time points the percentage of participants predicted (modelled) as ACR20 responders was significantly greater in the TwHF group. The TwHF group also demonstrated a higher percentage of ACR50 (P < 0.001) and ACR70 (P < 0.002) responders at all time points, and lower interleukin-6 levels and less radiographic progression (non-significant). Re-analysis response to treatment using ACR50 as a dichotomous variable supports this claim of a better response in the TwHF group compared with sulfalazine (RR 20.33, 95% CI 2.82 to 146.75; Analysis 5.2).

Adverse events

In the first two studies, more adverse reactions were seen among people receiving TwHF than people receiving placebo (Analysis 3.3; Analysis 4.3). In the first study, adverse reactions resulted in four withdrawals and a severe reaction (fever and aplastic anaemia) occurred in one participant following an overdose of TwHF (Tao 1989). One death occurred also, although not thought to be related to the intervention (Tao 1989). In the second study, four participants in the placebo group reported adverse reactions as did six participants in the high dose group and five participants in the low dose group (Tao 2002). In this study none of the adverse reactions were reported as severe, that is participants did not require hospitalisation. Commonly reported adverse reactions included diarrhea, headache and hair loss.

In the third study 53 participants in the TwHF group and 55 in the sulfalazine group reported adverse events, and the proportions were not significantly different (RR 0.98, 95% CI 0.87 to 1.11; Analysis 5.4), however a notably greater proportion of participants specified that they withdrew due to adverse events from the sulfalazine group than from the TwHF group such that the relative risk of withdrawal due to adverse events markedly favours the TwHF group (Analysis 5.5). Most adverse events affected the gastrointestinal tract (59% TwHF, 49% sulfalazine), and were more often moderate to severe in the sulfalazine group than in the TwHF group (P = 0.039) (Goldbach-Mansky 2009).

Phytodolor® N

Two studies compared a daily dose of 30 drops of Phytodolor® N (prepared from ash bark, aspen leaf, aspen bark, golden rod herb) to placebo, one over two weeks (Meier 1987) and the other over 12 months (Eberl 1988). Both studies were unpublished randomised controlled clinical trials conducted by the manufacturer (Steigerwald Pharmaceuticals) as part of product development and testing.

Because length of intervention and some of the measures differed between the trials, data could not be pooled for meta-analysis. For one study, mean changes from baseline were calculated from frequency tables reported in the paper (Eberl 1988). Standard deviations could not be calculated for some outcomes (eg, NSAID use), and thus such data could not be extracted for analysis in this review.

Data from single trials indicate no differences between participants treated with Phytodolor® N and placebo in terms of pain at two weeks (Analysis 6.1), joint swelling after two weeks of treatment (Analysis 6.2), or morning stiffness at 12 months follow-up (Analysis 6.3). There was more improvement in disease following treatment

with Phytodolor® N, as measured by the Ritchie index at 12 months (Analysis 6.4).

Both studies reported cumulative use of NSAIDs (diclofenac) over the course of the trial. Data could be extracted from one trial (Eberl 1988). There was no difference in the NSAID use in participants treated with Phytodolor® N group compared with participants treated with placebo at one month or 12 months. (Analysis 6.5).

For several herbal medicines, only one study was available.

SKI306X

In a single, well designed, multi-centre trial, the Korean herbal mixture SKI 306X was tested against celecoxib in a six-week head-to-head comparison (Song 2007). The authors reported prior studies as evidence of anti-inflammatory and analgesic effects, but these were in vitro or animal studies and were not suitable for inclusion in this review.

Pain, measured using a 100 mm visual analogue scale, decreased significantly in both groups over time (P < 0.01), as reported by the trial authors, but was not significantly different between groups (Analysis 7.1). These results provided moderate quality evidence that SKI306X was comparable to celecoxib for pain reduction in people with RA.

After three weeks of intervention, 16 participants in the SKI306X group and 24 participants in the celecoxib group satisfied the ACR20 improvement criteria. After six weeks of intervention, equal numbers of participants (n = 29) in both groups satisfied these criteria (Analysis 7.2). Considering each of these criteria individually: 28 tender joint count; 28 swollen joint count; patient's global assessment; investigator's gloal assessment; Health Assessment Questionaire Disability Index (HAQ-DI) score; Westergren erythrocyte sedimentation rate (ESR), c-reactive protein (CRP); there were no significant differences between the two groups at baseline, week three or week six on any measure except ESR (data not shown). The triallists reported that mean ESR was slightly but not significantly higher in the SKI306X group at baseline and dropped to significantly less than the mean ESR in the celecoxib group at both three-week (P < 0.04) and six-week (P = 0.01) measurements. These results offered moderate quality evidence that SKI306X and celecoxib had comparable effects on reducing disease activity in people with RA.

Adverse events did not differ significantly between the two groups (Analysis 7.3). Gastrointestinal complaints (epigastric pain, abdominal discomfort, nausea, anorexia, dyspepsia) were most common. In the SKI306X group, one participant who reported depression and one participant who reported epigastric pain discontinued the study medication. In the celecoxib group, three participants who reported pruritus, abdominal discomfort and skin rash, respectively, discontinued the study medication. The person who experienced depression in the SKI306X group was hospitalized and this incident was reported as a serious drug-related event.

Willow bark

A proprietary extract of willow bark (*Salix daphnoides*) equivalent to 240 mg salicin was compared with placebo in a small sample (n = 26) of people with RA. Over six weeks of intervention willow bark was not significantly more effective than placebo in producing a change from baseline in any clinical outcome: pain VAS 0 to 100 (Analysis 8.1); 28 tender joint count (Analysis 8.2); 28 swollen joint count (Analysis 8.3); patient assessment of efficacy (Analysis 8.4); physician assessment of efficacy (Analysis 8.5); HAQ-DI score (Analysis 8.7); SF-36 physical component summary score (Analysis 8.8); SF-36 mental component summary score (Analysis 8.9). This lack of statistical significance may be a Type II error in a small sample, underpowered study.

Two participants in the willow bark group and one participant in the placebo group satisfied ACR20 response criteria after six weeks of intervention; this difference was not statistically significant (Analysis 8.6). Similar numbers and severities of adverse events were reported for both the willow bark and placebo groups; seven adverse events were reported in each group, although it was unclear how many participants these reports represented.

Cat's claw

Uncaria tomentosa (cat's claw) was compared with placebo in a double-blind randomised controlled trial. The trialists report significant improvements in the 68 tender joint count both within and between groups after 24 weeks of daily use (P = 0.044) (Analysis 8.2). Also, significant within group improvements were found in the intervention group on measures of 66 tender joint count (P = 0.001) (Analysis 8.3), Ritchie index (P = 0.002) (Analysis 8.5) and duration of morning stiffness (P = 0.002) (Analysis 8.4). We could not verify the results independently as no appropriate measures of variance were available for the trial for extraction. The trialists report no improvements, either between or within groups, were reported for any other clinical or laboratory variables. Twelve participants in each group reported side effects and one participant from each group withdrew from the study because of these effects.

Feverfew

Daily use of dried, powdered feverfew (*Tanacetum parthenium*) was compared with placebo (cabbage) in 41 people with RA. Of the clinical outcomes (duration of morning stiffness, inactivity stiffness, pain 10 cm VAS, grip strength, Ritchie index) measured in this study (Pattrick 1989) data were presented for grip strength only. Grip strength was reported to be significantly improved in the feverfew group over time (P = 0.03) and in comparison to the placebo group after six weeks of intervention (P = 0.047) but re-calculation of the between group comparison for this review returned a non-significant difference between groups (MD 17.00mmHg; 95% CI -8.65 to 42.65mmHg) (Analysis 9.1). No significant differences were reported either between or within groups on any other clinical measures. One participant in each group reported mild side effects and the participant from the placebo group withdrew from the study because of these effects (Analysis 9.2).

RA-1

An Ayurvedic herbal mixture, RA-1, was compared with placebo in people with RA. Data from 182 participants were available for inclusion in an intention-to-treat analysis although only 165 participants completed the full 16-week trial. No statistically significant differences were identified between the groups on any clinical measures after 16 weeks of intervention, however change scores on all clinical variables were greater in the RA-1 group than in the placebo group.

Among participants who completed the entire 16-week trial, clinical outcomes were further assessed using the ACR core set of measures at the 20% and 50% improvement levels (Chopra 2000). Thir-

ty-nine out of 80 participants in the RA-1 group and 30 out of 85 participants in the placebo group satisfied the ACR20 improvement criteria at the end of the intervention period; this difference did not reach statistical significance (risk ratio 1.38; 95% CI 0.96 to 1.99) (Analysis 10.7). However, a significantly greater number of participants receiving RA-1 improved, as measured by the ACR50 improvement criteria: 15 out of 80 participants in the RA-1 group and 5 out of 85 participants in the placebo group (risk ratio 3.19; 95% CI 1.21 to 8.37) (Analysis 10.8).

Boswellia serrata

An extract of *Boswellia serrata* (H15) was tested in 78 participants with active RA in two randomised controlled trials in four centres. Results from 37 participants in one centre (Ratingen) were re-analysed and demonstrated no significant benefit over placebo in either clinical or laboratory outcomes (Sandler 1998). The data were not normally distributed and were consequently reported as median and range. Data in this form could not be extracted for analysis in this review. Median subjective pain assessments (VAS 0 to 10) worsened from 4.6 to 4.7 in the intervention group and improved from 3.9 to 3.8 in the placebo group, however the placebo group were somewhat favoured by lower baseline pain scores. Median subjective global assessment improved in both groups, from 5.0 to 4.9 in the intervention group and from 4.7 to 4.2 in the placebo group. Participant-reported adverse events did not differ between groups; three of 19 participants in the placebo group, and one of 18 in the treatment group had adverse events (Analysis 11.1).

Capsaicin - topical

Topical capsaicin for control of rheumatoid arthritic hand pain was compared to placebo in two studies of people with RA. In both studies the placebo was a vehicle cream prepared and packaged to appear indistinguishable from the active agent, but blinding and placebo validity may have been compromised by a local burning sensation that may occur as a side effect with topical capsaicin. In one study, burning at the site of application was noted by 44% of participants treated with capsaicin and by one treated with placebo (Deal 1991).

In the larger of the two trials (n = 31), four times daily topical use of 0.025% w/v capsaicin cream was compared to placebo (Deal 1991). Improvements in pain were measured on a 100 mm visual analogue pain scale and a categorical pain scale. On both measures participants in the capsaicin group reported greater improvement than participants in the placebo group. Percentage change in pain from baseline on the 100 mm VAS showed a MD of -25.00 mm (95% CI -51.76 to 1.76) (Analysis 12.1) and using the categorical pain scale showed a MD of -0.47 (95% 95% CI -1.08 to 0.14) (data not shown). Although these between group differences were not statistically significant, they demonstrated a trend to improvement. Small sample size meant that this study was probably underpowered, increasing the likelihood of Type II error. A change from baseline of the physician's global evaluation (-1 to 3, higher score indicating greater improvement) also favoured the treatment group and the difference between groups in this measure was statistically significant after four weeks of intervention (MD 1.36, 95% CI 0.52 to 2.20, P = 0.001) (Analysis 12.2). Burning at the site of application of the cream was the only adverse reaction reported in this study.

A further study compared a higher dose (0.075% w/v) of capsaicin cream to placebo (McCarthy 1992). The sample size of this study was very small; seven participants were recruited and five completed the four week trial. Although improvements in pain were measured using a 100 mm visual analogue pain scale, data from this study were not adequately reported to allow extraction for pooled analysis with the larger study.

Tripterygium wilfordii - topical

Sixty-one people with RA participated in a six-week, randomised, double-blind, placebo-controlled trial of a tincture of *Tripterygium wilfordii.* The placebo tincture was prepared and packaged to be indistinguishable from the intervention. The herbal medicine was applied topically to the swollen or tender joints up to six times per day and results were reported using the core set of ACR response criteria, aggregated into a slightly modified form of the 20% improvement level (ACR20). At the end of the intervention period, statistically significant differences, in favour of *Tripterygium wilfordii,* were identified on most clinical outcomes: 42 tender joint count (MD 1.50, 95% CI 0.58 to 2.42, P = 0.001) (Analysis 13.1), 40 swollen joint count (MD 4.40, 95% CI 2.76 to 6.04, P < 0.001) (Analysis 13.2), grip strength in kiloPascals (MD 39, 95% CI 25.70 to 52.30, P < 0.001) (Analysis 13.3) and duration of morning stiffness measured in hours (MD 0.80, 95% CI 0.54 to 1.06, P < 0.001) (Analysis 13.4).

Treatment with *Tripterygium wilfordii* resulted in improved disease activity, as measured by the number of ACR20 responders: 18 out of 31 participants in the intervention group compared with 6 out of 30 participants in the placebo group (risk ratio 2.90, 95% CI 1.34 to 6.31, P = 0.007) (Analysis 13.5).

***Ganoderma lucidum and* San Miao San**

Sixty-five participants were randomised to two groups: 32 participants received a Traditional Chinese Medicine preparation combining 4000 mg *Ganoderma lucidum* and San Miao San (SMS; comprising 2400 mg *Rhizoma atractylodis*, *2400 mg Cotex phellodendri*, and *2400 mg Radix achyranthes Bidentatae*) while 33 participants received a placebo (identical looking capsules containing starch and colouring agent) for 24 weeks (Li 2007). Outcome measures (tender joint count, swollen joint count, patient global assessment on 0-100mm VAS, physician global assessment on 0-100mm VAS, duration of morning stiffness, plasma C reactive protein level, ESR) were taken at baseline, and ever 4 weeks for 24 weeks. Primary outcome measure was the count of participants who achieved ACR20 criteria, and secondary outcomes were changes in the individual components of the ACR20 core set of measures. Some other laboratory investigations were included, but are of no importance in this review. Despite repeated measures, all analyses were reported as univariate tests (paired t-tests and Wilcoxon's signed rank test). Repeated outcomes were reported as percentage change and interquartile range at each time point. After 24 weeks of intervention 15% of the *Ganoderma lucidum* and SMS group and 9.1% of the placebo group achieved ACR20; this difference was not statistically different (RR 0.54, 95% CI 0.11 to 2.70; Analysis 14.1).

Treatment with *Ganoderma lucidum* and SMS resulted in significant improvement in self-reported pain from week 4, maintained to week 24 (mean ± SD score: 4.9 ± 2.3 at baseline, 4.1 ± 2.3 at week four, 3.9 ± 2.5 at week 24; P < 0.05). In addition, the patient global assessment also improved significantly at week 4 and was maintained to week 24 (mean ± SD score: 5.7 ± 2.5 at baseline, 5.3 ± 2.5 at week 4, 4.7 ± 2.6 at week 24; P < 0.05). Other ACR components remained unchanged in both groups. There were no differences between groups at the end of treatment in the percentage, absolute counts and ratios between CD4, CD8, natural killer and B lympho-

cytes. Also, CD3, CD4 and CD8 lymphocyte counts and markers of inflammation, including plasma interleukin-18 (IL-18), interferon (IFN)–inducible protein 10, monocyte chemoattractant protein 1, monokine induced by IFN and RANTES (egulated on Activation Normal T Cell Expressed and Secreted), were unchanged.

Thirteen patients reported 22 episodes (14 in the placebo group and eight in the *Ganoderma lucidum* and SMS group; Analysis 14.2) of mild adverse effects including gastrointestinal upset, palpitations and irregular period (most of these occuring in the placebo group). There were two episodes of sweating in the *Ganoderma lucidum* and SMS group with no such symptom reported in the placebo group (Li 2007).

DISCUSSION

See: Additional tables, 'Summary of findings'

Definition of herbal medicine and herbal medicinal products (HMPs) studied

According to the WHO guideline (WHO 1996), herbal medicines are defined as being finished, labelled medicinal products that contain aerial or underground parts of plants or other plant material, or combinations thereof, whether in the crude state or as plant preparations, as active ingredients. Plant materials combined with chemically defined active substances, including chemically defined, isolated constituents of plants, are not considered to be herbal medicines. Plant preparations include comminuted or powdered plant materials, extracts, tinctures, fatty or essential oils, expressed juices and preparations whose production involves fractionation, purification or concentration.

The HMPs studied included preparations from the root of *Tripterygium wilfordii*, *Clematis mandshurica*, *Trichosanthes kirilowii*, *Atractylodes macrocephala*, *Achyranthes bidentatae*; from the bark of *Salix daphnoides*, *Uncaria tormentosa*, *Populus tremula*, *Fraxinus excelsior*, *Phellodendron chinense*; from the herb of *Solidago virgaurea*; from the leaf of *Populus tremula*, *Tanacetum parthenium*; from the flower of *Prunella vulgaris*, from the seed of *Capsicum frutescens*, *Oenothera biennis*, *Ribes nigrum*, *Borago officinalis*; and from the gum resine of *Boswellia* species were used alone or as mixtures. Another HMP included the Ayurvedic mixture RA1.

The active principle of a herbal medicinal product which is the sum of all the constituents that produce a medicinal action has not yet been fully identified for any of the anti-inflammatory herbal medicinal products. Constituents that contribute to the anti-inflammatory or analgesic effects include triptolide and its derivatives (*Tripterygium wilfordii*), boswellic acids (*Boswellia* serrata), alkaloids (*Uncaria tormentosa*), flavonoids (*Salix daphnoides*), parthenolide (*Tanacetum parthenium*), gammalinolenic acid (seed oils of *Oenothera biennis*, *Ribes nigrum*, *Borago officinalis*), other unsaturated fatty acids (SKI306X®) and capsaicin (*Capsicum frutescens*). Salicin, the characteristic constituent of *Salix* species, is an ineffective prodrug; however, during absorption salicin is metabolized into co-active salicylic acid derivatives. Surprisingly, the amount of salicylic acid produced from a daily dose of *Salix* bark extract containing 240 mg of salicin corresponds to an aspirin dose of only 100 mg, a cardioprotective rather than an anti-inflammatory dose (Schmid 2001). However, this *Salix* extract dose cannot be used to replace aspirin as a blood thinner since it was shown not to have a major impact on blood clotting (Krivoy 2001).

Summary of main results

In general, we found minor evidence that three herbal medicines may have some effectiveness in the treatment of rheumatoid arthritis (RA). Oral *Tripterygium wilfordii* products (TwHF) may improve some symptoms of RA. Across all three trials the results favoured TwHF and in particular it appears that a dose between 180 mg and 360 mg of TwHF is superior to placebo and superior to, or at least as effective as, sulfasalzine, for some measures. The beneficial effect of TwHF may appear as soon as two weeks after commencing therapy. However, the oral use of *Triperygium wilfordii* may be associated with several side effects, some potentially severe, and therefore this product should be used with caution. Some of the adverse events described in the literature for this herbal medicine include dysmenorrhoea, decreased male fertility, renal insufficiency, hematotoxicity, embryotoxicity and immune suppression demonstrated by increased rate of infections (Canter 2006); the subacute toxicity showed pathological changes mainly in the lymphatic and reproductive systems. Therefore, *Tripterygium wilfordii* Hook F has a high risk-benefit ratio (Canter 2006). Future research could attempt to replicate the findings of these trials and perform a more comprehensive evaluation of the safety of this intervention.

There is moderate evidence of benefit for oils containing GLA (that is borage, blackcurrant, evening primrose oil (EPO)) but an adequate dose and the duration of treatment are unknown (Summary of findings for the main comparison). Some studies suggest that effects were not expected to occur for at least six to 12 weeks after commencing daily use of GLA (Leventhal 1993), with actual effects being seen at six months (Brzeski 1991) although some manufacturers of GLA suggest a 12-month period of treatment. In general, the studies included in this review administered lower doses of GLA over relatively short periods of time (between 525 mg and 540 mg for six to 12 weeks) or large doses over longer periods of time (1.4 g to 2.8 g over 24 weeks). The benefits appeared to be greater if dosages were at least 1.4 g per day and were administered for at least six-months duration (Summary of findings table 1). The authors do point out that a problem was encountered where larger doses of GLA were given since this resulted in a large number and large size of capsules having to be taken. We suggest that future studies evaluate the effects of lower dosages over longer periods of time. There is some concern over the safety of one source of GLA, EPO. For EPO, allergy or hypersensitivity has been reported but appears to be rare. Also, there have been several reports of seizures in individuals taking EPO, particularly in people with a history of seizure disorders or among individuals taking EPO in combination with anaesthetics or other centrally acting drugs (for example chlorpromazine, thioridazine, trifluoperazine or fluphenazine). Other possible adverse events include occasional headache, abdominal pain, nausea and loose stools. Although some animal studies showed that GLA decreased blood pressure, human studies do not show consistent changes in blood pressure. Even so, it is advised that people on blood pressure medications should closely monitor their blood pressure when taking EPO. Finally, there are suggestions in the literature that individuals should stop taking EPO two weeks prior to surgery that requires general anaesthesia. Since borage and blackcurrant seed oils also contain GLA, the adverse event profile of EPO might apply to these oils as well (NLM 2009).

There appears to be some evidence of efficacy for Phytodolor® N at a dose of 30 drops per day compared to placebo, as reported in two unpublished studies (Eberl 1988; Meier 1987). These studies were conducted by the product manufacturer. They were poorly reported and had different durations (two weeks versus 12 months), therefore they should be replicated by an independent group before we can definitively establish efficacy. Although the adverse effect profile for Phytodolor® N appears to be better than for the NSAIDs included in the trials, gastrointestinal complaints were reported (2.6%) and occasional allergic skin reactions. It has been proposed that some of the adverse effects are partly due to the alcohol content of Phytodolor® N (45.6% volume, 0.7 g per 40 drops) which may pose a health risk to children and to adults with liver disease, alcoholism, epilepsy or brain-damage. Caution is advised during pregnancy or lactation and for drivers and individuals who operate machinery although no impairment of consciousness or reactivity is expected to occur with 0.7 g of alcohol per dose. Animal studies on mutagenicity, teratogenicity and toxicity have indicated no evidence for toxic effects arising from the intake of the combination during pregnancy or the lactation period (Gundermann 2001).

All other herbal medicines that were included were tested in single trials only, most of which were at a high risk of bias and were poorly reported. Therefore no other herbal interventions have evidence for efficacy. See the characteristics of included studies for details of all the included trials.

Overall, it was difficult to make definitive conclusions in this review because of the poor reporting of important information in the included trials. To allow full and accurate assessment of future studies, we recommend that authors conform to the Consolidated Standards of Reporting Trials (CONSORT) (Moher 2001) and in particular the recent extension of the CONSORT statement for trials of herbal interventions (Gagnier 2006a; Gagnier 2006b).

The WHO guideline recommends that the manufacturing procedure should be described in detail (WHO 1996). If other substances are added during manufacture, in order to adjust the plant preparation to a certain level of active or characteristic constituents or for any other purpose, the added substances should be mentioned in the manufacturing procedures. A method for identification and, where possible, assay of the plant preparation should be added. If identification of an active principle is not possible, it should be sufficient to identify a characteristic substance or mixture of substances (for example 'chromatographic fingerprint') to ensure consistent quality of the preparation.

The minimum information given for a HMP in a publication should include the plant part, the brand name if the preparation has not been solely prepared for the study, the excipient added and the drug extract ratio if extracts were used, the daily dosage of powder or native extract (otherwise the extract dose may also contain additives) and the content of at least one characteristic substance in the daily dosage. Not all of the articles reporting the results of clinical trials with HMPs for the treatment of RA provided this information. The results of such studies are only attributable to the particular HMP used and cannot be transferred to other HMPs from the plant material unless these have shown to be bioequivalent (having the same active principle). HMPs with insufficient declaration included those from *Tripterygium wildordii* (topical preparation and T2), *Uncaria tomentosa*, *Boswellia serrata*, the Ayurvedic mixture RA1, a herbal mixture from *Atractylodes macrocephala*, *Phellodendron chinense* and *Achyranthes bidentatae* that also contained a mushroom extract. The studies providing sufficient declaration to repeat the clinical trial were those investigating HMPs from *Tripterygium wildordii* (study medication), *Salix daphnoides*, *Tanacetum parthenium*, the herbal mixtures SKI306X® and Phytodolor®, the active principle of *Capsicum frutescens* and the seed oils of *Oenothera biennis*, *Ribes nigrum* and *Borago officinalis*, all standardized with gammalinolenic acid. For the details see the 'Additional table'.

Further investigation of each herbal therapy is warranted, particularly via well designed, fully powered confirmatory clinical trials that use American College of Rheumatology criteria to measure outcomes (ACR 2002).

Overall completeness and applicability of evidence

As described above, although we included 22 randomised controlled clinical trials only three of the herbal medicinal products were tested in two or more trials. Therefore, there is inadequate evidence for most of the included herbal medicinal products. Also, for those herbal medicines that were tested in two or more trials, the trials frequently differed in important ways such that no single finding was supported by additional trials. Therefore, it is very difficult to make definitive conclusions except to say that this evidence as a whole is not complete and does not provide import to clinical practice. That is, the external generalizability of the data described in this review is poor. More research is needed to confirm any of the findings reported in this review. In addition, we suggest that more comparative trials are needed to determine how these interventions compare to other (standard) interventions for rheumatoid arthritis.

Quality of the evidence

Of the 22 studies included in this review only three were at a low risk of bias. All other studies were considered to be at a high risk of bias. Also, trials frequently under-reported important information necessary for the assessment of risk of bias. As described above, we suggest that authors refer to the Consolidated Standards of Reporting Trials (CONSORT) (Begg 1996; Moher 2001) and in particular the recent extension of the CONSORT statement for trials of herbal interventions (Gagnier 2006a; Gagnier 2006b). These widely published and accepted guidelines clearly describe the necessary information to be included in a report of a controlled trial of a herbal medicine intervention.

Furthermore, trials testing the same herbal species or product frequently differed in the participant, intervention and outcome measure characteristics. Due to the extensive heterogeneity, further clinical trials that are similar to those initially positive trials reported above are needed for convincing evidence of effectiveness. Also, many of the studies were inconsistent with current clinical trial standards in rheumatology. For example, only seven of the 22 studies used the set of outcome measure recommended by the American College of Rheumatology (ACR) since 1995 (Biegert 2004; Chopra 2000; Cibere 2003; Goldbach-Mansky 2009; Li 2007; Song 2007; Tao 2002). For future studies, we recommend that trialists use ACR outcome measures to allow comparison of effect sizes between different herbal medicines and to provide estimates of clinical relevance. In addition, very few trials compared herbal medicines against standard therapies. We recommend that future trials have comparative designs and include measures of the costs of care

so that the direct costs of these interventions might be compared with the costs of other RA treatments.

Although some of the trials included adverse event data, adequate evidence of safety is not available for any of the herbal medicinal products considered in this review. We recommend that future studies be done on genotoxicity, toxicokinetics and mechanisms as these are essential for preclinical safety assessment (ICH 2004). We also recommend pharmacological trials of six and nine-month chronic toxicity assessment in rodents and non-rodents, respectively. The herbal medicinal products considered in this review have not been subject to this rigorous non-clinical testing and, therefore, cannot be recommended during pregnancy or lactation. In addition, it is important to test for contaminants as herbal preparations may be contaminated with other herbs, pesticides, herbicides, heavy metals or drugs. However, contamination is unlikely if the manufacturer complies with the principles and guidelines of good manufacturing practice (GMP) (EFPIA 1996).

Potential biases in the review process

This review has several strengths. First, we conducted a comprehensive electronic search strategy. Next, we decided on inclusion of trials, extracted the data and performed risk of bias assessments in duplicate at a minimum. Also, we searched for and included trials in all languages and in any year. This review may have several drawbacks. First of all, the indexing of herbal medicine trials is not consistent across databases, therefore we might have missed trials. This is unlikely given our carefully developed search strategy. Finally, we did not conduct any meta-analyses due to the heterogeneity of the included trials but instead described the trials in a qualitative manner. In agreement with others, we feel that this form of qualitative description of trials is warranted in the face of a high degree of heterogeneity across trials included in a systematic review (Furlan 2009; Higgins 2008).

AUTHORS' CONCLUSIONS

Implications for practice

The current available evidence for herbal treatment of RA is generally sparse and reliant on small sample sizes and is therefore insufficient for any reliable assessment of efficacy to be made. The variability between studies indicates a need to establish efficacy, optimum dosage and duration of treatment for these interventions. The single studies are inconclusive.

Good tolerance of most of the herbal remedies was demonstrated although caution is warranted in interpreting safety due to small sample sizes of some studies and the incomplete examination of safety profiles of these interventions.

Implications for research

Although this review has not been able to provide conclusive evidence for the use of herbal therapy in RA, some of the studies are of sufficiently high quality to encourage further research, especially to confirm the efficacy and optimum dosage of GLA.

The trend for self-medication with over-the-counter herbal remedies, especially in the treatment of chronic disease, makes further research in the field desirable. Non-clinical studies are required to determine the toxicity profiles of almost all herbal medicines in common use for the treatment of RA.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Belch 1988

Methods	Randomised, double blind, placebo control, 3 parallel groups. Duration 12 months.
Participants	Randomised n=49, completed n=34. Age range 28-74 yr. Inclusion: classical or definite RA (ARA criteria), requiring NSAIDs but not DMARDs.
Interventions	Tradename not provided, *Oenothera biennis* (evening primrose), oil, 6000mg (12x500mg, approx 9% GLA, equivalent to 540mg GLA), capsules, oral. Concurrent intervention: usual NSAIDs for first 3 months only.
Outcomes	Morning stiffness (minutes), grip strength mmHg, Ritchie index, pain VAS 0-100, patient global.
Notes	Results favour intervention for reduction in pain and NSAID use. No evidence of disease-modifying effects.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Low risk	Active intervention and placebo not distinguished by look, taste, smell or packaging.
Incomplete outcome data addressed? All outcomes	Low risk	Reported withdrawals. Included intention-to-treat analyses.
Free of selective reporting?	Low risk	Reported adverse events.
Free of other bias?	Low risk	Diagnosis / assessment consistent with ACR criteria.

Biegert 2004

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 6 weeks.
Participants	Randomised n=26 (intervention n=13, control n=13), completed n=26 (intervention n=13, control n=13). Age (yr): intervention m=56.5 sd=8.9, control m=60.1 sd=11. Inclusion: ACR criteria RA stage I-III.
Interventions	Assalix*, *Salix daphnoides* cortex (willow bark), ethanolic extract, 1572.96mg (2x2x393.24mg, equivalent to 240mg salicin), tablets, oral.
Outcomes	Pain VAS 0-100, tender joint count, HAQ-DI, stiffness VAS 0-100, efficacy VAS 0-100, SF-36, ESR, CRP, ACR20.
Notes	Results equivocal.

Biegert 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomised to one of three groups using a computer generated random number sequence.
Allocation concealment?	Low risk	Adequate.
Blinding? All outcomes	Low risk	Active interventions and placebo not distinguished by look, taste, smell or packaging.
Incomplete outcome data addressed? All outcomes	Low risk	Reported withdrawals. Included intention-to-treat and per protocol analyses.
Free of selective reporting?	Low risk	Confirmatory study, statistical power reported.
Free of other bias?	Low risk	Diagnosis / assessment consistent with ACR criteria.

Brzeski 1991

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 6 months.
Participants	Randomised n=40 (intervention n=19, control n=21), completed n=30 (intervention n=13, control n=17). Age range 16-75 yr. Inclusion: classical or definite RA, all with probable gastro-intestinal lesions due to NSAIDs.
Interventions	Tradename not provided, *Oenothera biennis* (evening primrose), oil, 6000mg (12x500mg, approx 9% GLA, equivalent to 540mg GLA), capsules, oral.
Outcomes	Pain VAS 0-100, well-being score, morning stiffness (minutes), Ritchie index, HAQ, intake of NSAIDs and analgesics.
Notes	Results favour intervention for morning stiffness, equivocal for all other outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Unclear risk	Described as double-blind, method not reported.
Incomplete outcome data addressed? All outcomes	Unclear risk	Reported withdrawals.
Free of other bias?	Unclear risk	Placebo capsules contained olive oil and may not be inert. Reported ethics committee approval.

Chopra 2000

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 16 weeks.
Participants	Randomised n=182 (intervention n=89, control n=93), completed n=165 (intervention n=80, control n=85). Age (yr): intervention m=45, control m=45. Inclusion: ACR criteria RA stage I-III.
Interventions	RA-1, Ayurvedic formula, mixture of *Withania somnifera*, *Boswellia serrata*, *Zingiberis officinale*, *Ciruma longa*, 444mg, (3x2), tablets, oral.
Outcomes	20% or 50% reduction in individual core set variables, patient global assessment, physician global assessment, ARC20.
Notes	Results equivocal.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomised to one of two groups using a computer generated random number sequence.
Allocation concealment?	Low risk	Adequate
Blinding? All outcomes	Low risk	Active intervention and placebo not distinguished by look, taste, smell or packaging.
Incomplete outcome data addressed? All outcomes	Low risk	Reported withdrawals. Included intention-to-treat and per protocol analyses.
Free of selective reporting?	Low risk	Reported adverse events.
Free of other bias?	Low risk	Diagnosis / assessment consistent with ACR criteria. Reported ethics committee approval.

Cibere 2003

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 6 weeks.
Participants	Randomised n=61 (intervention n=31, control n=30). Dropouts not reported. Age (yr): intervention m=42, control m=39. Inclusion: ACR criteria RA (any stage).
Interventions	Tradename not provided, *Tripterygium wilfordii* (thunder god vine), tincture, 5-6 applications/day, topical.
Outcomes	Modified ACR20, 42 tender joint count, 40 swollen joint count, grip strength kPa, morning stiffness (hours), HAQ-DI, ESR, CRP, patient global, physician global.
Notes	Results favour intervention.

Risk of bias

Bias	Authors' judgement	Support for judgement

Cibere 2003 *(Continued)*

Adequate sequence generation?	Low risk	Randomised to one of two groups using a computer generated random number sequence.
Allocation concealment?	Low risk	Adequate
Blinding? All outcomes	Low risk	Active intervention and placebo not distinguished by look, taste, smell or packaging.
Incomplete outcome data addressed? All outcomes	Unclear risk	Withdrawals not reported. Included intention-to-treat analyses.
Free of selective reporting?	Unclear risk	Adverse events not reported. Confirmatory study.
Free of other bias?	Unclear risk	Diagnosis / assessment consistent with ACR criteria. Reanalysis of previous study.

Deal 1991

Methods	Randomised, double blind, placebo-control, 2 parallel groups. Duration 4 weeks.
Participants	Randomised n=31, completed n=29. Age range 20-79 yr. Inclusion: primary RA one/both knees, moderate to very severe knee pain (scale of 0-4), at least 3 ACR criteria for classic, definite, or probable RA.
Interventions	Zostrix, capsaicin 0.025% w v cream, topical, QID.
Outcomes	Pain VAS 0-100, pain 0-4, physician global -1-3.
Notes	Results favour intervention.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Unclear risk	Described as double-blind. Active intervention and placebo not distinguished by look, taste, smell or packaging, but placebo validity and blinding may be compromised by burning side effect of topical intervention.
Incomplete outcome data addressed? All outcomes	Low risk	Reported withdrawals.
Free of selective reporting?	Unclear risk	Variances reported as standard error of measurement (SEM). When converted to standard deviation (SD), data are skewed, violating an assumption of the inferential analyses. Reported adverse events.
Free of other bias?	Unclear risk	Diagnosis / assessment criteria for OA not specified.

Eberl 1988

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 12 months.
Participants	Randomised n=37 (intervention n=20, control n=17), completed n=24 (intervention n=15, control n=9). Age (yr): intervention m=61 sd=12, control m=59 sd=10. M:F=1:36. Inclusion: ACR criteria RA stage II or III.
Interventions	Phytodolor® N, mixture of ash bark, aspen leaf, aspen bark, golden rod herb, tincture, 3x30 drops, oral. Concurrent intervention: diclofenac 25mg/d, oral.
Outcomes	Joint stiffness, grip strength mmHg, Ritchie index.
Notes	Results favour intervention.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Unclear risk	Described as double blind, method not reported.
Incomplete outcome data addressed? All outcomes	Unclear risk	Reported withdrawals.
Free of selective reporting?	Low risk	Reported adverse events. Full data reported.
Free of other bias?	Low risk	Diagnosis / assessment consistent with ACR criteria.

Goldbach-Mansky 2009

Methods	Double-blind, randomised, controlled study. Duration 24 weeks.
Participants	Randomized n=121 (*Tripterygium wilfordii* n=60; Sulfasalazine n=61), completed n=62 (*Tripterygium wilfordii* n=37, Sufasalazine n=25). Age (yr): *Tripterygium wilfordii* m=54 sd=11, Sufasalazine m=51 sd=12. M:F = 1:1.2. Inclusion: ACR criteria RA, > 6 months.
Interventions	*Tripterygium wilfordii* HF (TwHF) extract, 180 mg/day. Sufasalazine 2g/day.
Outcomes	Primary end point: 20% improvement at 24 weeks, as defined by ACR criteria (ACR 20). Secondary end points: efficacy of TwHF in achieving ACR 50 and ACR 70 responses at 24 weeks, the improvement in the European League Against Rheumatism Disease Activity Score 28 (DAS 28) measure, and a change in the Sharp–van der Heijde score of the hand and foot radiographs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Goldbach-Mansky 2009 *(Continued)*

Adequate sequence generation?	Low risk	Computer-generated, pseudo-random code (with random, permuted blocks)
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Unclear risk	Described as double blind. Patients are likely blinded, though this is not stated. "A rheumatologist or trained staff member masked to treatment allocation assessed the patients."
Incomplete outcome data addressed? All outcomes	Unclear risk	There were a large number of drop-outs, all are accounted for with reasons and they state that they used: "A protocol-specified, last-observation-carried-forward approach for handling missing data..." It does appear that they did an ITT analysis for several of the outcomes including the primary outcome and report them in the text. All tables appear to be the per-protocol analyses.
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	Baseline differences: Less women in the TwHF group (73% vs 87%); CRP appeared to be slightly higher in the TwHF group (255.2 nmol/L vs 236.2 nmol/L); Slightly higher radiographic score in the TwHF group (40.0 vs 34).There is no discussion of differences in medications other than the interventions taking throughout the study. These differences were not tested for significance.

Jantti 1989

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 13 weeks; 1 week washout, 12 weeks intervention.
Participants	Randomised n=20 (intervention n=10, control n=10), completed n=18 (intervention n=9, control n=9). Age: intervention m=50, control m=38. M:F=2:18. Inclusion: definite or classical RA, prepared to abstain from NSAIDs for 13 weeks.
Interventions	Tradename not provided, *Oenothera biennis* (evening primrose), oil, 20 mls (2x10ml, approx 9% GLA, equivalent to 1800mg of GLA), oral.
Outcomes	Pain VAS 0-100, joint score (swollen and tender joint counts), duration of morning stiffness, grip strength.
Notes	Results equivocal.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Low risk	Active intervention and placebo not distinguished by look, taste, smell or packaging.
Incomplete outcome data addressed?	Low risk	Reported withdrawals.

Jantti 1989 *(Continued)*

All outcomes		
Free of other bias?	Unclear risk	Placebo capsules contained olive oil and may not be inert. Diagnosis / assessment criteria for OA not specified.

Leventhal 1993

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 24 weeks.
Participants	Randomised n=37 (intervention n=19, control n=18), completed n=27 (intervention n=14, control n=13). Age: intervention m=58, control m=50. Inclusion: 18-80 yrs, ACR criteria RA stage I-III, using NSAIDs, not using DMARDs.
Interventions	Boracelle, *Borago officinalis* (borage seed), oil, 7.2ml (3x4x0.6ml, approx 23% GLA, equivalent to 1400mg GLA), capsules, oral.
Outcomes	Pain VAS 0-100, pain 0-4, physician global 0-4, patient global 0-4, 68 tender joint count, 66 swollen joint count, joint tenderness score 0-3, joint swelling score 0-3, duration of morning stiffness, vocational activity score 0-3, grip strength mmHg.
Notes	Results favour intervention.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported. Baseline parameters compared for significant differences.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Unclear risk	Described as double-blind, method not reported.
Incomplete outcome data addressed? All outcomes	Low risk	Reported withdrawals.
Free of selective reporting?	Low risk	Reported adverse events.
Free of other bias?	Low risk	Diagnosis / assessment consistent with ACR criteria.

Leventhal 1994

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 24 weeks.
Participants	Randomised n=34 (intervention n=14, control n=20), completed n=14 (intervention n=7, control n=7). Age m=55. Inclusion: 18-80 yr, ACR criteria RA stage I-III, using NSAIDs, DMARDs stable for past 3 months.
Interventions	Tradename not provided, *Ribes nigrum* (blackcurrant seed), oil, 10500mg (15x700mg, approx 19% GLA, equivalent to 2000mg GLA), capsules, oral.

Leventhal 1994 *(Continued)*

Outcomes	Pain VAS 0-100, pain 0-4, physician global 0-4 and VAS 0-100, patient global 0-4 and VAS 0-100, 68 tender joint count, 66 swollen joint count, joint tenderness score 0-3, joint swelling score 0-3, morning stiffness (minutes), vocational activity score 0-3, grip strength mmHg.
Notes	Results favour intervention.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported. Baseline parameters compared for significant differences.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Unclear risk	Described as double-blind, method not reported.
Incomplete outcome data addressed? All outcomes	Low risk	Reported withdrawals. Included intention-to-treat analyses.
Free of selective reporting?	Low risk	Reported adverse events.
Free of other bias?	Low risk	Diagnosis / assessment consistent with ACR criteria.

Li 2007

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 24 weeks.
Participants	Randomised n=65 (intervention n=32, control n=33), completed n=58 (intervention n=28, control n=30). Age: intervention m=50, control m=50. M:F=1:1. Inclusion: ACR criteria.
Interventions	*Ganoderma lucidum* 4g per day together with San Miao San (a combination of *Rhizoma atractylodis, Cotex phellodendri, and Radix achyranthes Bidentatae*) 2.4 grams per day.
Outcomes	Primary outcome: ACR 20% response; Secondary outcomes: changes in ACR components including tender and swollen joint count, physician's and patient's global assessment, HAQ score, and ESR or CRP level, total antioxidant power of plasma, plasma ascorbic acid concentration.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated list in blocks of 5
Allocation concealment?	Low risk	The list was generated at the Institute of Chinese Medicine, The Chinese University of Hong Kong. Study medications were dispensed as sealed packages in consecutive numbers. A research nurse was responsible for dispensing study medications. The investigators, research nurse, and participants were not aware of the treatment assignments throughout the study.

Li 2007 *(Continued)*

		Treatment codes were only broken after completion of the study.
Blinding? All outcomes	Low risk	The investigators, research nurse, and participants were not aware of the treatment assignments throughout the study. Treatment codes were only broken after completion of the study.
Incomplete outcome data addressed? All outcomes	High risk	Three participants dropped out of the placebo group (2 due to inefficacy and 1 due to emigration); Four participants dropped out of the treatment group (all due to inefficacy; three at week 8 and one at week 12)
Free of selective reporting?	Low risk	All outcomes were reported
Free of other bias?	High risk	There are a selection of herbal medicines given in the active group. Also, participants in the active group had slightly longer standing RA (9.3 years VS 7.8 years) and a larger number of participants in the active group were taking sulphasalazine (8 VS 4). None of these differences were tested for statistical differences.

McCarthy 1992

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 4 weeks.
Participants	Randomised n=7, completed n=5. Age: m=52, sd=4. Inclusion: ACR criteria RA.
Interventions	Tradename not provided, capsaicin frutescens 0.075% wv cream, topical, QID.
Outcomes	Pain VAS 0-100, morning stiffness (Landsbury 2 question method), HAQ, grip strength mmHg, swelling (PIP, DIP circumference), tenderness (delorimeter).
Notes	B:1, W:1. Placebo validity and blinding may be compromised by burning side effect of topical intervention. Small sample size, underpowered study. Results equivocal.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Described as randomised, method of randomisation incompletely reported. Described as randomised according to a previously established randomisation schedule.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Unclear risk	Described as double-blind. Active intervention and placebo not distinguished by look, taste, smell or packaging, but placebo validity and blinding possibly compromised by burning side effect of topical intervention.
Incomplete outcome data addressed? All outcomes	Unclear risk	Reported no withdrawals. Included per protocol analyses.
Free of selective reporting?	Unclear risk	Variances reported as standard error of measurement (SEM). Reported adverse events.
Free of other bias?	Low risk	Diagnosis / assessment consistent with ACR criteria.

Meier 1987

Methods	Randomised, double blind, placebo control, non-intervention control, 3 parallel groups. Duration 2 weeks.
Participants	Randomised n=15 (intervention n=5, placebo n=5, non-intervention n=5), completed n=15 (intervention n=5, placebo n=5, non-intervention control n=5). Age range 23-76 yr; intervention m=62 sd=13, control m=63 sd=16. M:F=9:6. Inclusion: ACR crtieria RA stage II or III.
Interventions	Phytodolor^{R}N, mixture of ash bark, aspen leaf, aspen bark, golden rod herb, tincture, 3x30 drops, oral.
Outcomes	Diclofenac use, pain 0-3, joint swelling 0-3.
Notes	Results equivocal. Groups dissimilar at baseline. Change (reduction) in diclofenac use and pain was greatest in intervention group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, method of randomisation incompletely reported. Described as randomised according to a previously established randomisation schedule.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Unclear risk	Described as double-blind, method not reported. In other studies of Phytodolor® N, active intervention and placebo not distinguished by look, taste, smell or packaging. Non-intervention control group not blinded.
Incomplete outcome data addressed? All outcomes	Unclear risk	Reported no withdrawals.
Free of selective reporting?	Low risk	Full data reported.
Free of other bias?	Unclear risk	Diagnosis / assessment consistent with ACR criteria. Groups dissimilar at baseline.

Mur 2002

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 52 weeks; 24 weeks RCT, 28 weeks open trial.
Participants	Randomised n=40 (intervention n=21, control n=19), completed n=38 (intervention n=20, control n=18). Age: intervention m=53.1 sd=13.4, control m=54.9 sd=13.5. M:F intervention=20:1, control=15:4. Inclusion: ACR criteria RA stage II or III, DMARDs (sulfasalazine or hydrochloroquine) for 6 months, dose stable for past 6 weeks.
Interventions	Krallendorn, *Uncaria tomentosa* (cat's claw), aqueous dry extract of pentacylcic alkaloid chemotype, 60mg (3x20mg), capsules, oral.
Outcomes	66 swollen joint count, 68 tender joint count, Ritchie index, pain VAS 0-100, disease activity VAS 0-100, morning stiffness 0-5, HAQ (baseline and week 24 only).

Mur 2002 *(Continued)*

Notes	Results favour intervention.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Low risk	Active intervention and placebo not distinguished by look, taste, smell or packaging.
Incomplete outcome data addressed? All outcomes	Low risk	Reported withdrawals.
Free of selective reporting?	Low risk	Reported adverse events.
Free of other bias?	Low risk	Diagnosis / assessment consistent with ACR criteria.

Pattrick 1989

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 6 weeks.
Participants	Randomised n=41 (intervention n=20, control n=21), completed n=40 (intervention n=20, control n=20). Age range 28-65 yr. Inclusion: female, aged under 65 yr, classical or definite RA, poor symptomatic control.
Interventions	*Tanacetum parthenium* (feverfew), (70-86mg), oral.
Outcomes	Morning stiffness (minutes), inactivity stiffness, pain VAS 0-10, grip strength mmHg, Ritchie index, patient global, physician global.
Notes	Results equivocal.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Low risk	Active intervention and placebo not distinguished by look, taste, smell or packaging.
Incomplete outcome data addressed? All outcomes	Low risk	Reported withdrawals.

Pattrick 1989 *(Continued)*

Free of selective reporting?	Low risk	Reported adverse events.
Free of other bias?	Low risk	Diagnosis / assessment consistent with ACR criteria.

Sandler 1998

Methods	Randomised, double blind, placebo control, multi-centre trial, 2 parallel groups. Duration 12 weeks.
Participants	Randomised n=78 (all centres). Data from one centre (Ratingen) available for analysis; randomised n=37 (intervention n=18, control n=19), completed n=36 (intervention n=17, control n=19). Inclusion: Active RA, at least one painful join, stable corticosteroids.
Interventions	*Boswellia serrata,* 1200-3600mg, (3x400mg to 3x3x400mg), tablets, oral.
Outcomes	Ritchie index, pain VAS 0-10, NSAID consumption, patient global VAS 0-10.
Notes	Results equivocal.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Low risk	Active intervention and placebo not distinguished by look, taste, smell or packaging.
Incomplete outcome data addressed? All outcomes	Low risk	Reported withdrawals.
Free of selective reporting?	Low risk	Reported adverse events. Non-normal data reported as median and range.
Free of other bias?	Low risk	Diagnosis / assessment consistent with ACR criteria. Reported ethics committee approval.

Song 2007

Methods	Randomised, double blind, active control (celecoxib), 2 parallel group, multicentre trial. Duration 6 weeks.
Participants	Randomised n=183 (intervention n=91, control n=92), completed n=168 (intervention n=84, control n=84). Age (yr): intervention m=52.1 sd=12.6, control m=51.7 sd=10.9. M:F=1:8. Inclusion: ACR criteria RA stage I, II or III, disease duration >3 months, stable medications, pain (VAS 0-100) increase of 10+mm, and 6+ tender joints, and 3+ swollen joints after NSAID washout.
Interventions	SKI306X, extract mixture of *Clematis mandshurica*, *Prunella vulgaris*, *Trichosanthes kirilowii*, 600mg (3x200mg), tablets, oral.

Song 2007 *(Continued)*

Outcomes	Pain (VAS 0-100), rescue medication use (acetaminophen), ACR20.
Notes	Results indicate that intervention is not inferior to active control.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomised to one of two groups using a computer generated random number sequence. Baseline parameters compared for significant differences.
Allocation concealment?	Low risk	Adequate
Blinding? All outcomes	Low risk	Active intervention and placebo not distinguished by look, taste, smell or packaging.
Incomplete outcome data addressed? All outcomes	Low risk	Reported withdrawals. Included intention-to-treat and per protocol analyses.
Free of selective reporting?	Low risk	Reported adverse events. Confirmatory study.
Free of other bias?	Low risk	Diagnosis / assessment consistent with ACR criteria. Reported ethics committee approval.

Tao 1989

Methods	Randomised, double blind, placebo control, 2 groups crossover study. Duration 16 weeks: 12 weeks intervention 1st arm, 4 weeks intervention 2nd arm.
Participants	Randomised n=70, completed first arm n=58. Age: m=47 yr. Inclusion: classic or definite RA of at least 6 months duration with poor response to NSAIDs for at least 2 months.
Interventions	*Tripterygium wilfordii* hook F (thunder god vine), ethanolic extract, 60mg, capsules, oral.
Outcomes	Joint tenderness and swelling, grip strength, 15 metre walking time, morning stiffness, physician global, patient global.
Notes	Results favour intervention for short-term use (12 weeks), with cautions regarding adverse events.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Unclear risk	Described as double-blind, method not reported.
Incomplete outcome data addressed?	Low risk	Reported withdrawals.

Tao 1989 *(Continued)*

All outcomes		
Free of selective reporting?	Low risk	Reported adverse events.
Free of other bias?	Low risk	Reported ethics committee approval.

Tao 2002

Methods	Randomised, double blind, placebo control, 3 parallel groups. Duration 20 weeks.
Participants	Randomised n=35 (low dose n=12, high dose n=11, control n=12), completed 4 weeks n=32, completed n=21. Age: low dose m=54 sd=12, high dose m=57 sd=8, control m=51 sd=12. Inclusion: ACR criteria RA stage II-IV, for at least 1 year, active disease, 2+ swollen joints, and 2 of 6+ tender joints, morning stiffness >30min, ESR >28mm/h.
Interventions	*Tripterygium wilfordii* hook F (thunder god vine), ethanolic extract, low dose=180mg; high dose=360mg, capsules, oral.
Outcomes	ACR20, ACR50, ACR70, ESR, CRP, RF.
Notes	Results favour intervention.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported. Baseline parameters compared for significant differences.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Low risk	Active intervention and placebo not distinguished by look, taste, smell or packaging.
Incomplete outcome data addressed? All outcomes	Low risk	Reported withdrawals. Included intention-to-treat analyses.
Free of selective reporting?	Low risk	Reported adverse events.
Free of other bias?	Low risk	Diagnosis / assessment consistent with ACR criteria. Reported ethics committee approval.

Watson 1993

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 6 weeks.
Participants	Randomised n=50. Withdrawals not reported. Age: RA group m=40, health controls m=20 yr. Inclusion: definite RA, receiving only NSAIDs.

Watson 1993 *(Continued)*

Interventions	Tradename not provided, Ribes nigrum, (blackcurrant seed), oil, 3000mg (6x500mg, approx 19% GLA, equivalent to 525mg GLA), capsules, oral.
Outcomes	Morning stiffness, grip strength, Ritchie index, pain score, patient global.
Notes	Results equivocal.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Unclear risk	Described as double-blind, method not reported.
Incomplete outcome data addressed? All outcomes	High risk	Withdrawals not reported.
Free of selective reporting?	High risk	Adverse events not reported.
Free of other bias?	High risk	Data for clinical outcomes not reported.

Zurier 1996

Methods	Randomised, double blind, placebo control, 2 parallel groups. Duration 6 months (followed by 6 month single-blind phase, followed by 3 month placebo phase).
Participants	Randomised n=56, completed n=41. Age: m=56 yr. Inclusion: ACR criteria RA stage I-III, 1st line treatment stable for past 1 month, 2nd line treatment stable for past 3 months.
Interventions	GLA-70, *Borago officinalis* (borage seed), oil, 4ml (8x0.5ml, approx 70% GLA, equivalent to 2800mg GLA), capsules, oral.
Outcomes	Pain VAS 0-100, pain 0-4, physician global, patient global, joint swelling and tenderness, morning stiffness, grip strength, health assessment questionnaire, ACR20 (6 and 12 month follow up).
Notes	Results favour intervention.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised, method not reported. Baseline parameters compared for significant differences.
Allocation concealment?	Unclear risk	Unclear
Blinding? All outcomes	Unclear risk	Described as double blind, method not reported.

Zurier 1996 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Reported withdrawals.
Free of selective reporting?	Unclear risk	After communication with author, unable to confirm SD for morning stiffness in GLA group (table 2) therefore these data excluded from analysis.
Free of other bias?	Unclear risk	Placebo capsules contained sunflower oil and may not be inert. Diagnosis / assessment consistent with ACR criteria.

Unless otherwise stated, all oral medications are reported as total daily doses, which may have been administered in single or divided doses. * Indicates that the trade name was not provided in the manuscript, but has been determined through communication with the manufacturing company noted in the acknowledgements.
ARA: American Rheumatism Association
ACR: American College of Rheumatology
EULAR: European league Against Rheumatism
Allocation concealment may be listed as "unclear" if: (a) the authors reported adherence to the ICH Good Clinical Practice (GCP) guidelines did not describe the method of allocation concealment used, or (b) the reviewers were unable to agree upon the adequacy of allocation concealment as reported.
Unless subscales are named, outcome measures (eg: HAQ, SF-36, ACR20) were used in entirety. Unless specified, all measures were used, scaled, and scored to ACR/EULAR standards.
ACR core set of disease activity measures comprises tender joint count, swollen joint count, patient's assessment of pain, patient's and physician's global assessment of disease activity, patient's assessment of physical function (global assessment or HAQ-DI score), and laboratory investigations of one acute-phase reactant (ESR or C-reactive protein). ACR20 is defined as 20% improvements in tender joint count, swollen joint count, and three of the other disease activity measures. ACR50 and ACR70 are similarly defined, but at 50% and 70% thresholds.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anonymous 1993	Discussion paper.
Biswas 1997	Not placebo controlled.
Borigini 1996	Not randomised controlled trial.
Chrubasik 1998	Review paper.
Darlington 1987	Not placebo controlled.
DeLuca 1995	Review paper.
Dharmananda 1985	Discussion paper.
Falch 1997	Discussion paper.
Gendo 1997	Discussion paper.
Grahame 1981	Not randomised controlled trial.
Guo 1986	Not randomised controlled trial.
Hansen 1983	Not randomised controlled trial.

Study	Reason for exclusion
Hanyu 1989	Not randomised controlled trial.
Huber 1991	RA subgroup not distinguishable.
Jacobs 1991	Not a herbal intervention.
Jantti 1989b	No clinical outcomes reported.
Kou 1997	Case series, not a randomised controlled trial.
Larsen 1989	Not truly herbal intervention.
Linsheng 1997	Not randomised controlled trial.
Lipsky 1997	Review paper.
Loew 1996	Not a randomised controlled trial. Primary measures not consistent with the topic of this review.
Matsuta 1992	Discussion paper.
Mills 1996	RA subgroup not distinguishable.
Ohkaya 1988	Abstract only. Full text unavailable.
Ohkaya 1989	Abstract only. Full text unavailable.
Ramakrishanamacharya	Not randomised controlled trial.
Ramm 1996	Not randomised controlled trial.
Reuss 1981	Discussion paper.
Sagar 1988	Not randomised controlled trial.
Saley 1987	Not randomised controlled trial.
Srivastava 1989	Not randomised controlled trial.
Tao 1987	Not randomised controlled trial.
Vyas 1987	Not randomised controlled trial.
Wang 1985	Not randomised controlled trial.
Xu 1996	Not placebo controlled.
Yan 1985	Case series, not a randomised controlled trial.
Zell 1993	Not randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

Shamsi 2009

Trial name or title	A clinical trial to study the effects of a herbal drug Qurs Mufasil in patients with joint pain (Arthritis)
Methods	Randomized, parallel group, placebo controlled trial
Participants	Patients of 20-70 years of age fulfilling the criteria of American College of Rheumatology (ACR) for the diagnosis of Rheumatoid Arthritis, who had never received disease modifying anti/Rheumatoid Drugs (DMARDs). Presence of active disease as defined by the presence of >, 6 tender joints and >; 6 swollen joints.
Interventions	Qurs Mufasil:1000 mg daily for 3 months Placebo:1000 mg twice daily for 3 months
Outcomes	Reduction in Swollen Joint Count,Tender Joint Count, Intensity of Pain-VAS (0-100), Morning Stiffness, ESR and CRP Timepoint:4,8,12 weeks; Improvement in quality of life as assessed by Health Assessment Questionnaire (HAQ) Time Point: 3 months
Starting date	01-03-2003
Contact information	Yasmeen Shamsi Majeedia Hospital, Jamia Hamdard, 110062 New Delhi, India Email: yasmeen.ijum@gmail.com
Notes	Recruitment complete; http://apps.who.int/trialsearch/Trial.aspx?TrialID=CTRI/2009/091/000746

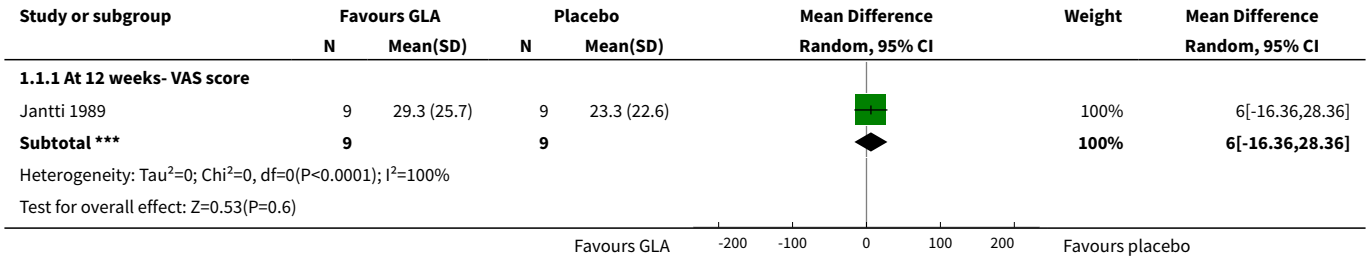
DATA AND ANALYSES

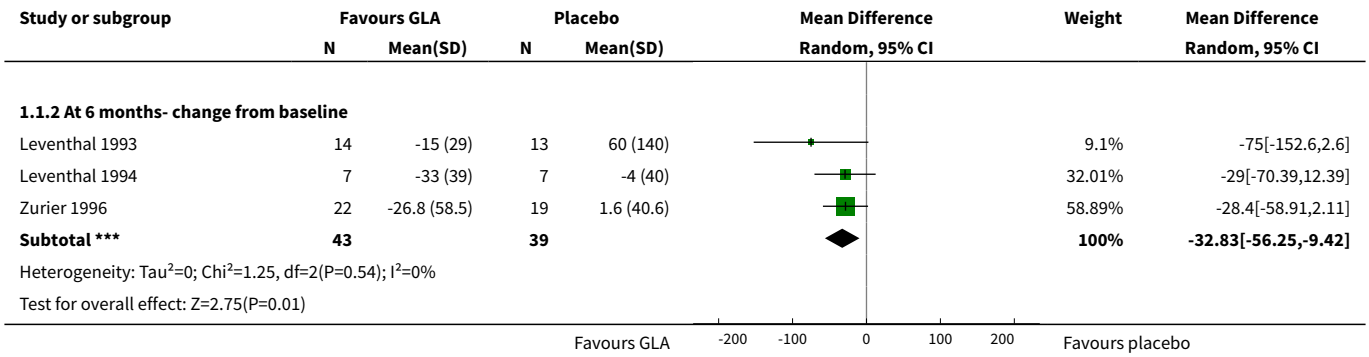
Comparison 1. Gamma-linolenic acid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain VAS 0-100	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 At 12 weeks- VAS score	1	18	Mean Difference (IV, Random, 95% CI)	6.00 [-16.36, 28.36]
1.2 At 6 months- change from baseline	3	82	Mean Difference (IV, Random, 95% CI)	-32.83 [-56.25, -9.42]
2 Morning stiffness (minutes)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 At 12 weeks- minutes	1	18	Mean Difference (IV, Random, 95% CI)	-5.0 [-41.68, 31.68]
2.2 At 6 months- change from baseline	3	82	Mean Difference (IV, Random, 95% CI)	-55.07 [-76.87, -33.27]
3 68 tender joint count percentage change from baseline	3	82	Mean Difference (IV, Random, 95% CI)	-53.80 [-95.61, -12.00]

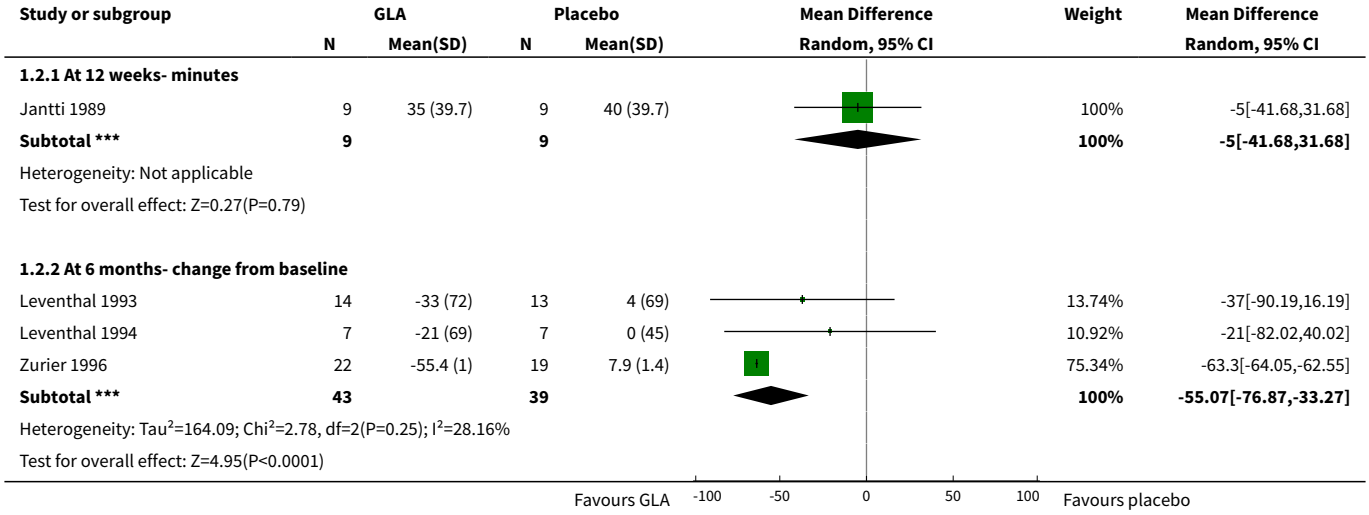
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 66 swollen joint count percentage change from baseline	3	82	Mean Difference (IV, Fixed, 95% CI)	-14.43 [-31.43, 2.56]
5 Joint tenderness (0 to 3) percentage change from baseline	3	82	Mean Difference (IV, Random, 95% CI)	-56.64 [-98.10, -15.17]
6 Joint swelling (0 to 3) percentage change from baseline	3	82	Mean Difference (IV, Random, 95% CI)	-24.02 [-70.80, 22.76]
7 HAQ disability score percentage change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Patient global (0 to 4) percentage change from baseline	3	82	Mean Difference (IV, Random, 95% CI)	-20.87 [-39.43, -2.31]
9 Physician global (0 to 4) percentage change from baseline	3	82	Mean Difference (IV, Random, 95% CI)	-21.28 [-70.52, 27.95]
10 Participants (n) reported reduced NSAID use	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 At 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 At 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Participants (n) reported adverse events	2	61	Risk Ratio (M-H, Random, 95% CI)	4.24 [0.78, 22.99]
11.1 GLA 540mg	1	34	Risk Ratio (M-H, Random, 95% CI)	5.59 [0.29, 108.38]
11.2 GLA 1400mg+	1	27	Risk Ratio (M-H, Random, 95% CI)	3.71 [0.47, 29.06]
12 Participants (n) withdrawn due to worsening disease	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Gamma-linolenic acid versus placebo, Outcome 1 Pain VAS 0-100.

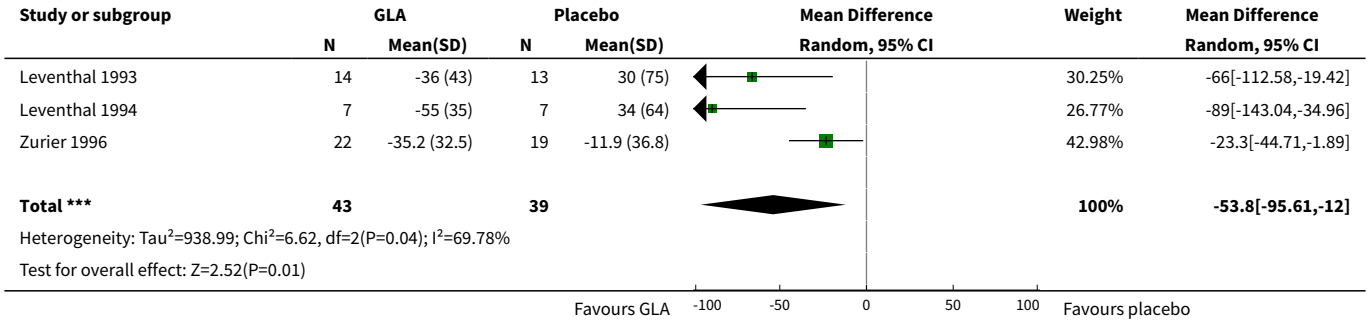




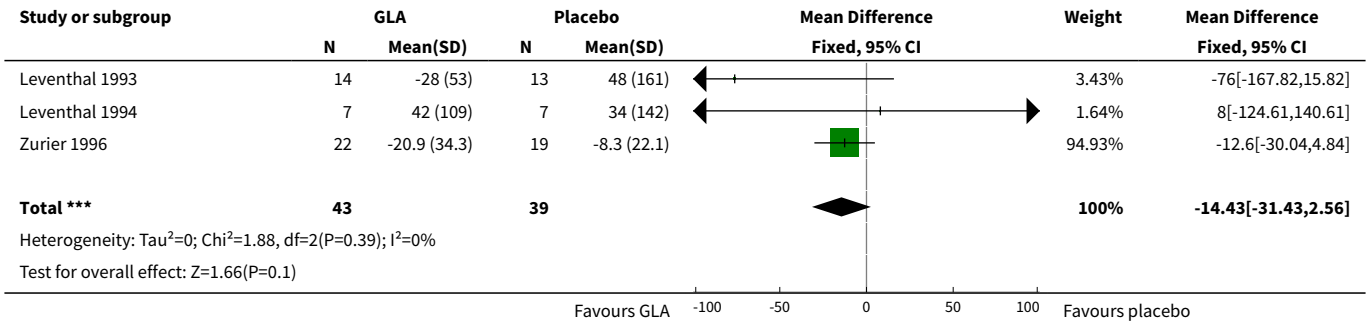
Analysis 1.2. Comparison 1 Gamma-linolenic acid versus placebo, Outcome 2 Morning stiffness (minutes).



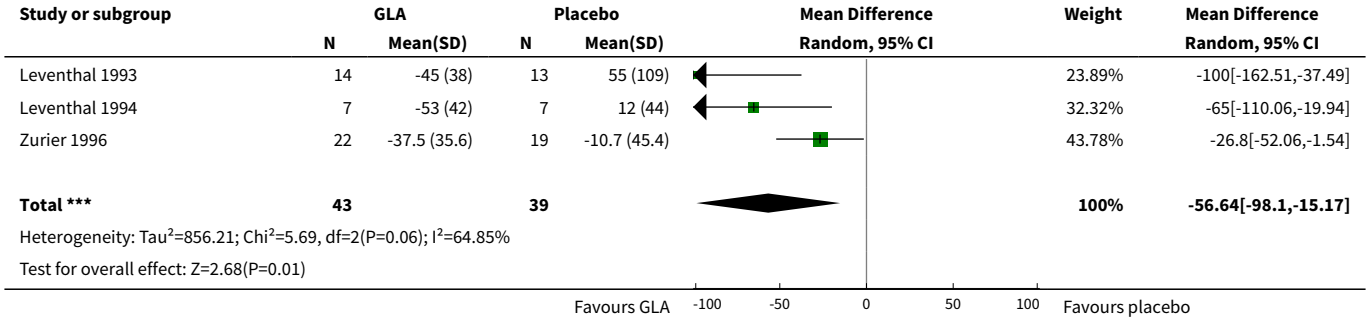
Analysis 1.3. Comparison 1 Gamma-linolenic acid versus placebo, Outcome 3 68 tender joint count percentage change from baseline.



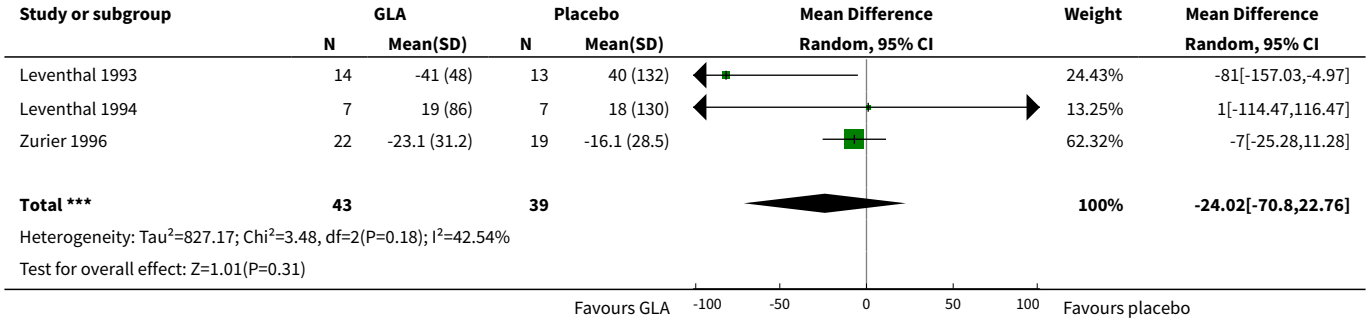
Analysis 1.4. Comparison 1 Gamma-linolenic acid versus placebo, Outcome 4 66 swollen joint count percentage change from baseline.



Analysis 1.5. Comparison 1 Gamma-linolenic acid versus placebo, Outcome 5 Joint tenderness (0 to 3) percentage change from baseline.



Analysis 1.6. Comparison 1 Gamma-linolenic acid versus placebo, Outcome 6 Joint swelling (0 to 3) percentage change from baseline.



Analysis 1.7. Comparison 1 Gamma-linolenic acid versus placebo, Outcome 7 HAQ disability score percentage change from baseline.

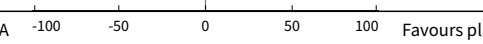
Study or subgroup	GLA N	GLA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Zurier 1996	22	-11 (19)	19	4.8 (17.9)		-15.75[-27.06,-4.44]

Analysis 1.8. Comparison 1 Gamma-linolenic acid versus placebo, Outcome 8 Patient global (0 to 4) percentage change from baseline.

Study or subgroup	GLA N	GLA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Leventhal 1993	14	-21 (33)	13	30 (85)		14.16%	-51[-100.33,-1.67]
Leventhal 1994	7	-1 (38)	7	24 (61)		12.16%	-25[-78.24,28.24]
Zurier 1996	22	-18.9 (35.6)	19	-4.5 (34.9)		73.69%	-14.4[-36.02,7.22]
Total ***	**43**		**39**			**100%**	**-20.87[-39.43,-2.31]**
Heterogeneity: Tau^2=0; Chi^2=1.8, df=2(P=0.41); I^2=0%							
Test for overall effect: Z=2.2(P=0.03)							

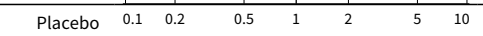
Analysis 1.9. Comparison 1 Gamma-linolenic acid versus placebo, Outcome 9 Physician global (0 to 4) percentage change from baseline.

Study or subgroup	GLA N	GLA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Leventhal 1993	14	-33 (28)	13	43 (81)		30.18%	-76[-122.41,-29.59]
Leventhal 1994	7	0 (56)	7	7 (19)		31.09%	-7[-50.81,36.81]
Zurier 1996	22	2.1 (34.6)	19	-7.8 (29.3)		38.72%	9.9[-9.66,29.46]
Total ***	**43**		**39**			**100%**	**-21.28[-70.52,27.95]**
Heterogeneity: Tau^2=1529.99; Chi^2=11.2, df=2(P=0); I^2=82.15%							
Test for overall effect: Z=0.85(P=0.4)							

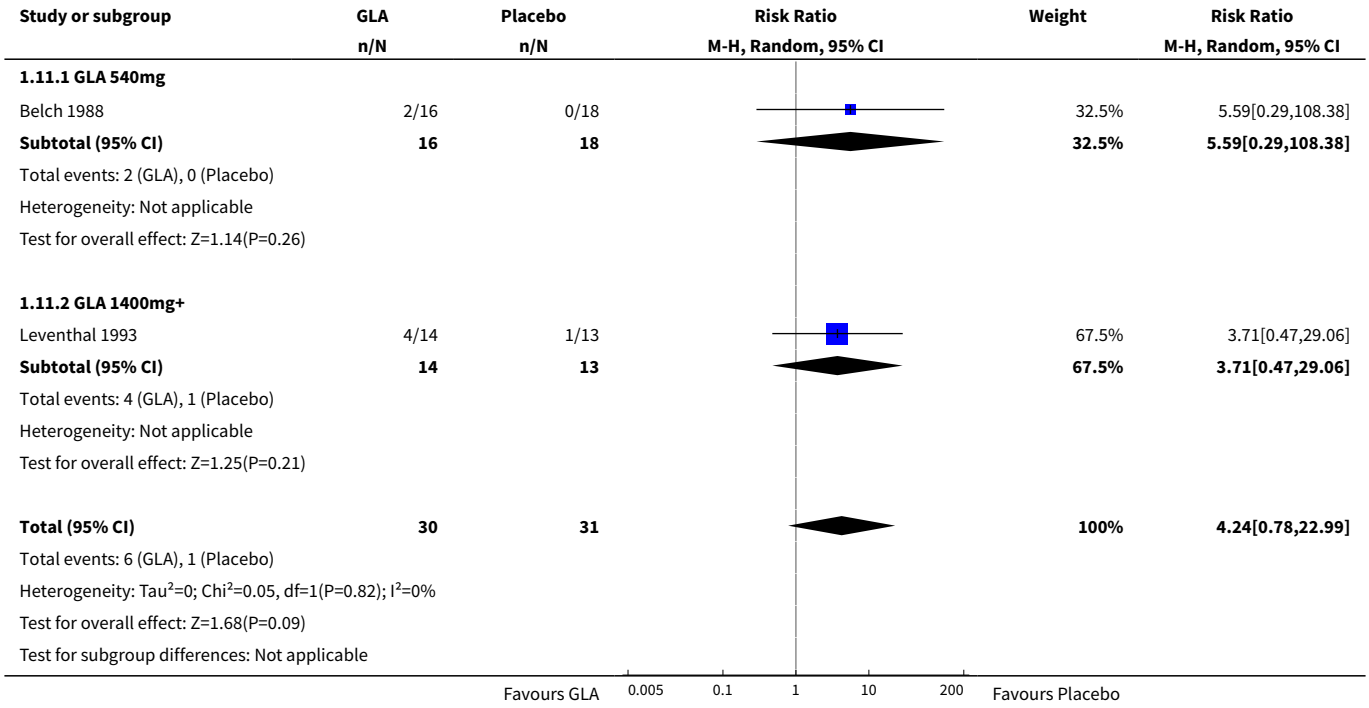


Analysis 1.10. Comparison 1 Gamma-linolenic acid versus placebo, Outcome 10 Participants (n) reported reduced NSAID use.

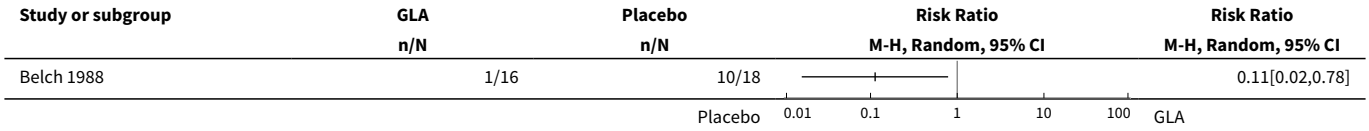
Study or subgroup	GLA n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.10.1 At 6 months				
Brzeski 1991	3/13	3/17		1.31[0.31,5.45]
1.10.2 At 12 months				
Belch 1988	11/15	5/15		2.2[1.01,4.79]



Analysis 1.11. Comparison 1 Gamma-linolenic acid versus placebo, Outcome 11 Participants (n) reported adverse events.



Analysis 1.12. Comparison 1 Gamma-linolenic acid versus placebo, Outcome 12 Participants (n) withdrawn due to worsening disease.



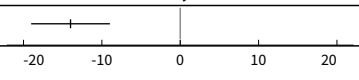
Comparison 2. *Tripterygium wilfordii* Hook F 60 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Joint tenderness (0 to 3)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 60 swollen joint count	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Morning stiffness (hours)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Grip strength (mmHg)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 15 metre walking time (seconds)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

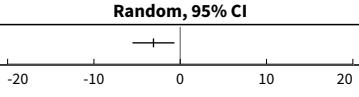
Analysis 2.1. Comparison 2 *Tripterygium wilfordii* Hook F 60 mg versus placebo, Outcome 1 Joint tenderness (0 to 3).

Study or subgroup	TwHF 60 mg N	TwHF 60 mg Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Tao 1989	27	7.9 (6.9)	31	21.9 (12.2)		-14[-19.02,-8.98]



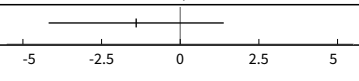
Analysis 2.2. Comparison 2 *Tripterygium wilfordii* Hook F 60 mg versus placebo, Outcome 2 60 swollen joint count.

Study or subgroup	TwHF 60 mg N	TwHF 60 mg Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Tao 1989	27	4.3 (3.2)	31	7.4 (6)		-3.1[-5.53,-0.67]



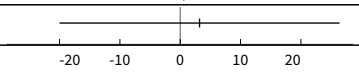
Analysis 2.3. Comparison 2 *Tripterygium wilfordii* Hook F 60 mg versus placebo, Outcome 3 Morning stiffness (hours).

Study or subgroup	TwHF 60 mg N	TwHF 60 mg Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Tao 1989	27	0.9 (1.2)	31	2.3 (7.8)		-1.4[-4.18,1.38]



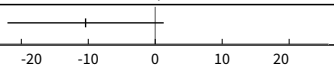
Analysis 2.4. Comparison 2 *Tripterygium wilfordii* Hook F 60 mg versus placebo, Outcome 4 Grip strength (mmHg).

Study or subgroup	TwHF 60 mg N	TwHF 60 mg Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Tao 1989	27	84.4 (39)	31	81.2 (51)		3.2[-20.01,26.41]



Analysis 2.5. Comparison 2 *Tripterygium wilfordii* Hook F 60 mg versus placebo, Outcome 5 15 metre walking time (seconds).

Study or subgroup	TwHF 60 mg		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Tao 1989	27	20.6 (7.7)	31	31 (32.1)		-10.4[-22.07,1.27]

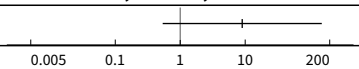


Comparison 3. *Tripterygium wilfordii* Hook F 180 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20 responders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 ACR50 responders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Participants (n) reported adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

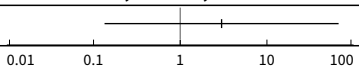
Analysis 3.1. Comparison 3 *Tripterygium wilfordii* Hook F 180 mg versus placebo, Outcome 1 ACR20 responders.

Study or subgroup	TwHF 180 mg	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Tao 2002	4/12	0/12		9[0.54,150.81]



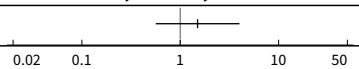
Analysis 3.2. Comparison 3 *Tripterygium wilfordii* Hook F 180 mg versus placebo, Outcome 2 ACR50 responders.

Study or subgroup	TwHF 180 mg	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Tao 2002	1/12	0/12		3[0.13,67.06]



Analysis 3.3. Comparison 3 *Tripterygium wilfordii* Hook F 180 mg versus placebo, Outcome 3 Participants (n) reported adverse events.

Study or subgroup	TwHF 180 mg	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Tao 2002	6/12	4/12		1.5[0.56,4]

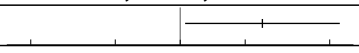


Comparison 4. *Triptrygium wilfordii* Hook F 360 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20 responders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 ACR50 responders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Participants (n) reported adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 *Triptrygium wilfordii* Hook F 360 mg versus placebo, Outcome 1 ACR20 responders.

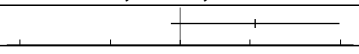
Study or subgroup	TwHF 360 mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Tao 2002	8/11	0/12		18.42[1.19,285.82]



Favours placebo — Favours TWHF

Analysis 4.2. Comparison 4 *Triptrygium wilfordii* Hook F 360 mg versus placebo, Outcome 2 ACR50 responders.

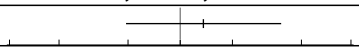
Study or subgroup	TwHF 360 mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Tao 2002	5/11	0/12		11.92[0.73,193.38]



Favours placebo — Favours TWHF

Analysis 4.3. Comparison 4 *Triptrygium wilfordii* Hook F 360 mg versus placebo, Outcome 3 Participants (n) reported adverse events.

Study or subgroup	TwHF 360 mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Tao 2002	5/11	4/12		1.36[0.49,3.82]



Favours TWHF — Favours placebo

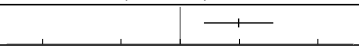
Comparison 5. *Tripterygium wilfordii* Hook F 180 mg versus sulfasalazine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20 responders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 ACR50 responders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Improvement more than 0.3 units on HAQ	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Participants (n) reported adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Participants (n) withdrawn due to adverse events	1	121	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.19, 0.94]

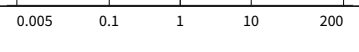
Analysis 5.1. Comparison 5 *Tripterygium wilfordii* Hook F 180 mg versus sulfasalazine, Outcome 1 ACR20 responders.

Study or subgroup	TwHF 180 mg n/N	Sulfasalazine n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Goldbach-Mansky 2009	39/60	20/61		1.98[1.32,2.97]



Analysis 5.2. Comparison 5 *Tripterygium wilfordii* Hook F 180 mg versus sulfasalazine, Outcome 2 ACR50 responders.

Study or subgroup	TwHF 180 mg n/N	Sulfasalazine n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Goldbach-Mansky 2009	20/60	1/61		20.33[2.82,146.75]



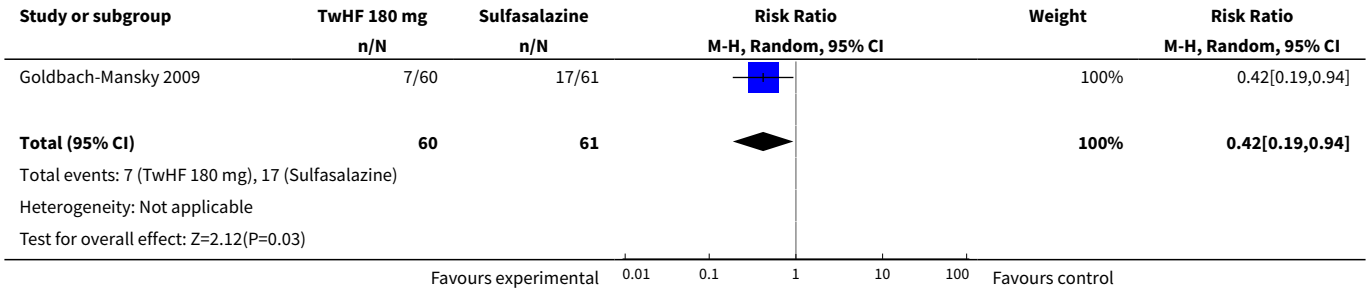
Analysis 5.3. Comparison 5 *Tripterygium wilfordii* Hook F 180 mg versus sulfasalazine, Outcome 3 Improvement more than 0.3 units on HAQ.

Study or subgroup	TwHF 180 mg n/N	Sulfasalazine n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Goldbach-Mansky 2009	21/60	7/61		3.05[1.4,6.64]

Analysis 5.4. Comparison 5 *Tripterygium wilfordii* Hook F 180 mg versus sulfasalazine, Outcome 4 Participants (n) reported adverse events.

Study or subgroup	TwHF 180 mg n/N	Sulfasalazine n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Goldbach-Mansky 2009	53/60	55/61		0.98[0.87,1.11]

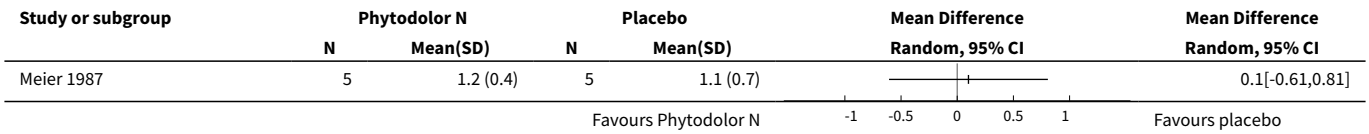
Analysis 5.5. Comparison 5 *Tripterygium wilfordii* Hook F 180 mg versus sulfasalazine, Outcome 5 Participants (n) withdrawn due to adverse events.



Comparison 6. Phytodolor N versus placebo

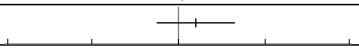
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (0 to 3) at 2 weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Joint swelling (0 to 3) at 2 weeks	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3 Morning stiffness (minutes) at 12 months	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4 Ritchie index at 12 months	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5 Cumulative NSAID use (diclofenac)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 At 1 month (tablets)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 At 12 months (tablets)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Phytodolor N versus placebo, Outcome 1 Pain (0 to 3) at 2 weeks.



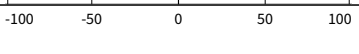
Analysis 6.2. Comparison 6 Phytodolor N versus placebo, Outcome 2 Joint swelling (0 to 3) at 2 weeks.

Study or subgroup	Phytodolor N		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Meier 1987	5	1 (0.9)	5	0.6 (0.5)		0%	0.4[-0.5,1.3]



Analysis 6.3. Comparison 6 Phytodolor N versus placebo, Outcome 3 Morning stiffness (minutes) at 12 months.

Study or subgroup	Phytodolor N		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Eberl 1988	20	54.5 (54.6)	16	30.6 (29.2)		0%	23.9[-3.98,51.78]

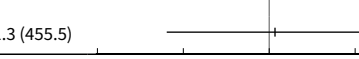


Analysis 6.4. Comparison 6 Phytodolor N versus placebo, Outcome 4 Ritchie index at 12 months.

Study or subgroup	Phytodolor N		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Eberl 1988	20	19.1 (3)	16	22.1 (5.3)		0%	-3[-5.91,-0.09]

Analysis 6.5. Comparison 6 Phytodolor N versus placebo, Outcome 5 Cumulative NSAID use (diclofenac).

Study or subgroup	Phytodolor N		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
6.5.1 At 1 month (tablets)						
Eberl 1988	20	116.8 (42.6)	16	106 (36.4)		10.8[-15.02,36.62]
6.5.2 At 12 months (tablets)						
Eberl 1988	20	1268.1 (507.4)	16	1251.3 (455.5)		16.8[-298.26,331.86]



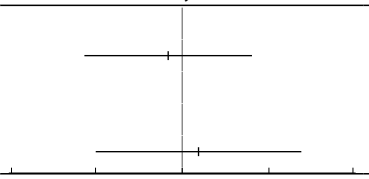
Comparison 7. SKI306X versus celecoxib

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain VAS 0-100 change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 At 3 weeks	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 At 6 weeks	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 ACR20 responders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 At 3 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 At 6 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Participants (n) reported adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

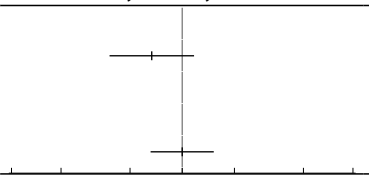
Analysis 7.1. Comparison 7 SKI306X versus celecoxib, Outcome 1 Pain VAS 0-100 change from baseline.

Study or subgroup	SKI306X N	SKI306X Mean(SD)	Celecoxib N	Celecoxib Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
7.1.1 At 3 weeks						
Song 2007	87	13.6 (16.6)	87	14.5 (15.9)		-0.81[-5.64,4.02]
7.1.2 At 6 weeks						
Song 2007	87	18.8 (20.8)	87	17.9 (19.1)		0.94[-4.99,6.87]



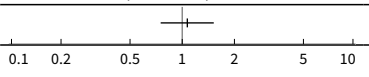
Analysis 7.2. Comparison 7 SKI306X versus celecoxib, Outcome 2 ACR20 responders.

Study or subgroup	SKI306X n/N	Celecoxib n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.2.1 At 3 weeks				
Song 2007	16/87	24/87		0.67[0.38,1.17]
7.2.2 At 6 weeks				
Song 2007	29/87	29/87		1[0.66,1.52]



Analysis 7.3. Comparison 7 SKI306X versus celecoxib, Outcome 3 Participants (n) reported adverse events.

Study or subgroup	SKI306X n/N	Celecoxib n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Song 2007	38/91	36/92		1.07[0.75,1.52]

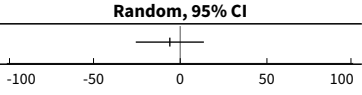


Comparison 8. *Salix purpurea* x daphnoides (willow bark) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain VAS 0-100 change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 28 tender joint count change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 28 swollen joint count change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Patient assessment of efficacy VAS 0-100 change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Physician assessment of effiacy VAS 0-100 change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 ACR20 responders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 HAQ disability index change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 SF-36 physical component summary score change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 SF-36 mental component summary score change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

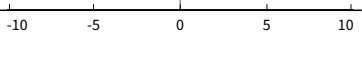
Analysis 8.1. Comparison 8 *Salix purpurea* x daphnoides (willow bark) versus placebo, Outcome 1 Pain VAS 0-100 change from baseline.

Study or subgroup	Willow bark N	Willow bark Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Biegert 2004	13	-8 (24)	13	-2 (27)		-6[-25.64,13.64]



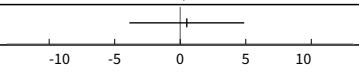
Analysis 8.2. Comparison 8 *Salix purpurea* x daphnoides (willow bark) versus placebo, Outcome 2 28 tender joint count change from baseline.

Study or subgroup	Willow bark N	Willow bark Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Biegert 2004	13	-1 (6.7)	13	-2.1 (2.8)		1.1[-2.85,5.05]



Analysis 8.3. Comparison 8 *Salix purpurea* x daphnoides (willow bark) versus placebo, Outcome 3 28 swollen joint count change from baseline.

Study or subgroup	Willow bark N	Willow bark Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Biegert 2004	13	-0.7 (7.4)	13	-1.2 (3.2)		0.5[-3.88,4.88]



Analysis 8.4. Comparison 8 *Salix purpurea* x daphnoides (willow bark) versus placebo, Outcome 4 Patient assessment of efficacy VAS 0-100 change from baseline.

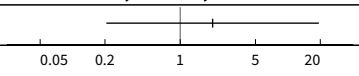
Study or subgroup	Willow bark N	Willow bark Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Biegert 2004	13	3 (17)	13	2 (25)		1[-15.43,17.43]

Analysis 8.5. Comparison 8 *Salix purpurea* x daphnoides (willow bark) versus placebo, Outcome 5 Physician assessment of effiacy VAS 0-100 change from baseline.

Study or subgroup	Willow bark N	Willow bark Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Biegert 2004	13	8 (23)	13	-2 (16)		10[-5.23,25.23]

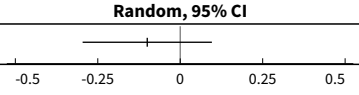
Analysis 8.6. Comparison 8 *Salix purpurea* x daphnoides (willow bark) versus placebo, Outcome 6 ACR20 responders.

Study or subgroup	Willow bark n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Biegert 2004	2/13	1/13		2[0.21,19.44]



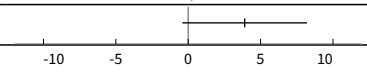
Analysis 8.7. Comparison 8 *Salix purpurea* x daphnoides (willow bark) versus placebo, Outcome 7 HAQ disability index change from baseline.

Study or subgroup	Willow bark N	Willow bark Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Biegert 2004	13	0 (0.3)	13	0.1 (0.2)		-0.1[-0.3,0.1]



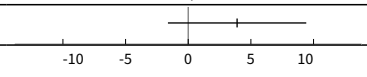
Analysis 8.8. Comparison 8 *Salix purpurea* x daphnoides (willow bark) versus placebo, Outcome 8 SF-36 physical component summary score change from baseline.

Study or subgroup	Willow bark N	Willow bark Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Biegert 2004	13	2.6 (5.4)	13	-1.3 (5.8)		3.9[-0.41,8.21]



Analysis 8.9. Comparison 8 *Salix purpurea* x daphnoides (willow bark) versus placebo, Outcome 9 SF-36 mental component summary score change from baseline.

Study or subgroup	Willow bark N	Willow bark Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Biegert 2004	13	0.6 (9)	13	-3.3 (4.7)		3.9[-1.62,9.42]

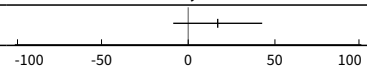


Comparison 9. Feverfew versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Grip strength (mmHg) at 6 weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Participants (n) reported adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9 Feverfew versus placebo, Outcome 1 Grip strength (mmHg) at 6 weeks.

Study or subgroup	Feverfew N	Feverfew Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Pattrick 1989	20	110 (49)	20	93 (32)		17[-8.65,42.65]



Analysis 9.2. Comparison 9 Feverfew versus placebo, Outcome 2 Participants (n) reported adverse events.

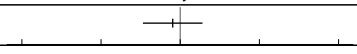
Study or subgroup	Feverfew n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Pattrick 1989	1/20	1/21		1.05[0.07,15.68]

Comparison 10. RA-1 versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain VAS 0-100 change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 68 tender joint count change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 66 swollen joint count change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Modified HAQ (Pune) change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Patient global (1 to 5) change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Physician global (1 to 5) change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 ACR20 responders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 ACR50 responders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

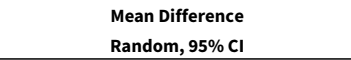
Analysis 10.1. Comparison 10 RA-1 versus placebo, Outcome 1 Pain VAS 0-100 change from baseline.

Study or subgroup	RA-1 N	RA-1 Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Chopra 2000	89	-1.4 (2.6)	93	-1.2 (2.6)		-0.19[-0.94,0.56]



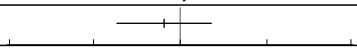
Analysis 10.2. Comparison 10 RA-1 versus placebo, Outcome 2 68 tender joint count change from baseline.

Study or subgroup	RA-1 N	RA-1 Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Chopra 2000	89	-13.5 (16.8)	93	-11.6 (17)		-1.86[-6.78,3.06]



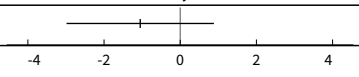
Analysis 10.3. Comparison 10 RA-1 versus placebo, Outcome 3 66 swollen joint count change from baseline.

Study or subgroup	RA-1 N	RA-1 Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Chopra 2000	89	-9.1 (9.6)	93	-8.2 (9.3)		-0.93[-3.68,1.82]



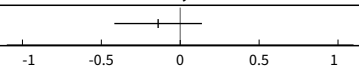
Analysis 10.4. Comparison 10 RA-1 versus placebo, Outcome 4 Modified HAQ (Pune) change from baseline.

Study or subgroup	RA-1 N	RA-1 Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Chopra 2000	89	-3.7 (7.3)	93	-2.7 (5.9)		-1.05[-2.98,0.88]



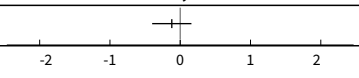
Analysis 10.5. Comparison 10 RA-1 versus placebo, Outcome 5 Patient global (1 to 5) change from baseline.

Study or subgroup	RA-1 N	RA-1 Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Chopra 2000	89	-0.5 (0.9)	93	-0.4 (1)		-0.14[-0.42,0.14]



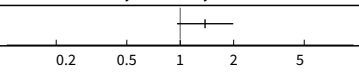
Analysis 10.6. Comparison 10 RA-1 versus placebo, Outcome 6 Physician global (1 to 5) change from baseline.

Study or subgroup	RA-1 N	RA-1 Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Chopra 2000	89	-0.9 (0.9)	93	-0.7 (1)		-0.12[-0.4,0.16]



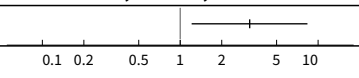
Analysis 10.7. Comparison 10 RA-1 versus placebo, Outcome 7 ACR20 responders.

Study or subgroup	RA-1 n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Chopra 2000	39/80	30/85		1.38[0.96,1.99]



Analysis 10.8. Comparison 10 RA-1 versus placebo, Outcome 8 ACR50 responders.

Study or subgroup	RA-1 n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Chopra 2000	15/80	5/85		3.19[1.21,8.37]

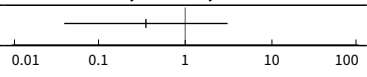


Comparison 11. *Boswellia serrata* versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants (n) reported adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 11.1. Comparison 11 *Boswellia serrata* versus placebo, Outcome 1 Participants (n) reported adverse events.

Study or subgroup	B serrata n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Sandler 1998	1/18	3/19		0.35[0.04,3.08]

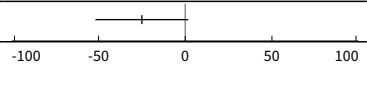


Comparison 12. Capsaicin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain VAS 0-100 percentage change at 4 weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Physician global (-1 to 3) change from baseline at 4 weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

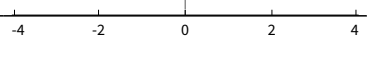
Analysis 12.1. Comparison 12 Capsaicin versus placebo, Outcome 1 Pain VAS 0-100 percentage change at 4 weeks.

Study or subgroup	Capsaicin N	Capsaicin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Deal 1991	14	-57.2 (36.3)	15	-32.2 (37.2)		-25[-51.76,1.76]



Analysis 12.2. Comparison 12 Capsaicin versus placebo, Outcome 2 Physician global (-1 to 3) change from baseline at 4 weeks.

Study or subgroup	Capsaicin N	Capsaicin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Deal 1991	14	1.4 (1.2)	15	0.1 (1.1)		1.36[0.52,2.2]



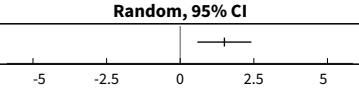
Comparison 13. *Tripterygium wilfordii* (topical) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 42 tender joint count at 6 weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 40 swollen joint count at 6 weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Grip strength (kPa) at 6 weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Morning stiffness (hours) at 6 weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 ACR20 responders at 6 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 13.1. Comparison 13 *Tripterygium wilfordii* (topical) versus placebo, Outcome 1 42 tender joint count at 6 weeks.

Study or subgroup	T wilfordi topical		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Cibere 2003	31	2.4 (2.4)	30	0.9 (1)		1.5[0.58,2.42]



Analysis 13.2. Comparison 13 *Tripterygium wilfordii* (topical) versus placebo, Outcome 2 40 swollen joint count at 6 weeks.

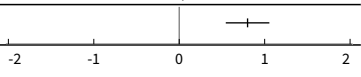
Study or subgroup	T wilfordi topical		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Cibere 2003	31	6.3 (3.9)	30	1.9 (2.5)		4.4[2.76,6.04]

Analysis 13.3. Comparison 13 *Tripterygium wilfordii* (topical) versus placebo, Outcome 3 Grip strength (kPa) at 6 weeks.

Study or subgroup	T wilfordi topical		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Cibere 2003	31	52 (35)	30	13 (14)		39[25.7,52.3]

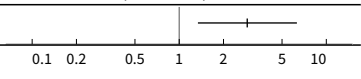
Analysis 13.4. Comparison 13 *Tripterygium wilfordii* (topical) versus placebo, Outcome 4 Morning stiffness (hours) at 6 weeks.

Study or subgroup	T wilfordi topical N	T wilfordi topical Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Cibere 2003	31	1 (0.6)	30	0.2 (0.4)		0.8[0.54,1.06]



Analysis 13.5. Comparison 13 *Tripterygium wilfordii* (topical) versus placebo, Outcome 5 ACR20 responders at 6 weeks.

Study or subgroup	T wilfordi topical n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Cibere 2003	18/31	6/30		2.9[1.34,6.31]

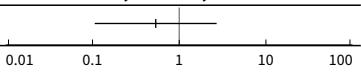


Comparison 14. *Ganoderma lucidum* and SMS versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20 responders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

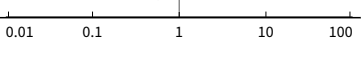
Analysis 14.1. Comparison 14 *Ganoderma lucidum* and SMS versus placebo, Outcome 1 ACR20 responders.

Study or subgroup	G lucidum + SMS n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Li 2007	2/28	4/30		0.54[0.11,2.7]



Analysis 14.2. Comparison 14 *Ganoderma lucidum* and SMS versus placebo, Outcome 2 Adverse events.

Study or subgroup	G lucidum + SMS n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Li 2007	8/22	14/22		0.57[0.3,1.08]



ADDITIONAL TABLES

Table 1. Details of the herbal medicinal products used for the treatment of RA

Botanical name	Plant part	Trade-name	Preparation	Drug/Extract	mg/day	Constituent marker	Marker mg/day	References
Populus tremula + *Fraxinus excelsior* + *Solidago virgaurea*	bark, herb, leaf	Phytodolor	fresh plant ethanolic (45,6%) extract	3 : 1 : 1	5-8 ml	total flavonoids	0.34-0.56	Eberl 1988; Meier 1987
Populus tremula	bark, leaf		fresh plant ethanolic (45,6%) extract			salicin	4.8-8.0	
Solidago virgaurea	herb		fresh plant ethanolic (45,6%) extract			salicyl alcohol	0.48-0.8	
Fraxinus excelsior	bark		fresh plant ethanolic (45,6%) extract			isofraxidin	0.67-1.1	
Salix daphnoides	bark	SM	$ ethanolic (70%) extract	8-14:1	1573	salicin	240	Biegert 2004
Tripterygium wilfordii Hook F	root	SM	ethanol / ethyl acetate extract	45:1	180	triptolide tripdiolide triptonide triptophenolide	0.194, 0.056, 0.0142, 0.746	Tao 1995, Goldbach-Mansky 2009
Tripterygium wilfordii Hook F	root	SM	ethanol / ethyl acetate extract	45:1	360	triptolide tripdiolide triptonide triptophenolide	0.389, 0.112, 0.284, 1.472	Tao 1995, Goldbach-Mansky 2009
Tripterygium wilfordii Hook F	root	T2	chloroform / methanol extract	not stated	60	tripdiolide triptdiolide triptonide triptophenolide	0.021, 0.041, 0.002, 0.002	Tao 1995
Tripterygium wilfordii (local)	root	Thunder God vine	not stated	not stated	topical 5-6 times per day	not stated	not stated	Cibere 2003
Tripterygium wilfordii Hook F	root	TwHF extract	ethanol / ethyl acetate extract	not stated	180	triptolide and tripdiolide	not stated	Goldbach-Mansky 2009

Table 1. Details of the herbal medicinal products used for the treatment of RA *(Continued)*

Withania somnifera, *Boswellia serrata*, *Zingiberis officinale*, *Curcuma longa*		RA-1	not stated	not stated	444 - 592	not stated	not stated	Chopra 2000
Clematis mandshurica, Prunella vulgaris, Trichosanthes kirilowii	root, flower, root; 1:1:2	SKI-306X	ethanol 30% extracts thereafter butanol extraction	7:1		oleanolic acid 4%, rosmarinic acids 0.2%, ursolic acids 0.5%, hydroxybenzoic acid 0.03%, hydroxymethoxybenzoic acid 0.03%, trans-cinnamic acid 0.05%		Song 2007
Uncaria tomentosa	bark	Krallendorn	aqueous acid axtract	not stated	60	pentacyclic oxindole alkaloids	0.88	Mur 2002
Tanacetum parthenium	leaf	SM	powder		76	parthenolide	2-3 micromol	Pattrick 1989
Capsicum (local)	fruit	Zostrix	not stated	0.025%	topical QID			Deal 1991
	fruit	Arlacel 165	not stated	0.075%	topical QID			McCarthy 1992
Oenothera biennis	semen	SM	oil	not stated	540	gamma-linolenic acid (GLA)	540	Belch 1988
	semen	SM	oil	9% GLA	6000	GLA	540	Brzeski 1991
	semen	SM	oil	not stated	20-30 ml	GLA	not stated	Jantti 1989
Ribes nigrum	semen	SM	oil	17% GLA	3000	GLA	525	Watson 1993
	semen	SM	oil	19% GLA	10500	GLA	2000	Leventhal 1994
Borago officinalis	semen	SM	oil	23% GLA	7.2 ml	GLA	1400	Leventhal 1993

Table 1. Details of the herbal medicinal products used for the treatment of RA *(Continued)*

	semen	SM	oil	70% GLA		GLA	2800	Zurier 1996
Ganoderma lucida (4g) + San Miao San (*Atractylodes macrocephala* root, *Phellodendron chinense* cortex, *Achyranthes bidentatae* root)	not stated	not stated	aqueous extract	not stated	*Rhizoma atractylodis 2.4g; Cotex phellodendri* 2.4g; *Radix achyranthes Bidentatae* 2.4g	not stated	not stated	Li 2007
		SM = study medication	$ ethanolic extract stated in the thesis (University of Tübingen) $ 50g/100 g gel, details from Bioforce AG/Schweiz					

APPENDICES

Appendix 1. Search Strategies

MEDLINE

1. exp arthritis, rheumatoid/

2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.

3. (felty$ adj2 syndrome).tw.

4. (caplan$ adj2 syndrome).tw.

5. (sjogren$ adj2 syndrome).tw.

6. (sicca adj2 syndrome).tw.

7. still$ disease.tw.

8. bechterew$ disease.tw.

9. or/1-8

10. exp Medicine, Herbal/

11. exp Plants, Medicinal/

12. exp Medicine, Traditional/

13. exp Drugs, Chinese Herbal/

14. herb$.tw.

15. (plant or plants).tw.

16. phytomedicine.tw.

17. botanical.tw.

18. weed$.tw.

19. algae.tw.

20. (fungi or fungus).tw.

21. ((traditional or chinese or herbal) adj medicine).tw.

22. ((oriental or chinese) adj tradition$).tw.

23. or/10-22

24. 9 and 23

EMBASE

1. exp arthritis, rheumatoid/

2. ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.

3. (felty$ adj2 syndrome).tw.

4. (caplan$ adj2 syndrome).tw.

5. (sjogren$ adj2 syndrome).tw.

6. (sicca adj2 syndrome).tw.

7. still$ disease.tw.

8. bechterew$ disease.tw.

9. or/1-8

10. exp Herbal Medicine/

11. exp Medicinal Plant/

12. exp Traditional Medicine/

13. exp Chinese Medicine/

14. herb$.tw.

15. (plant or plants).tw.

16. phytomedicine.tw.

17. botanical.tw.

18. weed$.tw.

19. algae.tw.

20. (fungi or fungus).tw.

21. ((traditional or chinese or herbal) adj medicine).tw.

22. ((oriental or chinese) adj tradition$).tw.

23. or/10-22

24. 9 and 23

The Cochrane Library **(Wiley InterScience)**

#1 MeSH descriptor Arthritis, Rheumatoid explode all trees

#2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) near/3 (arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab

#3 felty* NEAR/2 syndrome:ti,ab

#4 caplan* NEAR/2 syndrome:ti,ab

#5 sjogren* near/2 syndrome:ti,ab

#6 sicca near/2 syndrome:ti,ab

#7 still* next disease:ti,ab

#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

#9 MeSH descriptor Medicine, Herbal explode all trees

#10 MeSH descriptor Plants, Medicinal explode all trees

#11 MeSH descriptor Medicine, Traditional explode all trees

#12 MeSH descriptor Drugs, Chinese Herbal explode all trees

#13 herb*:ti,ab

#14 (plant or plants):ti,ab

#15 phytomedicine:ti,ab

#16 botanical:ti,ab

#17 weed*:ti,ab

#18 algae:ti,ab

#19 algae:ti,ab

#20 (fungi or fungus):ti,ab

#21 ((traditional or chinese or herbal) next medicine):ti,ab

#22 ((oriental or chinese) next tradition*):ti,ab

#23 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)

#24 (#8 AND #23)

CINAHL (Ovid) (to November 2008)

1 exp Arthritis, Rheumatoid/

2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.

3 (felty$ adj2 syndrome).tw.

4 (caplan$ adj2 syndrome).tw.

5 (sjogren$ adj2 syndrome).tw.

6 (sicca adj2 syndrome).tw.

7 still$ disease.tw.

8 bechterew$ disease.tw.

9 or/1-8

10 exp Medicine, Herbal/

11 exp Plants, Medicinal/

12 Medicine, Traditional/

13 exp Plant Extracts/

14 herb$.tw.

15 (plant or plants).tw.

16 phytomedicine.tw.

17 botanical.tw.

18 weed$.tw.

19 algae.tw.

20 (fungi or fungus).tw.

21 ((traditional or chinese or herbal) adj medicine).tw.

22 ((oriental or chinese) adj tradition$).tw.

23 or/10-22

24 9 and 23

CINAHL (EBSCOhost) (to May 2009)

S16 S14 and S15

S15 S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13

S14 S1 or S2

S13 TI traditional medicine or AB traditional medicine or TI chinese medicine or AB chinese medicine or TI herbal medicine or AB herbal medicine or TI oriental tradition* or AB oriental tradition* or TI chinese tradition* or AB chinese tradition*

S12 TI (fungi or fungus) or AB (fungi or fungus)

S11 TI algae or AB algae

S10 TI weed* or AB weed*

S9 TI botanical or AB botanical Search

S8 TI phytomedicine or AB phytomedicine
S7 TI (plant or plants) or AB (plant or plants)
S6 TI herb* or AB herb*

S5 (MH "Plant Extracts+")

S4 (MH "Medicine, Traditional+")

S3 (MH "Plants, Medicinal+")

S2 TI "bechterew* disease" or AB "bechterew* disease" or TI (arthritis N2 rheumat*) or AB (arthritis N2 rheumat*)

S1 (MH "Arthritis, Rheumatoid+") or TI (felty* N2 syndrome) or AB (felty* N2 syndrome) or TI (caplan* N2 syndrome) or AB (caplan* N2 syndrome) or TI (rheumatoid nodule) or AB (rheumatoid nodule) or TI (sjogren* N2 syndrome) or AB (sjogren* N2 syndrome) or TI (sicca N2 syndrome) or AB (sicca N2 syndrome)

AMED

1 exp Arthritis rheumatoid/

2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit $ or artrit$ or diseas$ or condition$ or nodule$)).tw.

3 (felty$ adj2 syndrome).tw.

4 (caplan$ adj2 syndrome).tw.

5 (sjogren$ adj2 syndrome).tw.

6 (sicca adj2 syndrome).tw.

7 still$ disease.tw.

8 bechterew$ disease.tw.

9 or/1-8

10 exp herbal drugs/

11 exp traditional medicine/

12 exp plant extracts/

13 exp plants medicinal/

14 herb$.tw.

15 (plant or plants).tw.

16 phytomedicine.tw.

17 botanical.tw.

18 weed$.tw.

19 algae.tw.

20 (fungi or fungus).tw.

21 ((traditional or chinese or herbal) adj medicine).tw.

22 ((oriental or chinese) adj tradition$).tw.

23 or/10-22

24 9 and 23

Web of Science

#1 Topic=(((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) and (arthrit* or artrit* or diseas* or condition* or nodule*))) OR Topic=((felty* or caplan* or sjogren* or sicca* or still*) and (disease or syndrome))

#2 Topic=(herb* or plant or plants or phytomedicine or botanical or weed* or algae or fungi or fungus)

#3 Topic=((oriental or chinese or traditional) and (medicine or therap*))

#4 #3 OR #2

#5 #4 AND #1

Dissertation Abstracts

Citation and abstract = rheum* or arthrit* or felty* or caplan* or sjogren* or sicca* or still*

AND

Citation and abstract = herb* or plant or plants or phytomedicine or botanical or weed* or algae or fungi or fungus oriental or chinese or traditional

AND

Citation and abstract = medicin* or therap*

WHAT'S NEW

Date	Event	Description
14 July 2010	New citation required and conclusions have changed	New authors completed the update; substantial changes were made, including incorporating updated Cochrane methods in searching for studies; assessing risk of bias; and collating summary of findings table to help interpretation of results. Inclusion criteria were expanded such that language of publication was no longer a barrier to inclusion, studies using active as well as placebo controls were included, and unpublished reports of randomised controlled trials were eligible for inclusion.
27 October 2009	New search has been performed	Search updated to 2009, unrestricted by language. To identify studies inadvertently omitted from the original review, we repeated the search strategy from 1966 to 1999. We added three additional trials to an update published in a peer review journal.

Date	Event	Description
		This amounted to a total of 12 new trials being added in this update compared to the last published Cochrane review.
30 April 2008	Amended	Converted to new review format. CMSG ID A009-R

CONTRIBUTIONS OF AUTHORS

Christine Little, Tessa Parsons, Melainie Cameron, Sigrun Chrubasik, and Joel Gagnier selected literature. Melainie Cameron, Sigrun Chrubasik, Tessa Parsons, Anette Bluemle, and Joel Gagnier extracted data from some studies. Melainie Cameron conducted the pooled data analyses. All authors wrote the updated review, then checked, proof-read and approved the updated review.

DECLARATIONS OF INTEREST

None known.

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- University of Freiburg, Germany.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this review update, we expanded inclusion criteria so studies that included an active control as well as placebo controls, randomised controlled trials published in any language, and unpublished reports of randomised controlled trials were eligible for inclusion. Changes to methods of quality assessment (replaced by assessment of 'risk of bias') and analysis and presentation of results are consistent with updated Cochrane Collaboration and Cochrane Musculoskeletal Group methods introduced since the original review.

One study included in the original review recruited participants with any form of arthritic disease (Mills 1996). This study was excluded from this update because data for the subgroup of participants with rheumatoid arthritis could not be distinguished from the overall data reported. In the original review, studies of the same herbal therapy that used the same outcome measure were pooled regardless of the length of the intervention period. In this update, these data and comparisons have been subgrouped according to intervention time, rather than pooled. The table of herbal interventions has been extensively revised so that it offers detailed information about the herbal medicines, including full botanical names, the part of the plant used, details of extraction methods, drug:extract ratios and co-active principles. Three further tables have been added; two cover current understandings of the mechanisms of action of herbal therapies and the other table summarises the clinical implications arising from this review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Phytotherapy; Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Placebo Effect; Plant Oils [*therapeutic use]; Primula; Randomized Controlled Trials as Topic; Tripterygium; gamma-Linolenic Acid [*therapeutic use]

MeSH check words

Humans