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Topical herbal therapies for treating osteoarthritis (Review)

Cameron M, Chrubasik S

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[Intervention Review]

Topical herbal therapies for treating osteoarthritis

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ABSTRACT

Background

Before extraction and synthetic chemistry were invented, musculoskeletal complaints were treated with preparations from medicinal plants. They were either administered orally or topically. In contrast to the oral medicinal plant products, topicals act in part as counterirritants or are toxic when given orally.

Objectives

To update the previous Cochrane review of herbal therapy for osteoarthritis from 2000 by evaluating the evidence on effectiveness for topical medicinal plant products.

Search methods

Databases for mainstream and complementary medicine were searched using terms to include all forms of arthritis combined with medicinal plant products. We searched electronic databases (Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, AMED, CINAHL, ISI Web of Science, World Health Organization Clinical Trials Registry Platform) to February 2013, unrestricted by language. We also searched the reference lists from retrieved trials.

Selection criteria

Randomised controlled trials of herbal interventions used topically, compared with inert (placebo) or active controls, in people with osteoarthritis were included.

Data collection and analysis

Two review authors independently selected trials for inclusion, assessed the risk of bias of included studies and extracted data.

Main results

Seven studies (seven different medicinal plant interventions; 785 participants) were included. Single studies (five studies, six interventions) and non-comparable studies (two studies, one intervention) precluded pooling of results.

Moderate evidence from a single study of 174 people with hand osteoarthritis indicated that treatment with *Arnica* extract gel probably results in similar benefits as treatment with ibuprofen (non-steroidal anti-inflammatory drug) with a similar number of adverse events. Mean pain in the ibuprofen group was 44.2 points on a 100 point scale; treatment with *Arnica* gel reduced the pain by 4 points after three weeks: mean difference (MD) -3.8 points (95% confidence intervals (CI) -10.1 to 2.5), absolute reduction 4% (10% reduction to 3% increase). Hand function was 7.5 points on a 30 point scale in the ibuprofen-treated group; treatment with *Arnica* gel reduced function by 0.4 points

(MD -0.4, 95% CI -1.75 to 0.95), absolute improvement 1% (6% improvement to 3% decline)). Total adverse events were higher in the *Arnica* gel group (13% compared to 8% in the ibuprofen group): relative risk (RR) 1.65 (95% CI 0.72 to 3.76).

Moderate quality evidence from a single trial of 99 people with knee osteoarthritis indicated that compared with placebo, *Capsicum* extract gel probably does not improve pain or knee function, and is commonly associated with treatment-related adverse events including skin irritation and a burning sensation. At four weeks follow-up, mean pain in the placebo group was 46 points on a 100 point scale; treatment with *Capsicum* extract reduced pain by 1 point (MD -1, 95% CI -6.8 to 4.8), absolute reduction of 1% (7% reduction to 5% increase). Mean knee function in the placebo group was 34.8 points on a 96 point scale at four weeks; treatment with *Capsicum* extract improved function by a mean of 2.6 points (MD -2.6, 95% CI -9.5 to 4.2), an absolute improvement of 3% (10% improvement to 4% decline). Adverse event rates were greater in the *Capsicum* extract group (80% compared with 20% in the placebo group, rate ratio 4.12, 95% CI 3.30 to 5.17). The number needed to treat to result in adverse events was 2 (95% CI 1 to 2).

Moderate evidence from a single trial of 220 people with knee osteoarthritis suggested that comfrey extract gel probably improves pain without increasing adverse events. At three weeks, the mean pain in the placebo group was 83.5 points on a 100 point scale. Treatment with comfrey reduced pain by a mean of 41.5 points (MD -41.5, 95% CI -48 to -34), an absolute reduction of 42% (34% to 48% reduction). Function was not reported. Adverse events were similar: 6% (7/110) reported adverse events in the comfrey group compared with 14% (15/110) in the placebo group (RR 0.47, 95% CI 0.20 to 1.10).

Although evidence from a single trial indicated that adhesive patches containing Chinese herbal mixtures FNZG and SJG may improve pain and function, the clinical applicability of these findings are uncertain because participants were only treated and followed up for seven days. We are also uncertain if other topical herbal products (Marhame-Mafasel compress, stinging nettle leaf) improve osteoarthritis symptoms due to the very low quality evidence from single trials.

No serious side effects were reported.

Authors' conclusions

Although the mechanism of action of the topical medicinal plant products provides a rationale basis for their use in the treatment of osteoarthritis, the quality and quantity of current research studies of effectiveness are insufficient. *Arnica* gel probably improves symptoms as effectively as a gel containing non-steroidal anti-inflammatory drug, but with no better (and possibly worse) adverse event profile. Comfrey extract gel probably improves pain, and *Capsicum* extract gel probably will not improve pain or function at the doses examined in this review. Further high quality, fully powered studies are required to confirm the trends of effectiveness identifed in studies so far.

PLAIN LANGUAGE SUMMARY

Topical herbal therapy for treating osteoarthritis

This summary of a Cochrane review presents what we know from research about the effects of herbal therapies applied to the skin in people with osteoarthritis.

The review shows that in people with osteoarthritis:

Arnica gel probably improves pain and function as well as non-steroidal anti-inflammatory drugs do;

Capsicum extract gel probably will not improve pain or function more than placebo;

Comfrey extract gel probably improves pain more than placebo;

Chinese herbal patches probably improve pain and function slightly more than placebo.

Herbal therapies may cause side effects; however we do not have precise information about side effects and complications. This is particularly true for rare but serious side effects. Possible side effects may include skin irritations.

What is osteoarthritis and what is herbal therapy?

Osteoarthritis (OA) is a disease of the joints (commonly knee, hip, hands). When joints lose cartilage, bone grows to try to repair the damage. Instead of making things better, however, the bone grows abnormally and makes things worse. For example, the bone can become misshapen and make the joint painful and limit movement. OA can affect your physical function, particularly your ability to use your joints.

Herbal medicines are defined as finished, labeled medicinal products that contain as active ingredients aerial or underground parts of plants, other plant material, or combinations thereof, whether in the crude state or as plant preparations (for example oils, tinctures).

Best estimate of what happens to patients with osteoarthritis who apply *Arnica* extract gel:

Arnica gel was compared to ibuprofen (a non-steroidal anti-inflammatory).

Pain (higher scores mean more severe pain): people who applied *Arnica* rated their pain to be 3.8 points lower (10.1 points lower to 2.5 points higher) than people who applied ibuprofen. After 3 weeks of treatment, people who applied *Arnica* rated their pain to be 40.4 and people who applied ibufrofen rated their pain to be 44.2 on a scale of 0 to 100.

Physical function (lower scores mean better function): people who applied *Arnica* rated their physical function to be 0.4 points lower (1.75 points lower to 0.95 points higher) than people who applied ibuprofen. After 3 weeks of treatment, people who applied *Arnica* rated their physical function to be 7.1 on a scale of 0 to 30, and people who applied ibufrofen rated their physical function to be 7.5.

Side effects: a greater proportion of people who applied *Arnica* reported side effects than did those who applied ibuprofen. Fourteen out of 105 people reported side effects with *Arnica*, and 8 out of 99 people reported side effects with ibuprofen.

Best estimate of what happens to patients with osteoarthritis who apply *Capsicum* extract gel

Capsicum extract gel was compared to placebo.

Pain (higher scores mean more severe pain): people who applied *Capsicum* rated their pain to be 1.0 point lower (6.76 points lower to 4.76 points higher) than people who applied placebo. After 4 weeks of treatment, people who applied *Capsicum* rated their pain to be 44.6, and people who applied placebo rated their pain to be 45.6 on a scale of 0 to 100.

Physical function (lower scores mean better function): people who applied *Capsicum* rated their physical function to be 2.64 points lower (9.51 points lower to 4.23 points higher) on a 0 to 96 point scale than people who applied placebo. After 4 weeks of treatment, people who applied *Capsicum* rated their physical function to be 32.15 on a scale of 0 to 96, and people who applied ibufrofen rated their physical function to be 34.79.

Side effects: more adverse events were reported among people who applied *Capsicum* than for those who applied placebo. Of the 338 adverse events reported, 272 occurred in people who applied *Capsicum* and 66 occured in people who applied placebo.

Best estimate of what happens to patients with osteoarthritis who apply comfrey extract cream

Comfrey extract cream was compared to placebo.

Pain (higher scores mean more severe pain): people who applied comfrey rated their pain to be 16.3 points lower (20.08 to 12.58 points lower) than people who applied placebo. After 3 weeks of treatment, people who applied comfrey rated their pain to be lower by 20.9 points from baseline, and people who applied placebo rated their pain to be lower by 4.6 points from baseline on a scale of 0 to 100.

Side effects: a smaller proportion of people who applied comfrey reported side effects than did those who applied placebo. Seven out of 110 people reported side effects with comfrey, and 15 out of 110 people reported side effects with placebo.

Chinese herbal medicine patches

Adhesive patches containing the Chinese herbal mixtures FNZG and SJG were compared to placebo. We are uncertain whether Chinese herbal patches affect osteoarthritis because this intervention was tested over seven days only.

Pain (higher scores mean worse or more severe pain): people who applied FNZG rated their pain to be 1.44 points lower (9.28 points lower to 6.40 points higher) and people who applied SJG rated their pain to be 1.08 points lower (6.28 points lower to 8.40 points higher) than people who applied placebo. People who applied FNZG rated their pain to be lower by 19.20 points from baseline, people who applied SJG rated their pain to be lower by 16.04 points from baseline, and people who applied placebo rated their pain to be lower by 17.68 points from baseline on a scale of 0 to 100.

Physical function (lower scores mean better function): people who applied FNZG rated their function to be 2.61 points lower (9.50 points lower to 4.28 points higher) and people who applied SJG rated their function to be 2.97 points lower (9.60 points lower to 3.66 points higher) than people who applied placebo. People who applied FNZG rated their physical function to be lower (better) by 5.04 points from baseline, people who applied SJG rated their physical function to be lower (better) by 6.71 points from baseline, and people who applied placebo rated their physical function to be lower (better) by 6.10 points from baseline on a scale of 0 to 96.

Side effects: a greater proportion of people who applied herbal patches reported side effects than did those who applied placebo patches. Five out of 60 people reported side effects with FNZG, 4 out of 60 people reported side effects with SJG, and 0 out of 30 people reported side effects with placebo.

Other topical products

We are uncertain whether other topical herbal products affect osteoarthritis pain and function because the evidence available from these studies was of low to very low quality. FNZG patches were compared head-to-head with SJG patches. Marhame-Mafasel compress was compared to placebo. Stinging nettle leaf was compared with two placebos in two different studies of people with osteoarthritis of the thumb or of the knee.

Summary of findings for the main comparison. Arnica versus ibuprofen for osteoarthritis of the hand

***Arnica* versus ibuprofen for osteoarthritis of the hand**

Patient or population: patients with osteoarthritis of the hand
Settings: Community, Switzerland
Intervention: *Arnica montana*
Comparison: Ibuprofen[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				NNT (95% CI)
	Ibuprofen	*Arnica*				
Pain VAS 0 to 100 (higher scores means worse) Follow-up: mean 3 weeks.	The mean pain in the control group was 44.2 points on a 100 point scale.	The mean pain in the intervention group was **3.8 lower** (10.1 lower to 2.5 higher).		174 (1 study)	⊕⊕⊕⊖ **moderate**[1, 2, 3]	Absolute reduction in pain was 4% (10% reduction to 3% increase); relative reduction in pain 5% (15% reduction to 4% increase); NNT n/a.[4]
Function Hand algofunctional index (higher scores means worse) Follow-up: mean 3 weeks.	The mean function in the control group was 7.5 points on a 30 point scale.	The mean hand function in the intervention group was **0.4 lower** (1.75 lower to 0.95 higher).		174 (1 study)	⊕⊕⊕⊖ **moderate**[1, 2, 3]	Absolute functional improvement was 1% (6% improvement to 3% decline); relative functional improvement was negligible[5]; NNT n/a.[4]
Adverse events Participants (n) reported events Follow-up: mean 3 weeks	**Study population**		**RR 1.65** (0.72 to 3.76)	204 (1 study)	⊕⊕⊕⊖ **moderate**[1, 2, 3]	Absolute risk of adverse events was 5% higher in the *Arnica* group (3% lower to 14% higher); NNT n/a. [4]
	81 per 1000	**133 per 1000** (58 to 278)				
Adverse events Participants (n) withdrew due to adverse effects			Not estimable			Reported NIL withdrawals due to adverse events.[6]

Adverse events Participants (n) reported serious adverse events		Not estimable	Reported NIL serious adverse events.[5]
Quality of life	Quality of Life 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; **OR:** Odds ratio.

GRADE Working Group grades of evidence
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] Single study. Treatment effect crosses midline (no effect).
[2] Non-inferiority hypothesis: that *Arnica* is not inferior to ibuprofen for the treatment of osteoarthritis of the hand.
[3] Confirmatory design, statistical power 80%, alpha 0.024.
[4] Number needed to treat (NNT) = not applicable (n/a) when result is not statistically significant. NNT for continuous outcomes calculated using Wells Calculator (CMSG editorial office). NNT for dichotomous outcomes calculated using Cates NNT calculator (http://www.nntonline.net/visualrx/).
[5] Negligible percentage change less than 1%.
[6] Reported one case of back pain due to a fall, leading to withdrawal from the study; this event is neither withdrawal due to adverse event, nor a serious adverse event, as defined for this review.

Summary of findings 2. Capsicum for osteoarthritis of the knee

***Capsicum* for osteoarthritis of the knee**

Patient or population: patients with osteoarthritis of the knee
Settings: Community, Thailand
Intervention: *Capsicum* extract

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments NNT (95% CI)
	Assumed risk	Corresponding risk				
	Control	*Capsicum* extract				
Pain VAS 0-100 (higher means worse) Follow-up: mean 4 weeks	The mean pain in the control group	The mean pain in the intervention group was		99 (1 study)	⊕⊕⊕⊖ **moderate**[1, 2]	Absolute reduction in pain was 1% (7% reduction to 5% increase); relative reduction

	was 45.6 points on a 100 point scale.	**1 lower** (6.76 lower to 4.76 higher)				in pain 2% (10% reduction to 7% increase); NNT n/a.[5]
Function WOMAC 0-4 (Function; higher means worse) Follow-up: mean 4 weeks[2]	Measured, but not reported.	Measured, but not reported.	Not estimable	99 (1 study)	⊕⊕⊕⊖ **moderate**[1, 2]	Crossover trial: WOMAC 0-4 (Function) reported for whole trial only (ie: both arms of crossover combined).
Function WOMAC 0-4 (Overall; higher means worse) Follow-up: mean 4 weeks[2]	The mean function in the control group was 34.79 on a 96 point scale.	The mean function in the intervention group was **2.64 lower** (9.51 lower to 4.23 higher)		99 (1 study)	⊕⊕⊕⊖ **moderate**[1, 2]	Absolute functional improvement 3% (10% improvement to 4% decline); relative functional improvement 5% (19% improvement to 9% decline); NNT n/a. [5]
Adverse events Event episodes (n) reported Follow-up: mean 4 weeks[2]	**Study population** **195 per 1000**	**805 per 1000** (738 to 858)	**Rate Ratio 4.12** (3.30 to 5.17)	676 (1 study)	⊕⊕⊕⊖ **moderate**[1, 2, 3]	Absolute risk of adverse events was 61% higher in the capsaicin group (55% to 67% higher); NNT = 1.64 (95% CI 1.82 to 1.50).
Adverse events Participants (n) withdrew due to adverse effects			Not estimable			Reported NIL withdrawals due to adverse events.
Adverse events Participants (n) reported serious adverse events			Not estimable			Reported NIL serious adverse events.
Quality of Life	Not measured or reported.					

*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; **OR:** Odds ratio.

GRADE Working Group grades of evidence
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] Single study. Treatment effect crosses midline (no effect).
[2] Randomisation and allocation concealment inadequately reported. Per protocol analysis only.
[3] Crossover trial: 4 week intervention arms plus 1 week washout.
[4] *Capsicum* extract gel stimulates heat receptors in the skin, which is part of the effect of this topical agent. Including "burning sensations" among the reported adverse events may have inflated this outcome. Insufficient blinding to the intervention may have confounded the reporting of adverse events.
[5] Number needed to treat (NNT) = not applicable (n/a) when result is not statistically significant. NNT for continuous outcomes calculated using Wells Calculator (CMSG editorial office). NNT for dichotomous outcomes calculated using Cates NNT calculator (http://www.nntonline.net/visualrx/).

Summary of findings 3. Comfrey for osteoarthritis of the knee

Comfrey for osteoarthritis of the knee

Patient or population: patients with osteoarthritis of the knee
Settings: Community, Germany
Intervention: Comfrey

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	Comfrey				
Pain VAS 0-100 (higher means worse) Follow-up: mean 3 weeks	The mean pain in the control group was 83.5 points on 100 point scale.[1]	The mean pain: change from baseline in the intervention groups was 41.5**lower** (34 to 48 lower)		220 (1 study)	⊕⊕⊕⊖ **moderate**[1,2,3]	Absolute reduction in pain was 42% (34% to 48% reduction); relative reduction in pain 48% (36% to 51% reduction); NNT = 1.84 (95% CI 1.7 to 2.1).[4]
Function: change from baseline WOMAC VAS (Function; higher means worse) Follow-up: mean 3 weeks	Not estimable [2]	Not estimable [2]	Not estimable [2]	220 (1 study)	⊕⊕⊕⊖ **moderate**[1,2]	Not estimable [2]
Adverse events Participants (n) reported adverse events Follow-up: mean 3 weeks	**Study population**		**RR 0.47** (0.20 to 1.10)	220 (1 study)	⊕⊕⊕⊖ **moderate** [2, 3]	Absolute risk of adverse events was 7% lower in the comfrey group (15% lower to 1% higher); NNT n/a. [4]
	136 per 1000	**64 per 1000** (26 to 148)				
Adverse events Participants (n) withdrew due to adverse effects			Not estimable			Withdrawal due to adverse events not reported.

Adverse events Participants (n) reported serious adverse events			Not estimable			Reported NIL serious adverse events.
Quality of life SF-36 [4]	Not estimable [2]	Not estimable [2]	Not estimable [2]	220 (1 study)	⊕⊕⊕⊖ **moderate**[2]	Not estimable [2]

*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; **OR:** Odds ratio.

GRADE Working Group grades of evidence
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] Standard deviations for pain measures were estimated from graphical data.
[2] Most outcome data reported as change scores, percentages, and graphs only, insufficient for extraction.
[3] Criteria for diagnosis of OA not specified at baseline. Diagnosis not consistent with ACR criteria, but likely to be OA.
[4] SF-36 has a recall period of 4 weeks. Participants are asked to recall their health perceptions "...over the last 4 weeks". Use of this outcome measure to investigate interventions less than 4 weeks duration is likely to be imprecise.

BACKGROUND

At times where extraction and synthetic chemistry were not yet invented, musculoskeletal complaints were treated all over the world with preparations from medicinal plants. Due to a legal decision in Germany in 1978, the Commission E of the Federal Health Agency re-evaluated the herbal drugs (Blumenthal 1998). Table 1 summarizes the monographs of approved medicinal plant parts and their preparations for topical use in the treatment of osteoarthritis (OA) complaints. In the course of the harmonization within Europe, the monographs of the European Scientific Cooperative on Phytotherapy (ESCOP) appeared continuously thereafter and were summarized in the second edition and a supplement (ESCOP 2003; ESCOP 2009) (Table 2). Parallel to this, the American Herbal Pharmacopeia (www.herbal-ahp.org) has been publishing comprehensive monographs accompanied by a Therapeutic Compendium since 1996, and the WHO its monographs on selected medicinal plants since 1999 (http://apps.who.int/medicinedocs/en/d/Js2200e/). Although the ESCOP, American and WHO monographs are not official, they provide scientific information on the safety, efficacy and quality of medicinal plants and provide recommendations for their use in clinical practice (for example doses, types of preparation, warnings). In contrast, the European Medicines Agency monographs (EMA monographs) serve as a guidance for application dossiers to obtain marketing authorization by the regulatory authorities of the individual countries in the European Union.

In the previous Cochrane review on herbal medicines for OA (Little 2000), oral and topical herbal medicines were considered together. However, due to the fact that the mechanism of action of topical medicinal plant products is different from that of oral products, in that they act as counterirritants via the skin or because they are toxic when orally applied, a separation of topical and oral medicinal plant preparations seemed advisable. For example, nettle leaf is covered with needle-like hairs that on contact pierce the skin injecting irritant substances like formic acid, acetic acid, serotonin or 5-hydroxytryptamine, histamine and acetylcholine (Anonymous 1998), which cause an irritant skin reaction. Already in the middle ages urtication (beating with nettle) belonged to the armentarium of treatments for (osteo)arthritic pain.

Menthol, contained in peppermint or other mint oils, is a topical counterirritant (Yosipovitch 1996). The terpene increases the perception of cooling and attenuates the perception of moderate warming (Green 1992) by triggering the cold-sensitive Transient Receptor Potential Melastatine 8 (TRPM8) receptors in skin sensory neurons (Yudin 2012). TRP-Ankyrin1 (A1), another cold-sensing channel, is also involved in the menthol cooling sensation (Karashima 2007). The activation of TRPM8 mediates the menthol spasmolytic effect (Johnson 2009). In vitro studies demonstrated menthol inhibition of the arachidonic acid cascade (cyclooxygenase-2 (COX-2), lipooxygenase) and cytokine release (Juergens 1998). Local anaesthetic (Galeotti 2001), antioxidative (Ka 2005) and analgesic (Taniguchi 1994) actions are other targets of the menthol mechanism of action, the latter based on a weak kappa opioid receptor agonistic effect (Galeotti 2002) and cumulative inactivation of voltage-gated sodium channels (Gaudioso 2012).

The capsaicinoids, the active principle of *Capsicum* species, act via the heat-sensitive Transient Receptor Potential Vanilloid-1 (TRPV1) receptors (Hayes 2000). Binding of capsaicin to this target is accompanied by a decrease in membrane resistance, depolarization and activation of synaptosomal neurotransmitter release (Buck & Burks 1986; Huang 2008; Sauer 2001; Zhao 1992). Following the initial activation, which is often associated with heat sensation, desensitation and depletion of neurotransmitters produce the capsaicinoid (expressed as capsaicin) analgesic effect. If capsaicin exposure persists, nerve terminals will degenerate (defunctionalization) (Dedov 2000; Dedov 2001; Nolano 1999), which causes the prolonged analgesic effect after the end of treatment. Other capsaicin effects include the inhibition of inducible COX-2 mRNA expression (Kim 2003) and LOX (Flynn 1986) and a free radical scavenging activity (Galano 2012; Luqman 2006).

Arnica and comfrey do not act as counterirritants. However, both are for topical use due to systemic toxicity (ESCOP 2003; ESCOP 2009) and should only be applied to intact skin. *Arnica* and comfrey inhibit COX-1 and COX-2 and have an antioxidative potential (ESCOP 2009; Schröder 1990; Verma 2010). So far, inhibition of LOX (Tornhamre 2001), elastase (Siedle 2002; Siedle 2003), cytokines (Jäger 2009; Klaas 2002; Lyss 1997), transcription factor NF-kappaB (Ekenäs 2008) and AP1 (Jäger 2009) has, however, only been demonstrated for the *Arnica* species. Some effects seem to be likely for comfrey, for example elastase inhibition (Melzig 2005), based on the comfrey ingredient rosmarinic acid for which inhibition of cytokines (Lee 2006) and anti-inflammatory activity has been demonstrated in various animal experiments (Englberger 1988; Moon 2010).

Description of the condition

Osteoarthritis (OA) is characterized by degeneration of the joints, for example the hip, knee and hand. The condition is widespread. Lawrence and co-workers (Lawrence 2008) estimated that among US adults, nearly 27 million had clinical osteoarthritis in 2005 (up from the estimate of 21 million for 1995). Women are more often affected with OA than men, and prevalence increases with increasing age. Overweight and heavy physical work may explain OA in some cases, but non-mechanical factors and genetic disposition are involved as well (van den Berg 2011; Zhang 2010). Diagnostically, primary OA is distinguished from secondary OA induced by traumatic events and endocrine or metabolic disorders. Both primary and secondary forms result in impaired quality of life due to pain and physical disability (Schmitz 2010). The OMERACT-Osteroarthritis Research Society International (OARSI) response criteria combine pain and functional impairments in the identification of treatment response (Pham 2003; Pham 2004) but unfortunately response criteria are not universally considered in clinical studies, making efficacy comparisons difficult.

Description of the intervention

For the purpose of this review we have adopted the World Health Organization (WHO) guidelines for the defintion of medicinal plant products, that is, "...finished, labeled, medicinal products that contain as active ingredients, aerial or underground parts of plants, or other plant material, or combinations thereof, whether in the crude state or as plant preparations. Plant preparations include comminuted or powdered plant materials, extracts, tinctures, fatty or essential oils, and any other substances of this nature. Herbal medicines may contain excipients in addition to the active ingredients. Medicines containing plant material combined with chemically defined active substances, including chemically

defined, isolated constituents of plants, are not considered to be herbal medicines." The WHO also notes that "exceptionally, in some countries herbal medicines may also contain, by tradition, natural organic or inorganic active ingredients which are not of plant origin", however in this review we have applied the strict definition and excluded herbal products combined with non-herbal materials. (apps.who.int/medicinedocs/en/d/Jh2984e).

How the intervention might work

Medicinal plant products used topically for the treatment of OA act as skin irritants (for example *Capsicum* extract, stinging nettle leaf) and may also act via the same pathways known for oral medicinal plant products, including inhibition of cyclooxygenase-1 and 2 (COX-1, COX-2), lipoxygenase (LOX), pro-inflammatory cytokines and enzymes that participate in cartilage destruction, such as elastase and hyaluronidase (for example *Capsicum*, *Arnica*, comfrey extracts) (Cameron 2009). Some broad mechanisms of action have been demonstrated in experimental studies (see Background) but the mechanisms have not yet been elucidated in full detail.

Why it is important to do this review

Topical medicinal plant preparations are part of the armentarium of traditional treatments used by patients suffering from rheumatic pain conditions. The effectiveness of some medicinal plant products is unknown or unclear, and may be associated with risks of harm. This review is important to summarize the evidence of effectiveness of medicinal plant products used topically for OA, and to update the information on these products that is currently captured in the monographs (see Table 1; Table 2). We have undertaken this research to investigate the effectiveness and adverse side effects of these products in the hope that patients with OA and their healthcare providers may make more informed decisions about the usefulness of these interventions.

In the previous Cochrane review on herbal medicines for OA (Little 2000), oral and topical herbal medicines were considered together. When the update of this review became particularly large, a separation of topical and oral medicinal plant products seemed advisable because a) only oral products are purported to have any effect on joint structure, b) topical herbal medicines may act as counterirritants via the skin (for example nettle, peppermint, *Capsicum*), and c) some products cannot be administered orally due to systemic toxicity (*Arnica*, comfrey).

OBJECTIVES

To update the existing Cochrane systematic review (Little 2000) by evaluating the evidence of effectiveness for topical medicinal plant products for the treament of osteoarthritis (OA) by adding data from relevant randomised controlled trials published in the period from January 2000 to February 2013.

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 topical herbal interventions for treating OA.

Types of participants

All persons diagnosed with OA according to the American College of Rheumatology (ACR) criteria (Altman 1986; Altman 1990; Altman 1991) or the equivalent European League Against Rheumatism (EULAR) criteria (Zhang 2009; Zhang 2010a). Studies with samples defined according to vague descriptions (for example 'joint pain') were not considered. Studies with participant samples defined according to incomplete or partial ACR or EULAR criteria were included, and notes were provided to identify possible weaknesses in sample selection in these studies.

Types of interventions

Any topically applied herbal intervention compared with an inert (placebo) or active control was included. Herbal intervention included any plant preparation (whole, powder, extract, standardised mixture) but excluded homeopathy, aromatherapy, or any preparation of synthetic origin.

In the methods published for the original review (Little 2000) herbal therapies used in conjunction with other treatments or combined with a non-herbal substance were also to be included if the effect of the non-herbal intervention was consistent among all groups and quantifiable such that the effect of the herbal intervention could be determined. In this review, however, we have confined interventions to those that comply with the WHO definition of herbal (http://apps.who.int/medicinedocs/en/d/Jh2984e/1.html). According to WHO, herbal therapy combined with a non-herbal substance is no longer herbal treatment. This definition is important because non-herbal substances may interact with the active principle (sum of action of all ingredients) and change effects, potency and safety profile. Even if the non-herbal substance occurs in the same concentration in the placebo control, as is the case in two excluded studies (Gemmell 2003, McKay 2003), the intervention-control comparison is not valid because the non-herbal substance may enhance the absorption of individual ingredients of the active principle or potentiate or reverse the effect of individual ingredients, thus changing the action of the active principle and not the placebo.

Types of outcome measures

The main outcome measures considered were consistent with those used across Cochrane Musculoskeletal Group (CMSG) systematic reviews of interventions for OA: pain, function, adverse events, and quality of life (Altman 1996; Pham 2004).

To assess the benefits of treatment:

- pain, measured on a visual analogue scale (VAS) (0 to 100), WOMAC pain subscale (0 to 4 or VAS 0 to 100), numerical rating scale (0 to 3), or other pain scales;
- physical function, measured by a VAS (0 to 100), WOMAC function subscale (0 to 4 or VAS 0 to 100), algofunctional index (0 to 3), or other validated functional scales.

To assess the safety of treatment:

- number of participants reporting any adverse event.

Minor outcomes included:

- general well-being or satisfaction indicator;
- withdrawals due to adverse events;

- serious adverse events;
- quality of life measured by the Short Form (SF)-36 or other validated scales.

We included the following outcomes in the summary of findings tables (derived from the list of outcomes recommended by the CMSG for inclusion in reviews of interventions for osteoarthritis): pain, function, number of participants experiencing any adverse event, withdrawals due to adverse events, serious adverse events, and quality of life. Because there is no purported mechanism for topical herbal medicines to alter joint structure in OA, we omitted radiographic joint changes as a reported outcome from the summary of findings tables.

Search methods for identification of studies

Electronic searches

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 November 2008, and updated the search again on 21 May 2009, 14 December 2010, 16 May 2011, 30 November 2011, 15 June 2012, and finally on 25 and 27 February 2013.

1. Cochrane Central Register of Controlled Trials (CENTRAL) (part of *The Cochrane Library*, accessed 25 February 2013).
2. DARE (part of *The Cochrane Library*, accessed 25 February 2013).
3. MEDLINE (via Ovid, 2000 to 25 February 2013).
4. MEDLINE (Ovid MEDLINE® In-Process & Other Non-Indexed Citations, to 25 February 2013).
5. EMBASE (via Ovid 2000 to 2011 Week 47)
6. CINAHL (via Ovid 2000 to 2008 Week 5; via EBSCO Host 2008 to 27 February 2013).
7. AMED (via Ovid, 1985 to 30 November 2011).
8. ISI Web of Knowledge (2000 to 27 February 2013).
9. Dissertation Abstracts, ProQuest (2000 to 27 February 2013).
10. WHO International Clinical Trials Registry Platform, (apps.who.int/trialsearch accessed 27 February 2013).

Thesaurus and free text searches appropriate to each database were performed to combine terms describing OA 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.

Searching other resources

We searched reference lists of included trials for any other potential studies.

Data collection and analysis

Selection of studies

This review was an update of a previous review. Two authors of the original review (CL, TP) and two other colleagues (JG, AB) made some contributions to this review and are acknowledged here as investigators, but because these investigators did not contribute to the totality of the review they are identified in the Acknowledgements rather than listed as authors of this review.

All titles and abstracts identified from electronic databases and other searches were independently examined by three investigators (MC, SC, CL). The full manuscript was retrieved for each record that had the possibility of meeting the review criteria.

Three investigators (MC, SC, CL) independently assessed the eligibility of retrieved studies for the review according to the inclusion criteria.

Data extraction and management

Data were extracted from each eligible study by two review authors acting independently. Because of the length of time taken to complete this review, and the associated review of oral medicinal plant products for OA, three investigators (MC, SC, TP) contributed to the data extraction.

Two review authors (MC, SC) independently extracted the following data from the included trials and entered the data into RevMan 5:

1) trial characteristics including size and location of the trial, and source of funding;

2) characteristics of the study population including age, and characteristics of the disease including diagnosis criteria and disease duration;

3) characteristics of the therapy in all trial arms including type and dose of therapy;

4) risk of bias domains as outlined in 'Assessment of risk of bias in included studies', below;

5) outcome measures as mean and standard deviation for continuous outcomes, and number of events for dichotomous outcomes (as outlined in Types of outcome measures).

If data were provided for a trial on more than one pain scale, we referred to a previously described hierarchy of pain-related outcomes (Juni 2006; Reichenbach 2007) and extracted data on the pain scale that was highest on this list:

1. global pain;
2. pain on walking;
3. Western Ontario and McMaster Universities Index of Osteoarthritis (WOMAC) osteoarthritis index pain subscore;
4. composite pain scores other than WOMAC;
5. pain on activities other than walking;
6. rest pain or pain during the night;
7. WOMAC global algofunctional score;
8. Lequesne osteoarthritis index global score;
9. other algofunctional scale;
10. patient's global assessment;
11. physician's global assessment.

If data on more than one function scale were provided for a trial, we extracted data according to the hierarchy presented below:

1. global disability score;
2. walking disability;
3. WOMAC disability subscore;
4. composite disability scores other than WOMAC;

5. disability other than walking;
6. WOMAC global scale;
7. Lequesne osteoarthritis index global score;
8. other algofunctional scale;
9. patient's global assessment;
10. physician's global assessment.

If pain or function outcomes were reported at several time points, we extracted the measure at the end of the intervention as the main outcome.

If data on more than one quality of life scale were provided for a trial, we extracted data according to the hierarchy presented below:

1. SF-36;
2. EuroQoL;
3. SIP (Sickness Impact Profile);
4. NHP (Nottingham Health Profile).

Adverse events were measured as the number of patients experiencing any adverse event, patients who were withdrawn or dropped out because of adverse events, and patients experiencing any serious adverse events. Serious adverse events were defined as events resulting in in-patient hospitalisation, prolongation of hospitalisation, persistent or significant disability, congenital abnormality or birth defect of offspring, life-threatening events, or death.

If additional data were required, we contacted the trial authors to obtain these data. Some data were converted to normalised scales prior to extraction and reporting. Where data were imputed or calculated (for example standard deviations calculated from standard errors, P values, or confidence intervals; or imputed from graphs or from standard deviations in other trials) we reported these adjustments (see Characteristics of included studies). Any disagreements were resolved by consensus.

Assessment of risk of bias in included studies

Two review investigators (MC, SC) independently assessed the risk of bias of each included trial 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 2011). Each of these criteria were explicitly judged as: (a) low, (b) unclear (either lack of information or uncertainty over the potential for bias), or (c) high risk of bias. Potential disagreements were discussed and resolved by referring to the original protocol and, if necessary, arbitration by member(s) of the editorial group.

Measures of treatment effect

When possible, the analyses were based on intention-to-treat data (outcomes provided for every randomised participant) from the individual trials. For each trial, we presented outcome data as point estimates with means and standard deviations for continuous outcomes and risk ratios (RRs) with corresponding 95% confidence intervals (CIs) for dichotomous outcomes. Where possible, for continuous outcomes we extracted end of treatment scores rather than change from baseline scores. For continuous data, results were presented as mean differences (MDs) and 95% CIs. We had planned that when different scales were used to measure the same outcome or concept, standardised mean difference (SMD) would be used.

Unit of analysis issues

Where a study was defined as a crossover trial, data were extracted only up to the point of crossover given the potential for carry-over effects of these particluar interventions to bias the treatment effect following crossover.

Dealing with missing data

For dichotomous outcomes, we used the number randomised as the denominator and made the assumption that any participants missing at the end of treatment did not have a positive outcome. For continuous outcomes with no standard deviation reported, if possible we calculated standard deviations from standard errors, P values, or CIs. For one study we converted the VAS data from a 10 cm scale to a 100 mm scale (Kosuwon 2010), and for another study we estimated means and standard deviations from graphical data (Grube 2007). Details of data conversion and imputation are explained in the characteristics of included studies and the associated table (see table Characteristics of included studies).

Assessment of heterogeneity

We assessed included trials for clinical homogeneity in terms of participants, interventions and comparators. For studies judged as clinically homogeneous, we quantified the possible magnitude of inconsistency (that is heterogeneity) across studies using the I^2 statistic, with a rough guide for interpretation as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% considerable heterogeneity (Deeks 2011).

Assessment of reporting biases

To examine the possibility of publication bias, we planned to construct funnel plots if at least 10 studies were available for the meta analysis of a primary outcome, however we identified too few trials for this analysis.

We planned to assess the presence of small study bias in the overall meta-analysis by checking if the random-effects model estimate of the intervention effect was more beneficial than the fixed-effect model estimate, but again there were too few trials for this analysis.

Data synthesis

As far as data extraction was possible, descriptive results are reported for all included studies. No studies could be subject to meta-analysis.

Subgroup analysis and investigation of heterogeneity

Our original plan, in order to explain the heterogeneity between the results of the included studies, was to included subgroup analyses by type and length of intervention. Once the review was divided into two reviews, covering topical and oral interventions separately, there were insufficient data in the trials of topical interventions to justify subgroup analyses according to time of intervention.

Sensitivity analysis

We planned a sensitivity analysis to investigate the robustness of the treatment effect on pain and function relative to allocation concealment and participant blinding by removing the trials that reported inadequate or unclear allocation concealment and lack of participant blinding from the meta-analysis to see if this changed the overall treatment effect. There were insufficent data to perform these analyses.

Summary of findings

See: Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3.

The main results (pain, function, adverse events, withdrawals due to adverse events, serious adverse events, quality of life) of the review are presented in summary of findings tables (Schunemann 2011a). The overall grading of the evidence using the GRADE approach to classify the evidence for each herbal intervention, as: (a) high, (b) moderate, (c) low, or (d) very low, is included as an indication of confidence in the results of the studies. Effect sizes were reported as relative risk and as number needed to treat (Schunemann 2011b).

RESULTS

Description of studies

See: Characteristics of included studies.

See: Characteristics of excluded studies.

A total of seven new studies were identified for inclusion in this updated review (Grube 2007; Kosuwon 2010; Randall 2000; Randall 2008; Soltanian 2010; Wang 2012; Widrig 2007). The one study of topical capsaicin that was included in the original review (Deal 1991) was excluded from this review when additional information that was provided by the manufacturer allowed us to identify that the capsaicin was extracted (that is a single extracted ingredient, which is not herbal) and not an extract from *Capsicum* fruits. The term capsaicin may be used to refer to capsaicinoids (extract, expressed as capsaicin) or synthetic or extracted capsaicin (single ingredient).

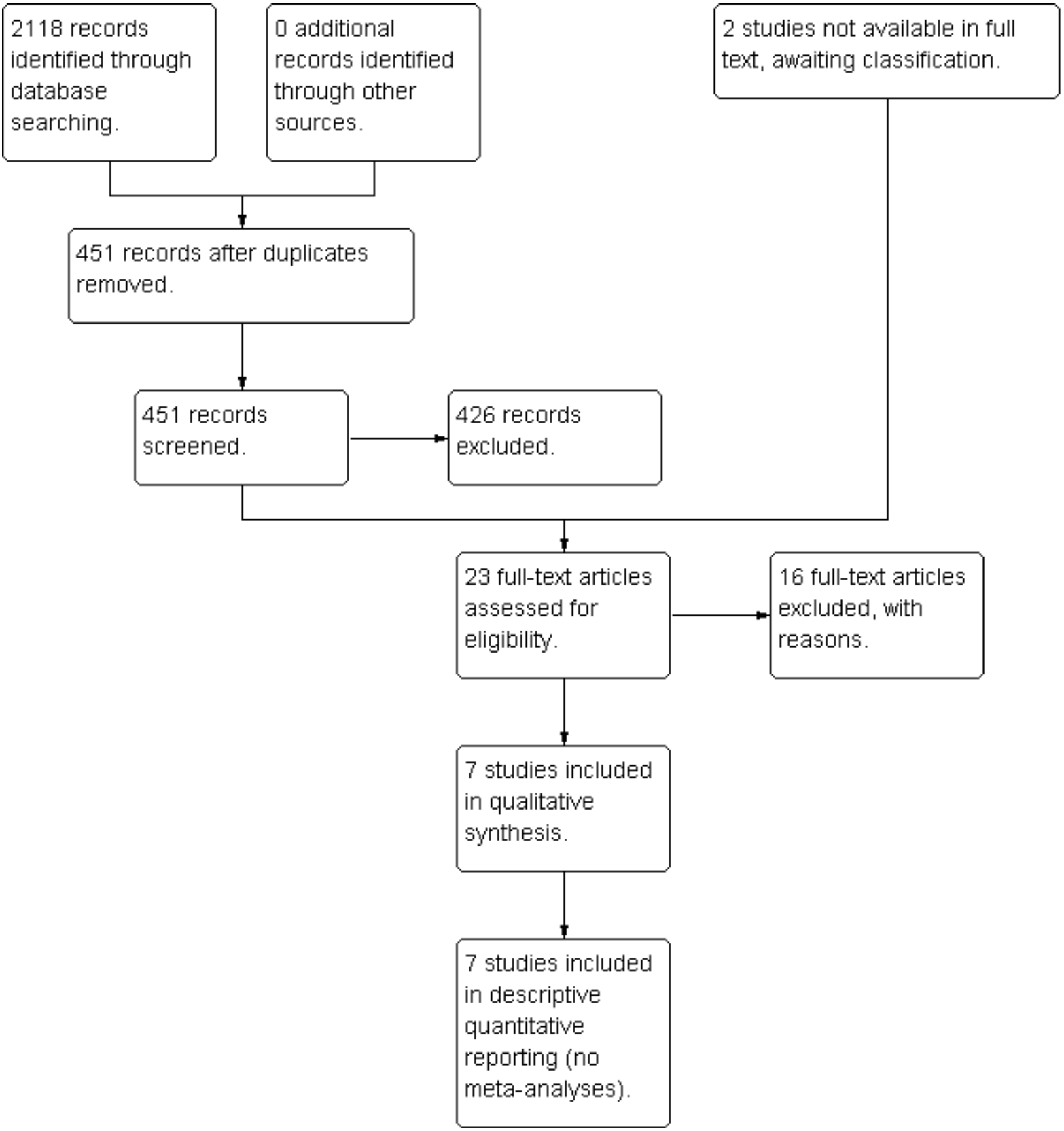
Two studies were of parallel design, with two groups comparing a herbal intervention to a placebo (inert) control (Grube 2007; Randall 2008). One study compared a herbal product with an active control (Widrig 2007). Another study compared two herbal products against each other as well as against a placebo control in a three-arm trial (Wang 2012). Three studies used crossover designs (Kosuwon 2010; Randall 2000; Soltanian 2010). Four studies were of a confirmatory design, with sufficient statistical power (80%) to identify significant effects at the alpha level 0.05 (Grube 2007; Kosuwon 2010; Wang 2012; Widrig 2007). The other three studies were exploratory, showing trends of effectiveness only.

The inclusion of three studies is open to question because: (a) participants entered the study with a presumptive diagnosis, not confirmed at baseline, or (b) the criteria by which OA was established were incomplete or inconsistent with ACR or EULAR requirements (Grube 2007; Randall 2000; Randall 2008).

Results of the search

This review was formed from the division of a broader review of herbal therapies for the treatment of OA. In the original review both topical and oral medicinal plant products were considered. The search strategy for this updated review was structured from the protocol used in the original review. The searches for this review update have been repeated several times since 2005. The most recent full search (December 2011) was completed before the current review was divided into two parts. Therefore, it is not possible to give an entirely accurate presentation of the search results as the number of references identified from the search. In the most recent full search of all databases we identified, after the removal of duplicates, 288 abstracts on topical or oral herbal medicines in the treatment of OA. From these abstracts, we identified only one new study that fulfilled the inclusion criteria for this divided review of topical medicinal plant products only. In more recent repeat searches (June 2012 and February 2013) we identified 1771 abstracts, reduced to 159 abstracts after removal of duplicates from previous searches, and from these abstracts four new studies were identified: one that fulfilled the criteria for inclusion, one that was excluded, and two studies available only in abstract form that are currently awaiting classification. See Figure 1 for our best estimate of results from the searches.

Figure 1. Study flow diagram.



Included studies

See: Characteristics of included studies.

Medicinal plant products used for the treatment of OA included crude stinging nettle leaf, standardised extracts from single plants (*Arnica*, Capsicum, and comfrey), and three mixtures of preparations from multiple plants known as Marhame-Mafasel, Fufang Nanxing Zhitong Gao (FNZG), and Shangshi Jietong Gao (SJG) (proprietary names) (see Table 3 for preparation details of all products).

A few key outcome measures were used but the reporting of measures differed among studies limiting the utility of studies for meta-analysis. All VAS were 100 mm lines, with anchor points identified as 0 (nil symptom) and 100 (worst possible symtom), but some authors reported VAS scores on a centimetre scale in the range 0 to 10. For ease of comparison between trials, we converted all VAS data to the 0 to 100 mm scale.

Several studies used WOMAC, but this index may be used with two possible scoring methods: a battery of 0 to 4 Likert scales or a battery of 100 mm VAS. Typically, the Likert scale scores are presented as aggregate scores (sums) for each of the three subscales (pain subscore range 0 to 20, stiffness subscore range 0 to 8, physical function subscore range 0 to 68), whereas the VAS are converted to normalised units (means) for each subscale (all subscales scored 0 to 100). Although both scoring systems are acceptable for clinical and research use, there is no agreed conversion ratio between them so studies using differing systems are not comparable. Specific details of all data conversions are included in the Characteristics of included studies.

Excluded studies

See: Characteristics of excluded studies.

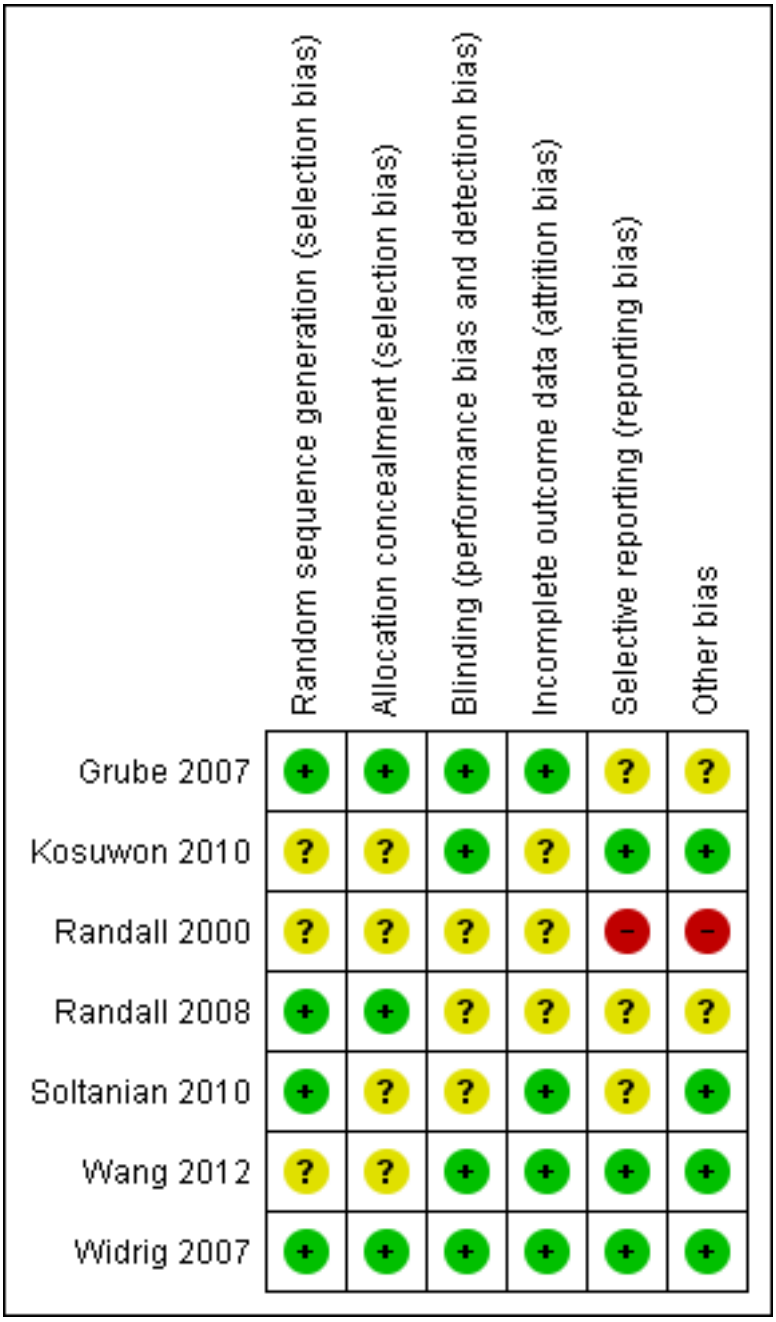
Reasons for excluding studies were: (a) not a randomised controlled trial (Rayburn 2009; Sagar 1988; Saley 1987; Yuelong 2011), (b) review or discussion paper (Kielczynski 1997; Linsheng 1997; Long 2001), or (c) not a herbal intervention (Altman 1994; Gemmell 2003; McCarthy 1992; McCleane 2000; McKay 2003; Schnitzer 1994; Smith 2011).

Risk of bias in included studies

See: Characteristics of included studies, 'Risk of bias' tables.

The methodological quality of each study was assessed independently by two review authors according to the criteria described in the methods (Higgins 2011; Schunemann 2011a). The quality of the included studies was variable and should be taken into account when interpreting the results. See Figure 2 for a summary of the risk of bias assessment.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Only one study adequately met all six validity criteria (Widrig 2007) and was classified as having low risk of bias. All studies were described as randomised. The method of randomisation was not reported in five studies (Grube 2007; Kosuwon 2010; Randall 2000; Wang 2012; Widrig 2007) but two of these studies were conducted in Germany and reported compliance with the International Harmonisation Conference Good Clinical Practice (IHC GCP) guidelines, which is anchored in German law and requires that adequate randomisation, allocation concealment and blinding were undertaken. Risk of bias in these two studies was assessed as low for these criteria (Grube 2007; Widrig 2007).

Allocation

Selection bias was rated as low in studies that recruited patients with diagnoses of OA confirmed according to ACR or EULAR criteria (Altman 1986; Altman 1990; Altman 1991; Zhang 2009; Zhang 2010a). In some studies, diagnostic criteria applied at recruitment were not labelled as ACR or EULAR criteria but were described in sufficient detail to be confident that they were fully consistent with the recommendations of these authorities or they were endorsed by other authorities (for example Chinese Orthopaedic Association criteria) (Wang 2012).

In two studies, ACR or EULAR criteria were not fully considered and these studies have been downgraded to unclear risk of selection

bias (Grube 2007; Randall 2008). In one study, selection criteria were so broad as to almost certainly have included recruitment of participants with conditions other than OA (Randall 2000). This study has been classified as having high risk of bias.

Allocation concealment was poorly described in most studies. Allocation concealment was assessed according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We attributed low risk of bias to one study (Randall 2008) in which allocation concealment was inferred from the description of the methods and the two studies in which it could reasonably be expected through reported compliance with ICH GCP guidelines (see Other potential sources of bias) (Grube 2007; Widrig 2007). Allocation concealment could not be determined in any other study; neither could failure to conceal allocation be determined. These studies have been classified as having unclear risk of bias for this criterion.

Blinding

Low risk of bias has been attributed to four studies (Grube 2007; Kosuwon 2010; Wang 2012; Widrig 2007) in which the herbal products and placebo or active controls could not be distinguished by colour, size, smell, shape, packaging or treatment regimen. In some studies, descriptions of blinding were not explicit but reference was made to compliance with relevant legislation that mandates blinding (see Other potential sources of bias), therefore we acknowleged that these studies also had low risk of bias.

In one study (Soltanian 2010), the method of blinding was inadequately described and no reference was made to governing guidelines. This study was classified as having an unclear risk of performance and detection bias. Two studies of stinging nettle were judged as having unclear risk despite reporting a complete description of the double-blinding method because we considered that placebo validity and blinding may be compromised by stinging side effects of this intervention (Randall 2000; Randall 2008). Although we considered it highly likely that these studies were sufficiently blinded, we have judged the risk of blinding as unclear. Risk of bias has been judged as high in studies that were open label, single blinded, or where interventions could be clearly distinguished.

In some studies where allocation concealment was inadequately described (see Allocation (selection bias)), it was unclear whether clinical examiners were blinded to treatment (detection bias). We have classified these studies as having unclear risk of bias in blinding of the outcome assessor.

Incomplete outcome data

Low risk of bias has been attributed to three studies in which participant withdrawals were fully reported and anayses conducted according to an intention-to-treat model (Grube 2007; Wang 2012; Widrig 2007). In these studies the methods for replacing missing data were fully reported. Unclear risk of attrition bias has been attributed to three studies in which withdrawals were reported but not considered in the anyalses (per protocol analysis only) (Kosuwon 2010; Randall 2000; Randall 2008). One study reported no participant withdrawals and no missing data (Soltanian 2010) and has been classified as having a low risk of bias for this criterion because in this case a per protocol analysis and intention-to-treat analysis should be identical. Studies that neither reported participant withdrawals nor applied any method for replacement of missing data were ascribed as at high risk of attrition bias.

Selective reporting

Low risk of bias has been attributed to three studies that use a confirmatory design; reported statistical power, effect, and sample size calculations; and provided results data in sufficient detail to allow extraction for re-analysis (Kosuwon 2010; Wang 2012; Widrig 2007). We have downgraded to unclear risk of reporting bias three studies that used either exploratory designs with small sample sizes (underpowered) (Randall 2008; Soltanian 2010) or where some data were insufficiently reported to allow extraction for re-analysis (Grube 2007). Examples of selective reporting include providing mean scores only (omission of standard deviations) at some or all time points. Similarly, data reported only as group change scores, percentages, or raw scores without measures of data spread, and data presented in graphical form only, were inadequate for re-analysis. One study was particularly poorly reported and has been classified as having high risk of bias for reporting (Randall 2000).

Other potential sources of bias

Selection bias due to diagnostic criteria (see Allocation (selection bias)) is reported under the heading 'other bias' in the risk of bias tables.

We attributed low risk of bias to studies that recruited and assessed participants consistent with the ACR or EULAR criteria, obtained ethics committee approval, with clinical trials registration, used validated outcome measures, and reported compliance with the Declaration of Helsinki and ICH GCP guidelines. Further, we considered that risk of bias could be assumed to be low if satisfying one of these conditions implied satisfaction of another. For example, the ICH GCP guidelines were recommended in Germany, France, Great Britain and Scandanavia from 1986 onwards, therefore we have assumed that Human Research Ethics Committee approvals granted for studies after this time in these countries necessitated compliance with these guidelines. In 1989, these guidelines were recommended across the European Community (EC) as then constituted. Again, we have assumed that from this date studies conducted in EC countries with ethics committee approval have complied with the guidelines regarding randomisation, allocation concealment, and blinding of participants and assessors.

In 1996, compliance with ICH CGP guidelines was required under German law governing clinical trials. The ICH GCP guidelines are now adopted by the WHO and most countries, including many developing countries, are listed as following these guidelines. Formally constituted Human Research Ethics Committees are charged with ensuring that clinical trials are conducted in compliance with these guidelines and associated regional legislation. We have classfied as low risk all studies that reported either compliance with ICH GCP guidelines or ethics committee approval, or both (Grube 2007; Kosuwon 2010; Randall 2008; Soltanian 2010; Wang 2012; Widrig 2007). High risk of bias has been attributed to the one study that did not report any form of ethical oversight of compliance with research design guidelines (ICH GCP guidelines or Delaration of Helsinki) (Randall 2000).

Effects of interventions

See: **Summary of findings for the main comparison** Arnica versus ibuprofen for osteoarthritis of the hand; **Summary of findings 2** Capsicum for osteoarthritis of the knee; **Summary of findings 3** Comfrey for osteoarthritis of the knee

See: Characteristics of included studies; Additional tables Table 3: Herbal medicinal products used for the treatment of OA.

Single source medicinal plant therapies investigated in studies of confirmatory study design were *Capsicum* (Kosuwon 2010), comfrey (Grube 2007), and *Arnica* (Widrig 2007). Results in two studies favoured the herbal interventions over placebo. The other study was a head-to-head comparison of a herbal intervention with an active control. Two studies of exploratory design investigated topical stinging nettle (Randall 2000; Randall 2008). These studies were conducted by the same team of researchers and reported results favouring the intervention, but only one study included sufficient numerical data suitable for extraction. Because of the stinging sensation produced by this intervention, neither study achieved adequate blinding. The single study of Marhame-Mafasel did not include complete details of the herbal product sufficient to replicate the study (Soltanian 2010). The same was true for the study of Chinese herbal patches (FNZG and SJG), however these products are priorietary and replication of these studies (multiple comparisons in one report) may be possible if the products were prepared according to manufacturing standards (Wang 2012). Results of all comparisons of interventions against placebo and head-to-head comparisons are reported for interest and completeness. No serious side effects were observed with any topical medicinal plant product.

Arnica montana (Arnica)

Three times daily topical application of a gel containing a tincture of*Arnica montana* was compared with a gel containing ibuprofen in 204 patients (174 participants per protocol) with OA of the hands over three weeks (Widrig 2007). Hand pain measured using a 100 mm VAS, hand function, 28 tender joint count, and duration and intensity of morning stiffness were not significantly different between groups, either as final end point measures or as changes from baseline scores. Mean cumulative doses of rescue medication (acetaminophen) differed only by 25 mg (MD 25, 95% CI 1066.47 to 1016.47; Analysis 1.6) over the intervention period. The number of participants reporting adverse events was similarly consistent between the two groups (odds ratio (OR) 1.75, 95% CI 0.70 to 4.37, P = 0.23; Analysis 1.7). These results suggested that short term topical use of *Arnica* gel afforded not inferior effects to those of ibuprofen gel, consistent with the research hypothesis. No comparison of *Arnica* gel to placebo was identified in this systematic review of the literature.

Capsicum species

In 99 patients studied over four weeks, three times daily application of a gel containing a tincture of *Capsicum* species was superior to placebo in reducing osteoarthritic knee pain measured using a 100 mm VAS (MD -1.00, 95% CI -6.76 to 4.76; Analysis 2.1) and overall OA measured using the composite WOMAC score (MD -2.64, 95% CI -9.51 to 4.23; Analysis 2.2). On both these measures the effect sizes were small and CIs crossed the midline indicating that *Capsicum* was not markedly better than placebo.

Fifty-seven participants reported a burning sensation in the skin during treatment with *Capsicum* extract gel but no participants withdrew from the study for this reason. Burning is a known side effect of *Capsicum*, associated with the mechanism of action of this medicinal plant, and may not be sufficently problematic to be classified as 'adverse', however when burning was included as an adverse event, the risk ratio of experiencing an adverse event while using *Capsicum* gel rather than placebo was 4.12 (95% CI 3.30 to 5.15; Analysis 2.3).

Symphytum officinale (comfrey)

In a large (n = 220) parallel group trial, three times daily topical use of an ointment containing comfrey root (*Symphyti offic. radix*) was compared with placebo over three weeks of intervention (Grube 2007). Grube 2007 found that treatment with comfrey root resulted in statistically significant improvements on the 100 mm VAS measures of total pain, pain at rest, and pain on movement; and on WOMAC scores of pain, stiffness, physical function and overall score. Data from this study could not be extracted for further analysis because the trial authors reported neither absolute scores nor measures of data spread (standard deviations, CIs) for any outcomes (Grube 2007). Mean within-group changes from baseline in pain at rest, pain on movement, WOMAC pain, stiffness, physical function and total scores, and SF-36 physical and mental component summary scores, are reported here for descriptive comparison (see Analysis 3.3 to Analysis 3.10).

Urtica dioica (stinging nettle)

Seven days of topical application of one stinging nettle leaf (freshly cut once a day and then applied directly to the painful area with gentle pressure and leaf movement) was compared with placebo (white dead nettle) for base of thumb pain (Randall 2000). This study was of limited use because the diagnosis of OA, although likely, was not established at baseline using ACR or EULAR criteria. This study was a crossover trial with two single weeks of intervention, each preceded by five weeks of washout. Randall 2000 reported that one week of treatment with stinging nettle afforded statistically significant improvements in pain measured using a 100 mm VAS (P = 0.026) and disability measured using the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI, P = 0.003) over placebo. Data reported in this study were presented per intervention rather than providing divided data for each stage of the crossover, and were insufficient to allow extraction for re-analysis.

A follow-up study by the same author team was a one week comparison of stinging nettle leaf against another *Urtica* species. This study included 16 weeks of follow-up. In between-group comparisons for pain at one week post-treatment (Analysis 5.1), and stiffness (Analysis 5.2) and physical function (Analysis 5.3) at four weeks post-treatment, stinging nettle was not significantly different to placebo. Because the stinging nettle group showed a greater within-group improvement in pain at one week post-treatment, the authors argued in favour of this treatment, however we noted that the stinging nettle group commenced the study with a greater mean pain score at baseline, so improvement in this group was not hampered by a floor effect.

Herbal mixture (Marhame-Mafasel)

A pomade of herbs known as Marhame-Mafasel was compared against placebo in a crossover study of 42 participants with OA of the knee. This study comprised two intervention periods of three

weeks each. No washout period occured between the intervention periods but this weakness in study design was accounted for in this review because we have extracted data from the first intervention period only (up to crossover). These results showed small effects for Marhame-Mafasel over placebo for improvements in pain (Analysis 4.1), physical function (Analysis 4.3), knee stiffness (Analysis 4.2) and overall disease severity (composite WOMAC score; Analysis 4.4). Although the authors reported a large and statistically significant omnibus effect for treatment (mean effect 3.94, SD 2.01), none of the univariate effect sizes appeared to be statistcally significant or clinically meaningful (minimal clinically important difference (MCID) not reported).

Further, although the authors reported no dropouts or withdrawals from the study, we question the meaningfulness of this claim because compliance with the intervention was low: "A patient was considered to comply with the assigned treatment if more than 75% of the pomade in the tubes was taken and moderate compliance if 25% to 75% of the pomade in the tubes was taken". Participants who used less than 25% of the pomade were classified as having poorly complied with the intervention, yet data from these participants were included unaltered in the study. It was possible that this classification of compliance was created post hoc as a stategy to include all data. We suggest that monitoring throughout the study and exclusion of non-complying participants, with replacement of missing data via the last observation carried forward method, would have been more robust and meaningful. Alternately, a post hoc multivariate analysis could have been undertaken to determine any confounding effect of poor participant compliance.

Chinese herbal patches

Chinese herbal patches containing either Fufang Nanxing Zhitong Gao (FNZG) or Shangshi Jietong Gao (SJG) were compared to placebo in a three-arm trial of 150 participants with OA of the knee. The intervention was maintained for seven days. The results showed modest effects in favour of both Chinese herbal patches over placebo, with effects being slightly larger in the FNZG group. Although the study was of a confirmatory design with sufficient power (80%) to detect changes, none of the effects were statistically significant.

Participants in the FNZG patch group rated their pain on walking (Analysis 6.1), pain due to OA (Analysis 6.2), and physical function (Analysis 6.4) as improved, compared with participants who used the placebo patches, but they also reported more adverse side effects (Analysis 6.6), notably skin irritation. Results were noted in a similar direction but with smaller effect sizes for SJG patches over placebo for pain on walking (Analysis 7.1), pain due to OA (Analysis 7.2), and physical function (Analysis 7.4); as well as similar rates of side effects (Analysis 7.6). A head-to-head comparison of the two patches was equivocal. No participants reported adverse effects from using the placebo patches.

DISCUSSION

Summary of main results

One confirmatory study is available for products from *Arnica montana* (Widrig 2007) (Summary of findings for the main comparison), *Capsicum* species (Kosuwon 2010) (Summary of findings 2), *Symphytum officinale* (Grube 2007) (Summary of findings 3), and two Chinese herbal patches (Wang 2012) (Table 4; Table 5; Table 6). Moderate quality evidence from one trial (174 participants) indicates that *Arnica montana* is equivalent to topical ibuprofen in terms of pain relief and improvement of hand function. We are less certain about the incidence of adverse events, which may be of concern with both topical *Arnica* extract and ibuprofen gel. Moderate evidence from one trial (99 participants) shows that topical *Capsicum* extract may possibly improve pain and overall function in people with osteoarthritis (OA) of the knee, but improvements are inconsistent (confidence intervals cross the midline) and some people may experience adverse effects, particularly skin irritation and burning.

Moderate evidence from one trial (150 participants) shows that patches containing two different formulations of Chinese herbs may possibly improve pain and function in people with OA of the knee, but the interventions were tested over seven days only, which may be insufficient for making judgements about clinical importance. We are uncertain about the clinical application of this evidence but the trial was quite well designed (double blind, randomised, controlled), thus we have graded the evidence for Chinese herbal patches as moderate but we have presented the summary of findings tables for these interventions under additional tables.

One exploratory study of the herbal mixture Marhame-Mafasel (42 particpants) identified a possible trend of effectiveness (confidence interval cross midline) that needs to be investigated in further rigorous trials (Soltanian 2010) (Table 7). Two pilot studies of topical nettle leaf returned disparate results; one study (crossover design) identified a trend for effectiveness (Randall 2000) (Table 8) but the follow-up study (parallel groups) returned equivocal results on between-group comparisons (Randall 2008) (Table 9). Both these studies were hampered by design flaws.

Overall completeness and applicability of evidence

The mechanism of action provides a rationale for topical medicinal plant products from *Arnica montana*, *Capsicum* species, *Symphytum officinale* and *Urtica dioica* as alternative options for the treatment of OA complaints. However, for the herbal mixtures the mechanism of action is less well ellucidated through in vitro studies, and the rationale for their use is unclear.

For none of the products is the quality or quantity of current scientific evidence of effectiveness sufficient. There is, at best, moderate evidence to support the use of *Arnica*, *Capsicum* and comfrey. However, for each of these interventions, further high quality clinical trials are likely to have an important impact on our confidence in the estimate of effect and may change the estimate. To be more confident in our estimates of clinical effectiveness we require well designed, randomised, double blind studies of a confirmatory study design with adequate power and sample size (n > 400) that test interventions over clinically relevant durations.

The results of studies undertaken with a proprietary product cannot be transferred to any preparation of the medicinal plant part (Chrubasik 2003). If the starting material and manufacturing process of products differ, active principles will differ and thus the sum of all actions of the ingredients. Due to insufficient declaration, the studies undertaken with *Arnica*, *Capsicum*, comfrey, and the herbal mixtures FNZG, SJG and Marhame-Mafasel are not repeatable unless the products

can be obtained from the producer or the laboratory. Even if these products can be obtained, due consideration must be given to the guidelines of Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP); these guidelines ensure that medicinal plant products are consistently produced and controlled to the quality standards appropriate to their intended use, and that the level of quality determined by the GMP and the properties of the products are maintained throughout the distribution (www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000154.jsp&mid=WC0b01ac0580027088&jsenabled=tru; www.who.int/vaccines-documents/DocsPDF/www9666.pdf).

It is a common but erroneous assumption that medicinal plant products are safer than other therapies for OA. All topical herbal medicinal products for the treatment of OA, except preparations from *Capsicum* species, have a low risk of adverse events when used in the suggested doses (Table 1; Table 2). Minor adverse reactions occurred with all medicinal plant treatments identified in this review, and only in the case of comfrey were these events more commonly reported among the placebo group (Analysis 3.11). Allergic reactions may occur with any of the topical medicinal plant products (ESCOP 2003; ESCOP 2009), but *Capsicum* species, comfrey and *Arnica* also contain toxic ingredients. Capsaicin is neurotoxic (Anonymous 2007; Nolano 1999) and a potential carcinogen (in animal and in vitro studies) (Anonymous 2007). The alkaloids in comfrey are hepatotoxic and carcinogenic (Li 2011). In vitro studies of *Arnica* raise concerns of cytotoxicity (Woerdenbag 1994). Because of the risk of cytotoxicity, comfrey and *Arnica* are recommended for external use only (ESCOP 2003; ESCOP 2009). In contrast to the other medicinal plant preparations, use of capsaicinoid containing preparations is restricted up to several weeks (ESCOP 2009) and the content of toxic alkaloid in the daily dose of topical comfrey has been limited to 100 µg per day (Blumenthal 1998).

Quality of the evidence

See: Characteristics of included studies, 'Risk of bias' tables.

Generally, the studies included in this review are of lower quality than desired, but we stress that these studies represent the current best quality evidence for the effectiveness of topical medicinal plant interventions in the treatment of OA.

Moderate evidence for estimate of effect: there is, at best, moderate evidence for creams and gels containing *Arnica*, comfrey, or *Capsicum* extract and Chinese herbal patches (FNZG and SJG) as topical herbal medicines in the treatment of OA. The evidence for these interventions is drawn from small (n < 400) single studies and is thus downgraded to moderate. Because the patches containing the two formulations of Chinese herbs were tested over seven days only, which may be insufficient for making judgements about clinical importance, we are uncertain about the clinical application of this evidence. We have graded the evidence for Chinese herbal patches as moderate but have presented the summary of findings table for these interventions under additional tables (Table 4; Table 5; Table 6).

Low evidence for estimate of effect: one exploratory study of the herbal mixture Marhame-Mafasel (42 particpants) identified a possible trend of effectiveness (confidence intervals cross midline) that needs to be investigated in further rigorous trials (Soltanian 2010) (Table 7).

Very low evidence for estimate of effect: two pilot studies of topical nettle leaf returned disparate results; one study (crossover design) identified a trend of effectiveness (Randall 2000) (Table 8) but the follow-up study (parallel groups) returned equivocal results on between-group comparisons (Randall 2008) (Table 9). Both these studies were hampered by design flaws.

Poorer quality studies using non-randomised, uncontrolled designs were excluded (for example Linsheng 1997). Similarly, we excluded clinical trials of products that are not strictly herbal so as to avoid misinterpretation of the results of these studies in herbal medicine practice (for example Altman 1994; Gemmell 2003). We note that more recent studies are typically of higher quality than older studies and commend researchers in this field for the improvement in research design and reporting.

Potential biases in the review process

This review is compromised by some poorly designed clinical trials that are underpowered and inadequately blinded. Herbal medicine is not a field known for the widespread adoption of evidence-based practice, however, in light of the small and low quality body of evidence in topical herbal treatment for OA, it is unsurprising that practitioners might continue to ignore the research and do what they 'have always done'. In this section, therefore, we have chosen to address some of the common biases in herbal medicine as well as in this review.

Agreements and disagreements with other studies or reviews

Evidence for topical capsaicin in the relief of osteoarthritic pain has previously been described as promising (Cameron 2007; Cameron 2009; Little 2000); however, because extracts reduced to single compounds are not herbal interventions according to the strictest WHO definitition, studies investigating the single extracted ingredient capsaicin were excluded from this review. The one study of an extract from *Capsicum* fruits that was included in this review showed small beneficial effects of the intervention, but not significantly greater than with placebo (Analysis 2.1; Analysis 2.2; Summary of findings 2). Favourable effects identified in the excluded studies (Altman 1994; Deal 1991; McCarthy 1992; McCleane 2000; Schnitzer 1994) are generally larger but are attributed to higher doses of capsaicin (0.025 to 0.05% v.v. in a vehicle cream) than the dose used in the included study (0.0125%). Even at the lower dose, the extract of *Capsicum* species is associated with a substantive risk of skin irritation (RR 4.12, 95% CI 11.61 to 24.84).

AUTHORS' CONCLUSIONS

Implications for practice

The current available evidence for topical herbal treatment of osteoarthritis (OA) is sparse and it is difficult to give clear recommendations regarding use of these products. Generally, high tolerance of the herbal medicinal products was demonstrated; however, caution is warranted in interpreting safety due to the small sample size in some of the studies. Accepting that there are few high quality randomised controlled trials of the efficacy or safety of topical medicinal plant products, in the absence of

more robust results we recommend that practitioners adopt the preparations, methods of administration, and doses of topical products suggested in the monographs (see Background).

The only recommendations we are confident to make for clinical practice are that a) *Arnica* gel probably improves pain and function as effectively as a gel containing non-steroidal anti-inflammatory drug, but with no better (and possibly worse) adverse event profile; and b) comfrey extract gel probably improves pain more than placebo. Effects of comfrey gel on physical function and quality of life in people with OA are not estimable from the data provided. *Capsicum* extract gel probably will not improve pain or function more than placebo at the dose examined in this review. Although patches containing the Chinese herbal mixtures FNZG and SJG probably slightly improve pain and function more than placebo, we are uncertain of the clinical applicability of these results because these interventions were tested over seven days only. There is insufficient evidence to make clinical recommendations for or against the use of other topical herbal medicines for the treatment of OA.

Implications for research

We recommend that future updates of this review focus on the topical herbal interventions for which there currently appears to be moderate evidence, *Arnica*, *Capsicum*, comfrey, and the Chinese herbal mixtures FNZG and SJG.

At this stage we cannot recommend that resources be invested in single small studies of untested herbal interventions or herbal interventions for which the current evidence is low or very low. Such studies do not add substantially to the body of evidence but increase confusion among practitioners.

Several studies were excluded from this review on the grounds that they did not investigate truly herbal products. Included studies are hampered by flawed research design, including unclear recruitment criteria, and inadequate characterisation of the herbal interventions. Other studies are of limited usefulness because the selection criteria were incomplete, methods were confusingly reported (Begg 1996; Moher 2001), or data were presented to support the authors' preferred conclusions (McGauran 2010). We recommend that future researchers give attention to the detail of study design, ensuring that participant samples are well defined according to ACR and EULAR criteria and recruited without bias, that herbal preparations are reported in detail, including dose, extraction method and active principle, and that study results are recorded using reliable, valid outcome measures.

Evidence for mechanisms of effect and toxicity are drawn from animal studies and in vitro designs rather than from human clinical trials. Well designed, fully powered clinical trials are required to confirm the efficacy of most topical medicinal plant products in humans. We encourage herbal medicine practitioners to consider involvement of themselves, their practices, and their patients in future clinical trials to ensure that representative patient groups are included and that trial results have broad applicability to everyday practice.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Grube 2007

Methods	Randomised, double-blind, placebo control, 2 parallel groups, 2 centre study. Duration 3 weeks.
Participants	Randomised n=220, Completed n=186. Mean age 58 years. M:F 67:153. Inclusion: OA knee (criteria not specified), pain VAS 0-100 >40mm.
Interventions	Kytta-Salbe® f: *Symphytum officinale* radix (comfrey root) extract, 6g (2g TID), ointment. Placebo control: ingredients not reported, ointment. Regimen: If bilateral OA, treat both knees, but outcome measures limited to most painful joint only. Massage 6cm long thread of ointment into skin covering the knee three times daily.
Outcomes	Pain at rest VAS 0-100, pain with movement VAS 0-100, WOMAC-VAS 0-100 (24 items, 3 subscales; all VAS 0 indicates no deficits, 100 indicates worst possible deficits).
Notes	Results favour intervention.
Risk of bias	

Grube 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as randomised, method not reported[1]. Baseline parameters compared for significant differences.
Allocation concealment (selection bias)	Low risk	Allocation concealment not reported[1].
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind. Active intervention and placebo not distinguished by look, taste, smell or packaging.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported withdrawals. Included full analyses (intention-to-treat) and valid case analyses (per-protocol).
Selective reporting (reporting bias)	Unclear risk	Confirmatory design, large sample size, statistical power not reported, alpha 0.05. (low risk) Most outcome data reported as change scores, percentages, and graphs only, insufficient for extraction. (unclear risk) Standard deviations for pain estimated from graphical data. Reported adverse events. (low risk)
Other bias	Unclear risk	Criteria for diagnosis of OA not specified at baseline. Diagnosis not consistent with ACR criteria, but likely to be OA. (unclear risk) Reported compliance with Declaration of Helsinki and ICH GCP guidelines. (low risk)

Kosuwon 2010

Methods	Randomised, double-blind, placebo control, 2 group, crossover study. Duration 4 weeks each arm, 1 week washout.
Participants	Randomised n=100, Completed n=99. Mean age 61 years, range 44-82 years. M:F = 100:0. Inclusion: OA knee (ACR criteria).
Interventions	Capsika gel: *Capsicum* (species not stated) extract. Placebo control: ingredients not reported. Regimen: TID, applied 2 inches of extruded gel around the knee and rubbed in until dry. Rescure mediccation permitted: paracetamol (acetaminophen) up to 1500mg (3 x 500mg).
Outcomes	Pain VAS 0-100 (0 indicates no pain, 100 indicates worst possible pain), WOMAC 0-4 (24 items, 3 subscales, higher scores indicate worse deficits).
Notes	Results favour intervention.

Risk of bias

Bias	Authors' judgement	Support for judgement

Kosuwon 2010 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Described as randomised, method not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind. Active intervention, placebo, and active controls not distinguished by look, taste, smell, packaging, or medication regimen.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reported withdrawals. (low risk) Per protocol analysis only. (unclear risk)
Selective reporting (reporting bias)	Low risk	Confirmatory design, sample size slightly smaller than planned, statistical power 80%, alpha 0.05. Outcome VAS 0-10 converted to 100mm scale for data extraction. Reported adverse events.
Other bias	Low risk	Diagnosis / assessment consistent with ACR criteria. Reported ethics committee approval. Reported clinical trials registration (IDNCT00471055). Reported financial and in kind support.

Randall 2000

Methods	Randomised, double-blind, placebo control, 2 group crossover. Duration 12 weeks (2 x 1 week intervention, each followed by 5 week washout).
Participants	Randomised n=27, Completed n=24. Mean age 60 yrs, range 45-82 yrs. M:F 4:23. Inclusion: persistent base of thumb pain (OA criteria not specified).
Interventions	Tradename not provided.*Urtica dioica* (stinging nettle). Placebo control: *Lamium album* (white dead nettle). Regimen: Whole leaf plucked from live plant, applied directly to skin of painful thumb, total contact with skin 30 seconds per day.
Outcomes	Pain VAS 0-100 (0 indicates no pain, 100 indicates worst possible pain), pain (verbal 5 point scale, 0 indicates no pain, 5 indicates worst possible pain), HAQ-DI (higher score indicates more disability), analgesics, NSAID use, and sleep (scales not reported).
Notes	Results favour intervention, but mean improvement in HAQ-DI score does not exceed accepted minimal clinically important difference.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, method not reported.

Randall 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Active intervention and placebo not distinguished by look, taste, or smell, but placebo validity and blinding may be compromised by stinging effect of active intervention.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reported withdrawals. (low risk) Per protocol analysis only. (unclear risk)
Selective reporting (reporting bias)	High risk	Exploratory study design; power, effect, and sample size not determined a priori. (unclear risk) Reported adverse events. (low risk) Included notes on unsatisfactory outcome measures. Most outcome data were reported as means only (not standard deviations) without confidence intervals. (unclear risk) Data for first and second periods were aggregated and insufficient for extraction from the first arm (up to crossover) only. (high risk) Aggregated data were extracted for the critical outcome of pain for inclusion in the summary of findings tables. An error was identified during this data extraction. (unclear risk)
Other bias	High risk	Criteria for diagnosis of OA not specified at baseline. Other arthritides are possible confounders. (high risk) Did not report ethical oversight.

Randall 2008

Methods	Randomised, single blind, placebo control, 2 parallel groups. Duration 1 week intervention, plus 15 weeks follow-up.
Participants	Randomised n=42, Completed intervention n=42, Completed follow up n=35. Mean age intervention group 65 yrs, control 67 yrs. M:F control 13:8, intervention 11:10. Inclusion: presumptive diagnosis of knee OA based on ACR criteria (Read diagnositic code/s for "knee pain" or "OA knee" in clinical records), aged 55-80 yrs, knee pain most days of the previous month, WOMAC pain subscale score of at least 4 at baseline.
Interventions	Tradename not provided. *Urtica dioica* (stinging nettle). Placebo control: *Urtica galeopsifolia* (non-stinging nettle). Regimen: Whole leaf plucked from live plant, applied directly to skin of painful knee, total contact with knee 1 minute per day.
Outcomes	WOMAC 0-4 (A, B, and C subscales; 24 items, 3 subscales, higher scores indicate worse deficits), pain at rest VAS 0-100, pain on walking VAS 0-100 (all VAS 0 indicates no pain, 100 indicates worst possible pain), patient global assessment of beneficial and adverse reactions, medication diary (scales not reported). Qualitative outcomes: focus groups discussions to explore participants' attitudes and experiences of the trial.

Randall 2008 *(Continued)*

Notes	Results equivocal; stinging nettle not superior to placebo. Outcome scores for participants who returned poorly kept nettle plants did not differ significantly from group means.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated, block randomisation.
Allocation concealment (selection bias)	Low risk	Adequate allocation concealment can be inferred. "Plants in serially numbered, opaque pots."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Active intervention and placebo not distinguished by look, taste, or smell, but placebo validity and blinding may be compromised by stinging effect of active intervention.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reported withdrawals. (low risk) Per protocol analysis only. (unclear risk)
Selective reporting (reporting bias)	Unclear risk	Exploratory study design; power, effect, and sample size not determined *a priori.* (unclear risk) Reported adverse events. (low risk)
Other bias	Unclear risk	Diagnosis not consistent with ACR criteria. OA not distinguished from other causes of knee pain in older adults at baseline (presumptive diagnosis). Although OA is the most likely cause of knee pain in older adults, other arthritides are possible confounders. (unclear risk) Reported ethics committee approval. (low risk)

Soltanian 2010

Methods	Randomised, placebo control, double blind, single centre, crossover. Duration 6 weeks (2 x 3 week intervention, no washout).
Participants	Randomised n=42; intervention n=21, control n=21. Completed n=42; intervention n=21, control n=21. OA knee (EULAR criteria).
Interventions	Marhame-Mafasel: *Arnebia euchroma* and *Matricaria chamomilla* pomade. Placebo control: ingredients not reported, pomade. Regimen: 4.5g/day (1.5g TID) of pomade massaged firmly into skin until completely disappeared.
Outcomes	WOMAC VAS 0-100 (24 items, 3 subscales, higher scores indicate worse deficits).
Notes	Results favour intervention. In all between and within-group comparisons, improvements in osteoarthritic pain, function, and stiffness were greater in people using Marhame-Mafasel over placebo. Improvement scores attributed to Marhame-Mafasel were somewhat greater in the second arm of the crossover, suggesting that there may be a concurrent benefit from vigorous massage over time.

Risk of bias

Soltanian 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as randomised. "Randomized according to a random number table."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double blind. Active interventions not distinguished by look, taste, smell or packaging. (low risk) Blinding of assessors not reported. (unclear risk)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported no missing data, no withdrawals, no participants lost to follow up. (low risk) Per protocol analysis only. (low risk if no missing data)
Selective reporting (reporting bias)	Unclear risk	Exploratory study design; power, effect, and sample size not determined a priori. (unclear risk) Reported adverse events. (low risk)
Other bias	Low risk	Diagnosis / assessment consistent with ACR crtieria. (low risk) Reported ethics committee approval. (low risk) Reported that not all participants "completed" the intervention and that some participants displayed poor compliance with the intervention, but it is unclear how lack of compliance influenced results.

Wang 2012

Methods	Randomised, placebo control, double blind, single centre, 3 parallel groups (2 interventions). Duration 7 days.
Participants	Randomised n=150; intervention A n=60, intervention B n=60, control n=30. Completed n=42; intervention n=21, control n=21. OA knee (Chinese Orthopaedic Association criteria), baseline pain >20mm on 100mm VAS.
Interventions	Intervention A: topical patch containing Fufang Nanxing Zhitong Gao (FNZG) Chinese herbal mixture. Intervention B: topical patch containing Shangshi Jietong Gao (SJG) Chinese herbal mixture. Placebo control: topical patch made of acrylic, adhesive tape (no ingredients). All patches applied to skin of right or left knee for 8 hours per day (overnight).
Outcomes	Pain VAS 0-100, WOMAC, Traditional Chinese Medicine Syndrome Questionnaire (TCMSQ).
Notes	Results favour FNZG patches.

Risk of bias

Bias	Authors' judgement	Support for judgement

Wang 2012 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Described as randomised, method not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation reported as concealed, method not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Active interventions and placebo control not distinguished by look, taste, smell or packaging.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported withdrawals. Included per protocol and intention-to-treat analyses. Missing data replaced using last observation carried forward method.
Selective reporting (reporting bias)	Low risk	Confirmatory design, statistical power 80%, alpha 0.05. All data reported as means and confidence intervals. Standard deviations calculated during data extraction. Reported adverse events.
Other bias	Low risk	Diagnosis and assessment consistent with ACR criteria. Reported eithics committee approval, and clinical trials registration.

Widrig 2007

Methods	Randomised, double blind, active control (ibuprofen 5% topical gel), 2 parallel groups, 20 centre study. Duration 3 weeks.
Participants	Randomised n=204, Completed n=174. Mean age 64 yrs. M:F 57:147. Inclusion: OA hand (ACR criteria).
Interventions	A. Vogel *Arnica* Gel: *Arnica montana* (mountain arnica), tincture 50% v v.
Outcomes	Pain VAS 0-100 (0 indicates no pain, 100 indicates worst possible pain), hand algofunctional index 0-3 (10 items, higher score indicates worse function), tender joint count, morning stiffness intensity and duration, patient evaluation of efficacy, patient acceptance of treatment, physician evaluation of efficacy, acetaminophen use.
Notes	*Arnica* equally effective as ibuprofen on all primary and secondary measures. Post-intervention pain scores high with large standard deviation in both groups.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Described as randomised, method not reported[1].
Allocation concealment (selection bias)	Low risk	Allocation concealment not reported[1].
Blinding (performance bias and detection bias)	Low risk	Active interventions not distinguished by look, taste, smell or packaging.

Widrig 2007 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported withdrawals. Included per protocol and intention-to-treat analyses.
Selective reporting (reporting bias)	Low risk	Confirmatory design, statistical power 80%, alpha 0.024. Reported adverse events. Non-inferiority hypothesis, MCID determined *a priori* at 12%.
Other bias	Low risk	Diagnosis / assessment consistent with ACR criteria. Reported eithics committee approval, and complince with ICH GCP guidelines and Declaration of Helsinki.

Unless otherwise stated, all oral medications are reported as total daily doses, which may have been administered in single or divided doses.
Unless subscales are named, outcome measures (eg: WOMAC, HAQ, COAT) were used in entirety. Unless specified, all outcome measures were administered, scored, and scaled according to OARSI standards.
1. Reported compliance with ICH GCP guidelines (ICH 2004) anchored in European law, so adequate randomisation, allocation concealment, and blinding can be assumed.

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

Study	Reason for exclusion
Altman 1994	Intervention included extracted capsaicin, therefore not herbal as per WHO definition.
Deal 1991	Intervention included extracted capsaicin, therefore not herbal as per WHO definition.
Gemmell 2003	Intervention included capsaicin and menthol (extracted or synthetic), therefore not herbal as per WHO definition. Ingredients not listed in sufficient detail, therefore study is only repeatable using the proprietary product.
Kielczynski 1997	Discussion paper.
Linsheng 1997	Not a randomised controlled trial. Case series.
Long 2001	Review paper.
McCarthy 1992	Intervention included extracted capsaicin, therefore not herbal as per WHO definition.
McCleane 2000	Intervention included extracted capsaicin, therefore not herbal as per WHO definition.
McKay 2003	Intervention included capsaicin and menthol (extracted or synthetic), therefore not herbal as per WHO definition. Ingredients not listed in sufficient detail, therefore study is only repeatable using the proprietary product.
Rayburn 2009	Not a randomised controlled trial.
Sagar 1988	Not a randomised controlled trial.
Saley 1987	Not a randomised controlled trial. Case series.
Schnitzer 1994	Intervention included extracted capsaicin, therefore not herbal as per WHO definition.

Study	Reason for exclusion
Smith 2011	Intervention included tannic acid (extracted or synthetic), therefore not herbal as per WHO definition.
Wadnap 2006	Not a randomised controlled trial (observational study).
Yuelong 2011	Not a randomised controlled trial. Protocol for a randomised controlled trial only.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Zahmatkash 2011

Methods	RCT
Participants	n=92
Interventions	Intervention: herbal ointment containing cinnamon, ginger, mastic (Saghez) and sesame oil. Active control: salicylate ointment.
Outcomes	Pain VAS 0-100, stiffness VAS 0-100, limited motion VAS 0-100.
Notes	Head to head comparison, non-inferiority hypothesis. Abstract only available. *Pakistan Journal of Biological Science* is not indexed. Full manuscript sought in hard copy via inter-library loan.

Zhong 2006

Methods	RCT
Participants	n=88 (intervention n=44, control n=44)
Interventions	Intervention: Bushen Quhan Tongluo herbs by orally or externally washing. Bushen Quhan. Tongluo: Hutaorou (12 g), Buguzhi (12 g), Chaoduzhong (12 g), Shudi (15 g), Dahuixiang (9 g), Luoshiteng (15 g), Zhichuanwu (9 g), Sanqi (6 g), Wugong (3 g), Jixieteng (15 g). The prescription for external washing: Tuogucao (40 g), Danggui (15 g), Sumu (15 g), Shengdahuang (15 g), Shengnanxing (10 g), Ruxiang (10 g), Meyao (10 g), Bingpian (3 g). Topical administration: The medicine that dissolved in 500 mL of 100 degreesC boiled water was adopted to wash both knees while the temperature down to 35 degreesC one dose upon a time and twice a day). Patients in the control group were given sulfated glucosamine (Weiguli Capsule. Each capsule contains 314 mg of sulfated glucosamine crystal, which is equal to 250 mg of sulfated glucosamine) two capsules a time and 3 times a day as well as piroxicam (Yantong Xikang Pill) once a day and 20 mg each time. Patients in both groups were administrated for 12 weeks.
Outcomes	WOMAC
Notes	Unable to distinguish oral administration internvention group from topical administration intervention group results from abstract alone. Abstract only available. *Chinese Journal of Clinical Rehabilitation* not indexed. Full manuscript sought in hard copy via inter-library loan.

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

Youxin 2012

Trial name or title	Rehabilitation protocol of the Traditional Chinese Medicine on patients with dyskinesia of the knee osteoarthritis: A randomized controlled trial study in community
Methods	Randomised, controlled, parallel 2-group trial.
Participants	Community dwelling male and female adults aged 40-75 years, with knee OA (Chinese Orthopaedic Association criteria); n = 722 (intervention n= 361, control n = 361).
Interventions	Foundation treatment of Chinese medicinal herb washing and traditional exercises training method, plus blood-letting puncture, acupuncture, massage, and analgesics.
Outcomes	Pain, swelling, knee range of motion, muscle strength, average walking distance, stair climbing and descent, activities of daily living, analgesic use, quality of life, safety, health economic evaluation, global effect.
Starting date	Unknown. Ethics committee approval from 27/09/2012.
Contact information	Su Youxin: No. 1, HuaTuo road, Shangjie town, Minhou county, Fujian, Fuzhou, China; +86 1330 502 1666; suyouxin777@hotmail.com
Notes	Prospective registration, ongoing clinical trial.

DATA AND ANALYSES

Comparison 1. Arnica versus ibuprofen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain VAS 0-100	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 28 painful joint count change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Intensity of morning stiffness (1 to 5) change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Duration of morning stiffness (1 to 5) change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Hand algofunctional index (0 to 30)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Cumulative dose of analgesics (acetominophen mg) over 3 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Participants (n) reported adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Arnica versus ibuprofen, Outcome 1 Pain VAS 0-100.

Study or subgroup	Arnica gel		Ibuprofen gel		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Widrig 2007	89	40.4 (21.5)	85	44.2 (20.9)		-3.8[-10.1,2.5]

Favours arnica -100 -50 0 50 100 Favours ibuprofen

Analysis 1.2. Comparison 1 Arnica versus ibuprofen, Outcome 2 28 painful joint count change from baseline.

Study or subgroup	Arnica gel		Ibuprofen gel		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Widrig 2007	89	-3 (4.4)	85	-2.5 (3.2)		-0.5[-1.64,0.64]

Favours arnica -10 -5 0 5 10 Favours ibuprofen

Analysis 1.3. Comparison 1 Arnica versus ibuprofen, Outcome 3 Intensity of morning stiffness (1 to 5) change from baseline.

Study or subgroup	Arnica gel		Ibuprofen gel		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Widrig 2007	89	-0.9 (1.1)	85	-1 (0.8)		0.1[-0.18,0.38]

Favours arnica -10 -5 0 5 10 Favours ibuprofen

Analysis 1.4. Comparison 1 Arnica versus ibuprofen, Outcome 4 Duration of morning stiffness (1 to 5) change from baseline.

Study or subgroup	Arnica gel		Ibuprofen gel		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Widrig 2007	89	-0.9 (1.3)	85	-0.8 (1.1)		-0.1[-0.46,0.26]

Favours arnica -10 -5 0 5 10 Favours ibuprofen

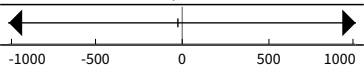
Analysis 1.5. Comparison 1 Arnica versus ibuprofen, Outcome 5 Hand algofunctional index (0 to 30).

Study or subgroup	Arnica gel		Ibuprofen gel		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Widrig 2007	89	7.1 (4.8)	85	7.5 (4.3)		-0.4[-1.75,0.95]

Favours arnica -20 -10 0 10 20 Favours ibuprofen

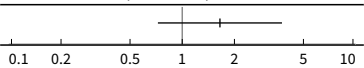
Analysis 1.6. Comparison 1 Arnica versus ibuprofen, Outcome 6 Cumulative dose of analgesics (acetominophen mg) over 3 weeks.

Study or subgroup	Arnica gel N	Arnica gel Mean(SD)	Ibuprofen gel N	Ibuprofen gel Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Widrig 2007	89	5625 (3400)	85	5650 (3600)		-25[-1066.47,1016.47]



Analysis 1.7. Comparison 1 Arnica versus ibuprofen, Outcome 7 Participants (n) reported adverse events.

Study or subgroup	Arnica gel n/N	Ibuprofen gel n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Widrig 2007	14/105	8/99		1.65[0.72,3.76]

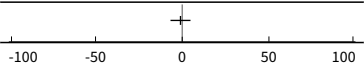


Comparison 2. Capsaicin 0.0125% versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain VAS 0-100	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 WOMAC 0-4 (Overall)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Adverse event episodes (n) reported	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Capsaicin 0.0125% versus placebo, Outcome 1 Pain VAS 0-100.

Study or subgroup	Capsicum gel N	Capsicum gel Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Kosuwon 2010	65	44.6 (14.6)	34	45.6 (13.5)		-1[-6.76,4.76]

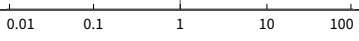


Analysis 2.2. Comparison 2 Capsaicin 0.0125% versus placebo, Outcome 2 WOMAC 0-4 (Overall).

Study or subgroup	Capsicum gel N	Capsicum gel Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Kosuwon 2010	65	32.2 (19.2)	34	34.8 (15)		-2.64[-9.51,4.23]

Analysis 2.3. Comparison 2 Capsaicin 0.0125% versus placebo, Outcome 3 Adverse event episodes (n) reported.

Study or subgroup	Capsaicin n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kosuwon 2010	272/338	66/338		4.12[3.3,5.15]



Comparison 3. Comfrey versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain VAS 0-100	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Pain VAS 0-100 change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Pain VAS 0-100 (at rest) change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Pain VAS 0-100 (movement) change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 WOMAC-VAS (Pain) change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 WOMAC-VAS (Stiffness) change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 WOMAC-VAS (Function) change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 WOMAC-VAS (Overall) change from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 Change in SF-36 physical component summary score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Change in SF-36 mental component summary score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11 Participants (n) reported adverse events	1		Risk Difference (M-H, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Comfrey versus placebo, Outcome 1 Pain VAS 0-100.

Study or subgroup	Comfrey N	Comfrey Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Grube 2007	110	42 (28)	110	83.5 (24)		-41.5[-48.39,-34.61]

Analysis 3.2. Comparison 3 Comfrey versus placebo, Outcome 2 Pain VAS 0-100 change from baseline.

Study or subgroup	Comfrey		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Grube 2007	110	-51.6 (0)	110	-10.1 (0)		Not estimable

Favours comfrey -100 -50 0 50 100 Favours placebo

Analysis 3.3. Comparison 3 Comfrey versus placebo, Outcome 3 Pain VAS 0-100 (at rest) change from baseline.

Study or subgroup	Comfrey		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Grube 2007	110	-20.9 (0)	110	-4.6 (0)		Not estimable

Favours comfrey -100 -50 0 50 100 Favours placebo

Analysis 3.4. Comparison 3 Comfrey versus placebo, Outcome 4 Pain VAS 0-100 (movement) change from baseline.

Study or subgroup	Comfrey		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Grube 2007	110	-30.7 (23.3)	110	-5.6 (20)		-25.1[-30.84,-19.36]

Favours comfrey -100 -50 0 50 100 Favours placebo

Analysis 3.5. Comparison 3 Comfrey versus placebo, Outcome 5 WOMAC-VAS (Pain) change from baseline.

Study or subgroup	Comfrey		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Grube 2007	110	12.1 (0)	110	2.7 (0)		Not estimable

Favours comfrey -100 -50 0 50 100 Favours placebo

Analysis 3.6. Comparison 3 Comfrey versus placebo, Outcome 6 WOMAC-VAS (Stiffness) change from baseline.

Study or subgroup	Comfrey		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Grube 2007	110	4.8 (0)	110	1.2 (0)		Not estimable

Favours comfrey -100 -50 0 50 100 Favours placebo

Analysis 3.7. Comparison 3 Comfrey versus placebo, Outcome 7 WOMAC-VAS (Function) change from baseline.

Study or subgroup	Comfrey		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Grube 2007	110	43.4 (0)	110	10.7 (0)		Not estimable

Favours comfrey -100 -50 0 50 100 Favours placebo

Analysis 3.8. Comparison 3 Comfrey versus placebo, Outcome 8 WOMAC-VAS (Overall) change from baseline.

Study or subgroup	Comfrey		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Grube 2007	110	60.4 (0)	110	14.7 (0)		Not estimable

Favours comfrey -100 -50 0 50 100 Favours placebo

Analysis 3.9. Comparison 3 Comfrey versus placebo, Outcome 9 Change in SF-36 physical component summary score.

Study or subgroup	Comfrey		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Grube 2007	110	11.9 (0)	110	1.3 (0)		Not estimable

Favours placebo -10 -5 0 5 10 Favours comfrey

Analysis 3.10. Comparison 3 Comfrey versus placebo, Outcome 10 Change in SF-36 mental component summary score.

Study or subgroup	Comfrey		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Grube 2007	110	4.2 (0)	110	1.1 (0)		Not estimable

Favours placebo -10 -5 0 5 10 Favours comfrey

Analysis 3.11. Comparison 3 Comfrey versus placebo, Outcome 11 Participants (n) reported adverse events.

Study or subgroup	Comfrey	Placebo	Risk Difference	Risk Difference
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Grube 2007	7/110	15/110		-0.07[-0.15,0.01]

Favours comfrey -10 -5 0 5 10 Favours placebo

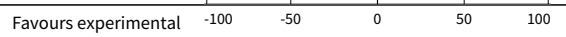
Comparison 4. Marhame-Mafasel versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 WOMAC-VAS (Pain) change from baseline	1	42	Mean Difference (IV, Fixed, 95% CI)	-5.62 [-17.84, 6.60]
2 WOMAC-VAS (Stiffness) change from baseline	1	42	Mean Difference (IV, Fixed, 95% CI)	-14.3 [-28.22, -0.38]
3 WOMAC-VAS (Function) change from baseline	1	42	Mean Difference (IV, Fixed, 95% CI)	-1.09 [-9.40, 7.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 WOMAC-VAS (Overall) change from baseline	1	42	Mean Difference (IV, Fixed, 95% CI)	-6.01 [-15.67, 3.65]
5 Participants (n) reporting adverse events	1	42	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 98.27]

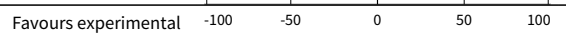
Analysis 4.1. Comparison 4 Marhame-Mafasel versus placebo, Outcome 1 WOMAC-VAS (Pain) change from baseline.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Soltanian 2010	21	-14 (18.4)	21	-8.4 (21.8)		100%	-5.62[-17.84,6.6]
Total ***	**21**		**21**			**100%**	**-5.62[-17.84,6.6]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.9(P=0.37)							



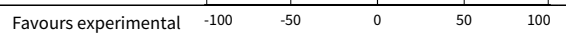
Analysis 4.2. Comparison 4 Marhame-Mafasel versus placebo, Outcome 2 WOMAC-VAS (Stiffness) change from baseline.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Soltanian 2010	21	-21.1 (28.7)	21	-6.8 (15.3)		100%	-14.3[-28.22,-0.38]
Total ***	**21**		**21**			**100%**	**-14.3[-28.22,-0.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.01(P=0.04)							

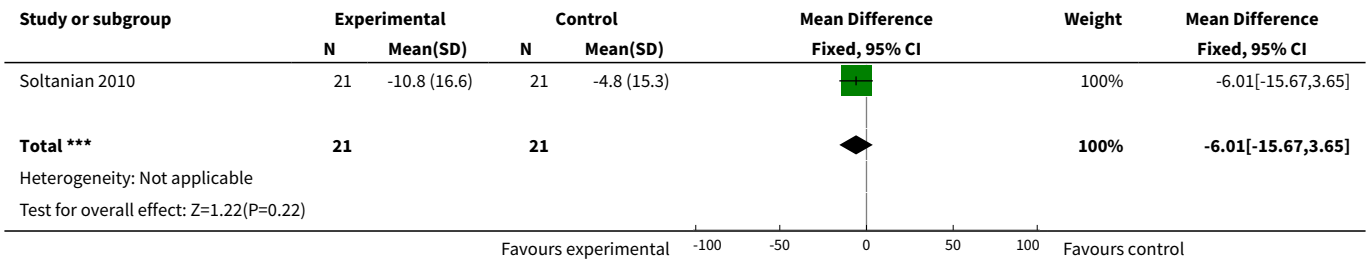


Analysis 4.3. Comparison 4 Marhame-Mafasel versus placebo, Outcome 3 WOMAC-VAS (Function) change from baseline.

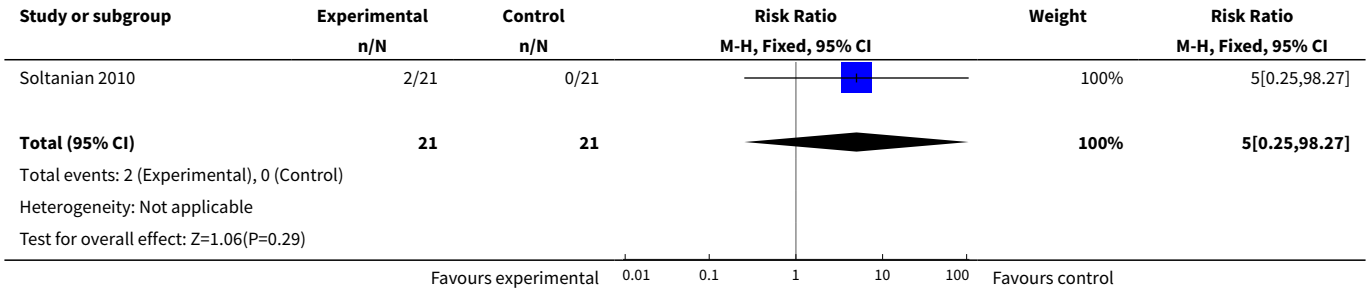
Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Soltanian 2010	21	-10.4 (13.3)	21	-9.3 (14.2)		100%	-1.09[-9.4,7.22]
Total ***	**21**		**21**			**100%**	**-1.09[-9.4,7.22]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.26(P=0.8)							



Analysis 4.4. Comparison 4 Marhame-Mafasel versus placebo, Outcome 4 WOMAC-VAS (Overall) change from baseline.



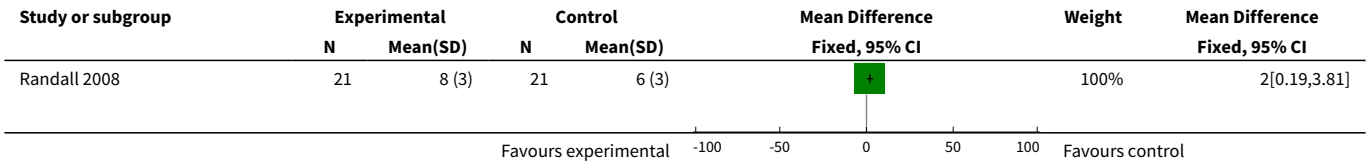
Analysis 4.5. Comparison 4 Marhame-Mafasel versus placebo, Outcome 5 Participants (n) reporting adverse events.

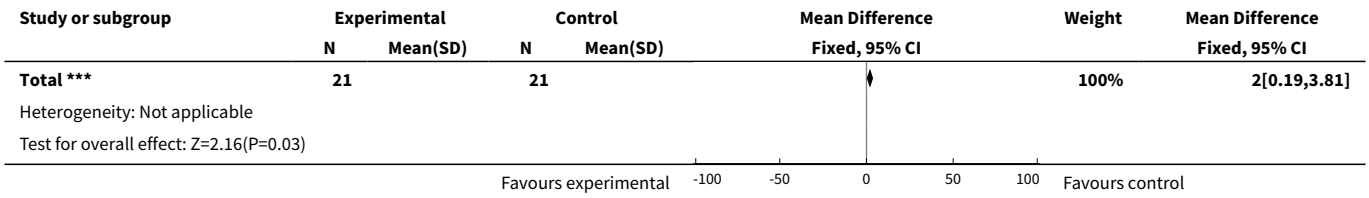


Comparison 5. Stinging nettle versus placebo

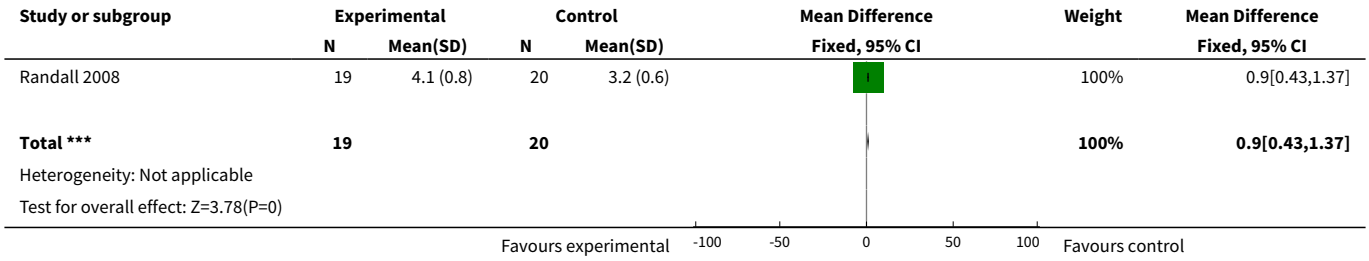
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 WOMAC 0-4 (Pain) at 1 week	1	42	Mean Difference (IV, Fixed, 95% CI)	2.0 [0.19, 3.81]
2 WOMAC 0-4 (Stiffness) at 4 weeks	1	39	Mean Difference (IV, Fixed, 95% CI)	0.90 [0.43, 1.37]
3 WOMAC 0-4 (Function) at 4 weeks	1	39	Mean Difference (IV, Fixed, 95% CI)	5.0 [0.90, 9.10]
4 Participants (n) reported adverse events	1	42	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.20, 20.41]

Analysis 5.1. Comparison 5 Stinging nettle versus placebo, Outcome 1 WOMAC 0-4 (Pain) at 1 week.

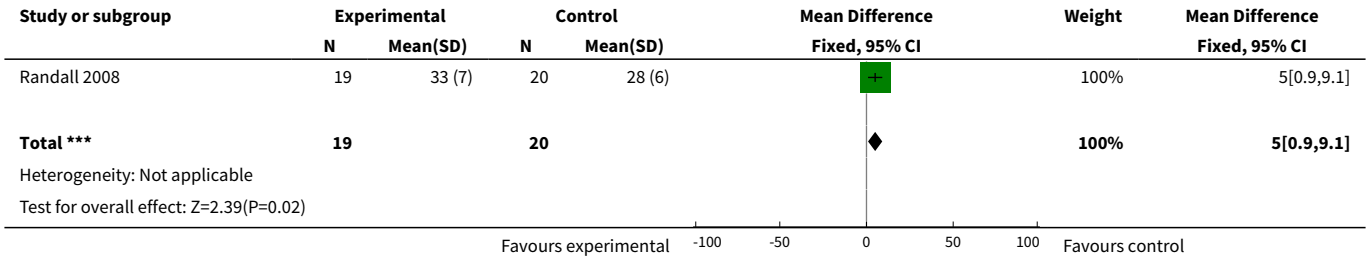




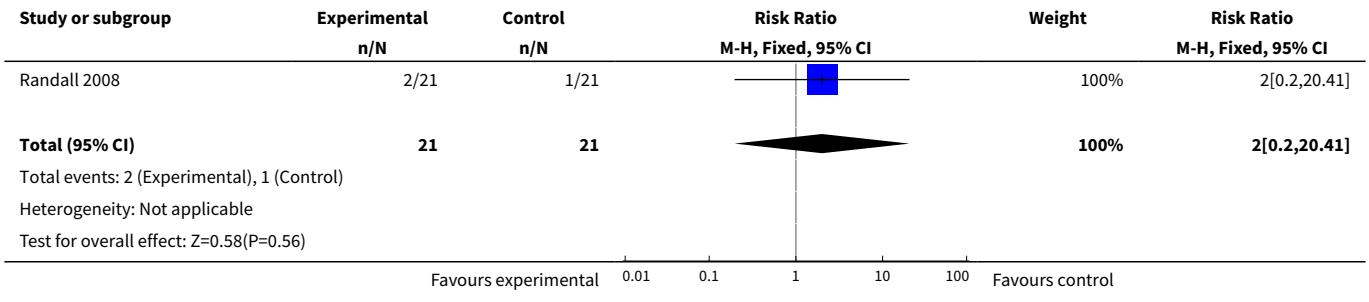
Analysis 5.2. Comparison 5 Stinging nettle versus placebo, Outcome 2 WOMAC 0-4 (Stiffness) at 4 weeks.



Analysis 5.3. Comparison 5 Stinging nettle versus placebo, Outcome 3 WOMAC 0-4 (Function) at 4 weeks.



Analysis 5.4. Comparison 5 Stinging nettle versus placebo, Outcome 4 Participants (n) reported adverse events.

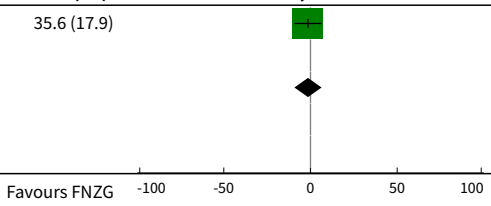


Comparison 6. FNZG versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on walking VAS 0-100	1	90	Mean Difference (IV, Fixed, 95% CI)	-1.44 [-9.28, 6.40]
2 WOMAC 0-4 (Pain)	1	90	Mean Difference (IV, Fixed, 95% CI)	-1.14 [-3.07, 0.79]
3 WOMAC 0-4 (Stiffness)	1	90	Mean Difference (IV, Fixed, 95% CI)	-0.42 [-1.29, 0.45]
4 WOMAC 0-4 (Function)	1	90	Mean Difference (IV, Fixed, 95% CI)	-2.61 [-9.50, 4.28]
5 WOMAC 0-4 (Overall)	1	90	Mean Difference (IV, Fixed, 95% CI)	-4.22 [-13.70, 5.26]
6 Participants (n) reported adverse events.	1	90	Odds Ratio (M-H, Fixed, 95% CI)	6.05 [0.32, 113.05]

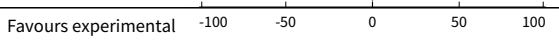
Analysis 6.1. Comparison 6 FNZG versus placebo, Outcome 1 Pain on walking VAS 0-100.

Study or subgroup	FNZG patch N	FNZG patch Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wang 2012	60	34.2 (17.9)	30	35.6 (17.9)		100%	-1.44[-9.28,6.4]
Total ***	**60**		**30**			**100%**	**-1.44[-9.28,6.4]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.36(P=0.72)							



Analysis 6.2. Comparison 6 FNZG versus placebo, Outcome 2 WOMAC 0-4 (Pain).

Study or subgroup	FNZG patch N	FNZG patch Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wang 2012	60	7.5 (4.3)	30	8.6 (4.5)		100%	-1.14[-3.07,0.79]
Total ***	**60**		**30**			**100%**	**-1.14[-3.07,0.79]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.15(P=0.25)							

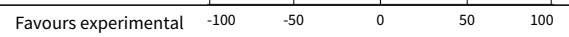


Analysis 6.3. Comparison 6 FNZG versus placebo, Outcome 3 WOMAC 0-4 (Stiffness).

Study or subgroup	FNZG patch N	FNZG patch Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wang 2012	60	2.6 (1.9)	30	3 (2)		100%	-0.42[-1.29,0.45]
Total ***	**60**		**30**			**100%**	**-0.42[-1.29,0.45]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.95(P=0.34)							

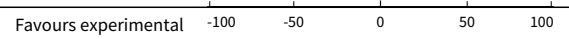
Analysis 6.4. Comparison 6 FNZG versus placebo, Outcome 4 WOMAC 0-4 (Function).

Study or subgroup	FNZG patch N	FNZG patch Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wang 2012	60	19.8 (14.5)	30	22.4 (16.3)		100%	-2.61[-9.5,4.28]
Total ***	**60**		**30**			**100%**	**-2.61[-9.5,4.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.74(P=0.46)							



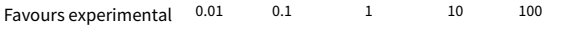
Analysis 6.5. Comparison 6 FNZG versus placebo, Outcome 5 WOMAC 0-4 (Overall).

Study or subgroup	FNZG patch N	FNZG patch Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wang 2012	60	29.7 (20.1)	30	33.9 (22.4)		100%	-4.22[-13.7,5.26]
Total ***	**60**		**30**			**100%**	**-4.22[-13.7,5.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.87(P=0.38)							



Analysis 6.6. Comparison 6 FNZG versus placebo, Outcome 6 Participants (n) reported adverse events..

Study or subgroup	FNZG patch n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Wang 2012	5/60	0/30		100%	6.05[0.32,113.05]
Total (95% CI)	**60**	**30**		**100%**	**6.05[0.32,113.05]**
Total events: 5 (FNZG patch), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.2(P=0.23)					

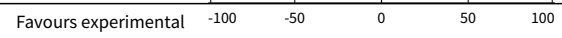


Comparison 7. SJG versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on walking VAS 0-100	1	90	Mean Difference (IV, Fixed, 95% CI)	1.08 [-6.24, 8.40]
2 WOMAC 0-4 (Pain)	1	90	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-3.62, 0.02]
3 WOMAC 0-4 (Stiffness)	1	90	Mean Difference (IV, Fixed, 95% CI)	-0.37 [-1.19, 0.45]
4 WOMAC 0-4 (Function)	1	90	Mean Difference (IV, Fixed, 95% CI)	-2.97 [-9.60, 3.66]
5 WOMAC 0-4 (Overall)	1	90	Mean Difference (IV, Fixed, 95% CI)	-5.12 [-14.27, 4.03]
6 Participants (n) reported adverse events	1	90	Odds Ratio (M-H, Fixed, 95% CI)	4.86 [0.25, 93.27]

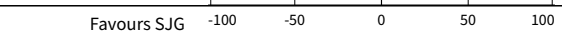
Analysis 7.1. Comparison 7 SJG versus placebo, Outcome 1 Pain on walking VAS 0-100.

Study or subgroup	SJG N	SJG Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wang 2012	60	36.7 (14)	30	35.6 (17.9)		100%	1.08[-6.24,8.4]
Total ***	**60**		**30**			**100%**	**1.08[-6.24,8.4]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.29(P=0.77)							



Analysis 7.2. Comparison 7 SJG versus placebo, Outcome 2 WOMAC 0-4 (Pain).

Study or subgroup	SJG N	SJG Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wang 2012	60	6.8 (3.4)	30	8.6 (4.5)		100%	-1.8[-3.62,0.02]
Total ***	**60**		**30**			**100%**	**-1.8[-3.62,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.94(P=0.05)							

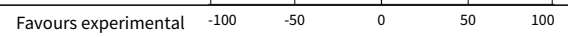


Analysis 7.3. Comparison 7 SJG versus placebo, Outcome 3 WOMAC 0-4 (Stiffness).

Study or subgroup	SJG N	SJG Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wang 2012	60	2.6 (1.6)	30	3 (2)		100%	-0.37[-1.19,0.45]
Total ***	**60**		**30**			**100%**	**-0.37[-1.19,0.45]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.88(P=0.38)							

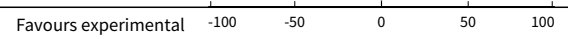
Analysis 7.4. Comparison 7 SJG versus placebo, Outcome 4 WOMAC 0-4 (Function).

Study or subgroup	SJG N	SJG Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wang 2012	60	19.4 (12.5)	30	22.4 (16.3)		100%	-2.97[-9.6,3.66]
Total ***	**60**		**30**			**100%**	**-2.97[-9.6,3.66]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.88(P=0.38)							



Analysis 7.5. Comparison 7 SJG versus placebo, Outcome 5 WOMAC 0-4 (Overall).

Study or subgroup	SJG N	SJG Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wang 2012	60	28.8 (17.5)	30	33.9 (22.4)		100%	-5.12[-14.27,4.03]
Total ***	**60**		**30**			**100%**	**-5.12[-14.27,4.03]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.1(P=0.27)							



Analysis 7.6. Comparison 7 SJG versus placebo, Outcome 6 Participants (n) reported adverse events.

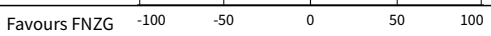
Study or subgroup	SJG n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Wang 2012	4/60	0/30		100%	4.86[0.25,93.27]
Total (95% CI)	**60**	**30**		**100%**	**4.86[0.25,93.27]**
Total events: 4 (SJG), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.29)					

Comparison 8. FNZG versus SJG

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on walking VAS 0-100	1	120	Mean Difference (IV, Fixed, 95% CI)	-2.52 [-8.24, 3.20]
2 WOMAC 0-4 (Pain)	1	120	Mean Difference (IV, Fixed, 95% CI)	0.66 [-0.73, 2.05]
3 WOMAC 0-4 (Stiffness)	1	120	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.68, 0.58]
4 WOMAC 0-4 (Function)	1	120	Mean Difference (IV, Fixed, 95% CI)	0.36 [-4.49, 5.21]
5 WOMAC 0-4 (Overall)	1	120	Mean Difference (IV, Fixed, 95% CI)	0.89 [-5.74, 7.52]
6 Participants (n) reported adverse events	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.32, 4.99]

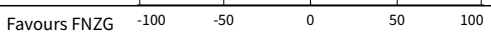
Analysis 8.1. Comparison 8 FNZG versus SJG, Outcome 1 Pain on walking VAS 0-100.

Study or subgroup	FNZG N	FNZG Mean(SD)	SJG N	SJG Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wang 2012	60	34.2 (17.9)	60	36.7 (13.9)		100%	-2.52[-8.24,3.2]
Total ***	**60**		**60**			**100%**	**-2.52[-8.24,3.2]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.86(P=0.39)							



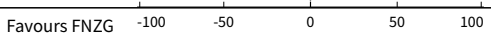
Analysis 8.2. Comparison 8 FNZG versus SJG, Outcome 2 WOMAC 0-4 (Pain).

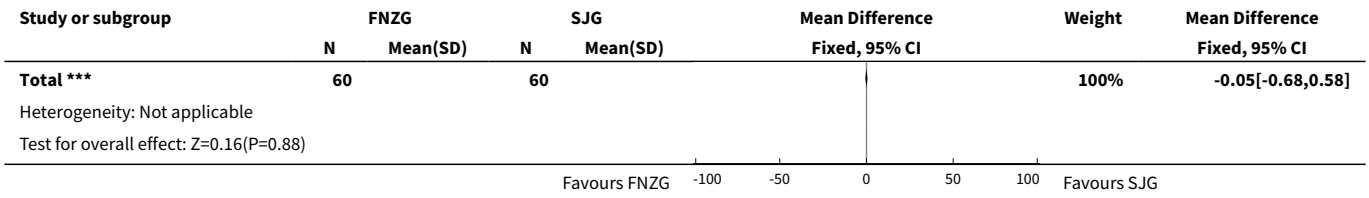
Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wang 2012	60	7.5 (4.3)	60	6.8 (3.4)		100%	0.66[-0.73,2.05]
Total ***	**60**		**60**			**100%**	**0.66[-0.73,2.05]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.93(P=0.35)							



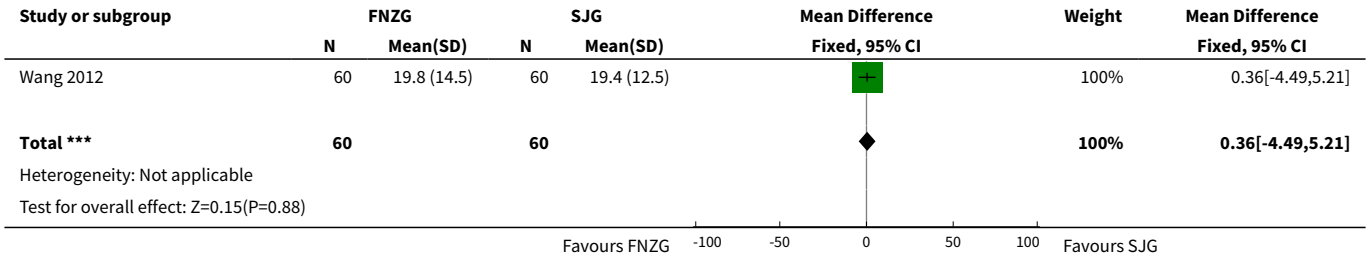
Analysis 8.3. Comparison 8 FNZG versus SJG, Outcome 3 WOMAC 0-4 (Stiffness).

Study or subgroup	FNZG N	FNZG Mean(SD)	SJG N	SJG Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wang 2012	60	2.6 (1.9)	60	2.6 (1.6)		100%	-0.05[-0.68,0.58]

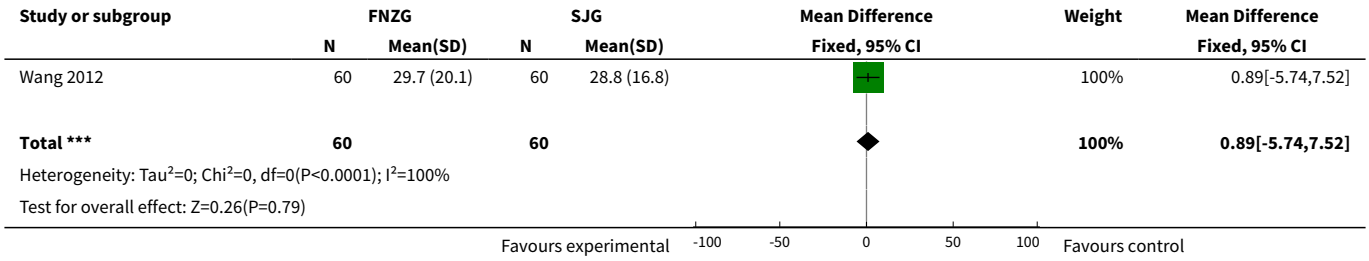




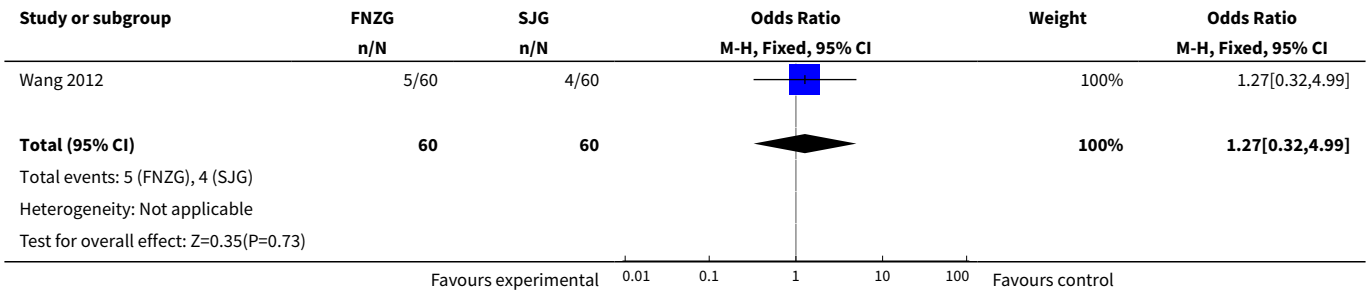
Analysis 8.4. Comparison 8 FNZG versus SJG, Outcome 4 WOMAC 0-4 (Function).



Analysis 8.5. Comparison 8 FNZG versus SJG, Outcome 5 WOMAC 0-4 (Overall).



Analysis 8.6. Comparison 8 FNZG versus SJG, Outcome 6 Participants (n) reported adverse events.



ADDITIONAL TABLES

Table 1. Commision E approved monographs of medicinal plants for musculoskeletal complaints

Species	Plant part	Preparations	Dosage	Treatment duration	Adverse events
Arnica montana *Arnica chamissonis*	flower (fresh or dried)	tincture ointment oil	3-10 times diluted 20-25% tincture or 15% oil 1:4 fatty oil		skin reactions
Capsicum species[1]	dried fruit	extracts with capsaicinoids	semi-liquid: 0.02-0.05% capsaicinoids liquid: 0.005-0.01% capsaicinoids poultices: 10-40ug capsaicinoids/cm2	2 days 14 days 2-14 days	skin reactions: local hyperaemic and nerve damaging
Mentha arvensis	fresh flowering herb	essential oil[2]	several drops rubbed into the skin 5-20% oil or semisolid preparations		
Mentha piperita	fresh flowering sprigs	essential oil[3]	several drops rubbed into the skin dilutions in oil or semisolid preparations		skin reactions
Pica species[4]	tips of branches	essential oil	not stated		skin reactions
Pinus species[5]	fresh boughs with needles and tips	5-50% essential oil	several drops rubbed into the skin dilutions in oil or semisolid preparations		skin reactions
Symphytum officinale	herb and leaf root	ointment	5-20% dried drug[6] 5-20% fresh or dried drug[6]	restricted to 4-6 weeks	None known
Urtica dioica *Urtica urens*	herb and leaf (fresh)	crude material	not stated		

1. eg: *C. fructescens.*
2. 3-17% menthyl acetate, 42% menthol, 40% menthone.
3. 4.5-10% menthyl acetate, 44% menthol, 15-32% menthone.
4. *P. arbies, P. excelsa, P. alba, P. sachalinensis, P. sibirica.*
5. *P. sylvestris, P. mugo, P. nigra.*
6. with less that 100 µg pyrrolizidin alkaloids/day.

Table 2. ESCOP monographs for musculoskeletal complaints based on experimental and clinical studies

Species	Starting material	Preparations	Dosage	Treatment duration	Adverse events
Arnica montana	flower with 4% helenalin (sesquiterpene laactones)	tincture ointment cream gel	dilutions from 5-25% tincture or fluid extract: 1:3 to 1:10		skin reactions

Table 2. ESCOP monographs for musculoskeletal complaints based on experimental and clinical studies *(Continued)*

		compress			
Capsicum species[1]	friut (dried) with not less than 0.4% capsaicinoids	liquid	0.025-0.075% capsaicinoids	3 weeks	skin reactions local hyperaemic
		semiliquid	poultice: 10-40ug capsaicinoids cm^{-2}		
Mentha piperita	fresh flowering herb	essential oil 1.25-16%[2]	several drops rubbed into the skin dilutions in semi(liquid) preparations		skin reactions
Symphytum officinale	root with up to 4.7% allantoin	ointment	35% root extract (DER 1:2, solvent ethanol 60%) 3-4/day	restricted in some EU countries	None reported
Urtica dioica *Urtica urens*	fresh herb or leaf	crude material	30 seconds / daily		

1. eg: *C. frutescens, C. annuum.*
2. 30-55% menthol, 14-32% menthone, 2.8-10% menthyl acetate, 1-9% menthofuran, 3.5-14% cineol, etc.

Table 3. Herbal medicinal products used for the treatment of osteoarthritis

Botanical name	Plant part/s	Tradename	Preparation	Drug/Extract	mg/day	Constituent marker	Quantity of marker	References
Arnica montana (local)	herb	A. Vogel *Arnica* Gel	tincture, 50% ethanol[1]	20:1	3 x 4 cm	not stated		Widrig 2007.
Capsicum species	fruit	Capsika gel	extract, ethanol (concentration not stated)	0.0125%	TID x 2 inches gel	capsaicin	0.365	Kosuwon 2010
Symphytum officinale (local)	root	Kytta Salbe f	ethanolic (60%) extract	2:1	6 (3 x 2mg)	allantoin	0.2-0.5%	Grube 2007.
Urtica dioica (local)	leaf	study medication	crude leaf					Randall 2000, Randall 2008.
Arnebia euchroma + *Matricaria chamomilla* + other medicinal plant parts	not stated	Marhame-Mafasel	not stated	not stated	4500mg	not stated		Soltanian 2010
rhizoma *Arisaematis*, radix *Aconiti*, flos *Caryophylli*, cortex *Cinnamomi*, radix *Angelicae dahuricae*, herba *Asari*, rhizoma *Chuanxiong*, radix *Cynanchi panicuclati*, *Olibanum*, *Myrrha, Camphora, Borneolum syntheticum*.	see previous column	Fufang Nanxing Zhitong Gao (FNZG)[2]	not stated	not stated	not stated (patch 10cm x 13cm)	hypaconitine (C33H45NO10); eugenol (C10H12O2)	not stated	Wang 2012
rhizoma *Arisaematis*, radix *Aconiti*, radix *Angelicae Dahuricae*, cortex *Cinnamomi*, *Camphora*, *Borneolum Syntheticum*, radix *Angelicae Pubescentis*, cortex *Acanthopanacis*, rhizoma *Curcuma Longae*, flos *Carthami*, folium *Artemisiae argyi*, rhizoma *Atractylodis*, rhizoma *Pinellia*, semen *Sinapis*, semen *Vaccariae*, radix *Aconiti kusnezoffii*, herba *Menthae*.	see previous column	Shangshi Jietong Gao (SJG)[2]	not stated	not stated	not stated (patch 10cm x 13cm)	hypaconitine (C33H45NO10); eugenol (C10H12O2)	not stated	Wang 2012

1. Information provided by manufacturer but not reported in paper.
2. Jiangsu Nanxing Pharmaceutical Company.

Table 4. Summary of findings: FNZG patches for osteoarthritis of the knee

FNZG patches for osteoarthritis of the knee						
Patient or population: patients with osteoarthritis of the knee **Settings:** Community, China **Intervention:** FNZG patches						
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	**FNZG**				
Pain Pain on walking VAS 0-100 Follow-up: mean 7 days		The mean pain in the intervention groups was **1.44 lower** (9.28 lower to 6.4 higher)		90 (1 study)	⊕⊕⊕⊖ **moderate**[1,2]	
Function WOMAC 0-4 (Function) Follow-up: mean 7 days		The mean function in the intervention groups was **2.61 lower** (9.5 lower to 4.28 higher)		90 (1 study)	⊕⊕⊕⊖ **moderate**[1,2]	
Adverse events Participants (n) reported adverse events. Follow-up: mean 7 days	**Study population**		**OR 6.05** (0.32 to 113.05)	90 (1 study)	⊕⊕⊕⊖ **moderate**[1,2]	
	0 per 1000	**0 per 1000** (0 to 0)				
Adverse events Participants (n) withdrew due to adverse effects Follow-up: mean 7 days	0/30	1/60	Not estimable	90 (1 study)	⊕⊕⊕⊖ **moderate**[1,2]	
Adverse events Participants (n) reported serious adverse events Follow-up: mean 7 days			Not estimable	90 (1 study)	⊕⊕⊕⊖ **moderate**[1,2]	Reported nil serious adverse events.
Quality of Life	Not measured or reported.					

*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; **OR:** Odds ratio.

GRADE Working Group grades of evidence
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] Single study.
[2] Confirmatory design, statistical power 80%, alpha 0.05.

Table 5. Summary of findings: SJG patches for osteoarthritis of the knee

SJG patches for osteoarthritis of the knee						
Patient or population: patients with osteoarthritis of the knee **Settings:** Community, China **Intervention:** SJG						
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	**SJG**				
Pain Pain on walking VAS 0-100 Follow-up: mean 7 days		The mean pain in the intervention groups was **1.08 higher** (6.24 lower to 8.4 higher)		90 (1 study)	⊕⊕⊕⊖ **moderate**[1], 2.	
Function WOMAC 0-4 (Function) Follow-up: mean 7 days		The mean function in the intervention groups was **2.97 lower** (9.6 lower to 3.66 higher)		90 (1 study)	⊕⊕⊕⊖ **moderate**[1], 2.	
Adverse events Participants (n) reported adverse events Follow-up: mean 7 days	**Study population**		**OR 4.86** (0.25 to 93.27)	90 (1 study)	⊕⊕⊕⊖ **moderate**[1], 2.	
	0 per 1000	**0 per 1000** (0 to 0)				
Adverse events Participants (n) withdrew due to adverse effects Follow-up: mean 7 days	0/30	0/60	Not estimable	90 (1 study)	⊕⊕⊕⊖ **moderate**[1], 2.	Reported nil withdrawals due to adverse events.
Adverse events Participants (n) reported serious adverse events Follow-up: mean 7 days	0/30	0/60	Not estimable	90 (1 study)	⊕⊕⊕⊖ **moderate**[1], 2.	Reported nil serious adverse events.
Quality of Life	Not measured or reported.					

*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; **OR:** Odds ratio.

GRADE Working Group grades of evidence
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] Single study.

[2] Confirmatory design, statistical power 80%, alpha 0.05.

Table 6. Summary of findings: FNZG patches versus SJG patches for osteoarthritis of the knee

FNZG patches versus SJG patches for osteoarthritis of the knee						
Patient or population: patients with osteoarthritis of the knee **Settings:** **Intervention:** FNZG versus SJG						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	SJG	**FNZG**				
Pain Pain on walking VAS 0-100 Follow-up: mean 7 days		The mean pain in the intervention groups was **2.52 lower** (8.24 lower to 3.2 higher)		120 (1 study)	⊕⊕⊕⊖ **moderate**[1],[2]	
Function WOMAC 0-4 (Function) Follow-up: mean 7 days		The mean function in the intervention groups was **0.36 higher** (4.49 lower to 5.21 higher)		120 (1 study)	⊕⊕⊕⊖ **moderate**[1],[2]	
Adverse events Participants (n) reported adverse events Follow-up: mean 7 days	**Study population**		**OR 1.27** (0.32 to 4.99)	120 (1 study)	⊕⊕⊕⊖ **moderate**[1],[2]	
	67 per 1000	**83 per 1000** (22 to 263)				
Adverse events Participants (n) withdrew due to adverse effects Follow-up: mean 7 days	**Study population**		Not estimable	120 (1 study)	⊕⊕⊕⊖ **moderate**[1],[2]	
	17 per 1000	**0 per 1000** (0 to 0)				
Adverse events Participants (n) reported serious adverse events Follow-up: mean 7 days	0/60	0/60	Not estimable	120 (1 study)	⊕⊕⊕⊖ **moderate**[1],[2]	Reported nil serious adverse events.
Quality of Life	Not measured or reported.					

*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; **OR:** Odds ratio.

GRADE Working Group grades of evidence
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] Single study.

[2] Confirmatory design, statistical power 80%, alpha 0.05.

Table 7. Summary of findings: Marhame-Mafasel for osteoarthritis of the knee

Marhame-Mafasel for osteoarthritis of the knee						
Patient or population: patients with osteoarthritis of the knee **Settings:** Community, Iran **Intervention:** Marhame-Mafasel						
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	**Marhame-Mafasel**				
Pain due to OA: change from baseline WOMAC VAS (Pain; higher means worse) Follow-up: mean 3 weeks[1]		The mean pain due to OA: change from baseline in the intervention groups was **5.62 lower** (17.84 lower to 6.6 higher)		42 (1 study)	⊕⊕⊖⊖ **low** [2, 3]	
Function due to OA: change from baseline WOMAC VAS (Function; higher means worse) Follow-up: mean 3 weeks		The mean function due to OA: change from baseline in the intervention groups was **1.09 lower** (9.4 lower to 7.22 higher)		42 (1 study)	⊕⊕⊖⊖ **low** [2, 3]	
Adverse events Participants (n) reported adverse events Follow-up: mean 3 weeks	**Study population**		**RR 5.00** (0.25 to 98.27) **OR 5.51** (0.25 to 122.08)	42 (1 study)	⊕⊕⊖⊖ **low** [2, 3]	
	0 per 1000	**0 per 1000** (0 to 0)				
Adverse events Participants (n) withdrew due to adverse effects						
Adverse events Participants (n) reported serious adverse events						
Quality of Life	Not measured or reported.					

*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; **OR:** Odds ratio.

GRADE Working Group grades of evidence

Table 7. Summary of findings: Marhame-Mafasel for osteoarthritis of the knee *(Continued)*

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] Crossover trial: 3 week interventions arms, without washout period.
[2] Single study.
[3] Exploratory study design; power, effect, and sample size not determined *a priori.*

Table 8. Summary of findings: stinging nettle for osteoarthritis of the thumb

Stinging nettle for osteoarthritis of the thumb						
Patient or population: patients with osteoarthritis of the thumb[1] **Settings:** Community, England **Intervention:** Stinging nettle						
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	**Stinging nettle**				
Pain VAS 0-100 (higher means worse) Follow-up: mean 1 weeks	The mean pain in the control groups was **37.04 mm**	The mean pain in the intervention groups was **13.37 lower** (0 to 0 higher)		54 (1 study)	⊕⊝⊝⊝ **very low**[1, 2, 3]	
Function	Not measured or reported.					
Adverse events Participants (n) reported adverse events					⊕⊝⊝⊝ **very low**[1, 2, 3]	Crossover trial: Participants (n) with adverse events reported for whole trial only (ie: both arms of crossover combined).
Adverse events Participants (n) withdrew due to adverse effects	Not measured or reported.					
Adverse events Participants (n) reported serious adverse events					⊕⊝⊝⊝ **very low**[1, 2, 3]	Reported nil serious adverse events.
Quality of life					⊕⊝⊝⊝ **very low**[1, 2, 3]	Crossover trial: HAQ reported for whole trial only (ie: both arms of crossover combined).

Table 8. Summary of findings: stinging nettle for osteoarthritis of the thumb *(Continued)*

Health Assessment Questionnaire (HAQ)

*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.

GRADE Working Group grades of evidence
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] Single study.
[2] Criteria for diagnosis of OA not specified at baseline. Other arthritides are possible confounders.
[3] Most outcome data were reported as means only (not standard deviations) without confidence intervals. Data for first and second periods were aggregated and are insufficient for extraction from the first arm (up to crossover) only. We have presented aggregated data for pain (VAS 0-100) after 1 week of intervention and re-calculated the mean difference between groups at this time point. We note that the mean difference between groups is -13.37, not 15.08, which is the sum of the within-groups mean changes reported by the authors as mean difference.

Table 9. Summary of findings: stinging nettle for osteoarthritis of the knee

Stinging nettle for osteoarthritis of the knee

Patient or population: patients with osteoarthritis of the knee
Settings: Community, England
Intervention: Stinging nettle

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	Stinging nettle				
Pain WOMAC 0-4 (Pain; higher means worse) Follow-up: mean 1 weeks		The mean pain due to OA in the intervention groups was **2 higher** (0.19 to 3.81 higher)		42 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3,4]	
Function WOMAC 0-4 (Function; higher means worse) Follow-up: mean 4 weeks[5]		The mean function due to OA in the intervention groups was **5 higher** (0.9 to 9.1 higher)		39 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3,4]	
Adverse events Participants (n) reported adverse events Follow-up: mean 1 weeks[5]	**Study population**		**RR 2.00** (0.20 to 20.41) **OR 2.11** (0.18 to 25.17)	42 (1 study)	⊕⊕⊖⊖ **low**[1,2,3,6]	
	48 per 1000	**95 per 1000** (9 to 557)				
	Moderate					

Table 9. Summary of findings: stinging nettle for osteoarthritis of the knee *(Continued)*

	48 per 1000	**96 per 1000** (9 to 559)	
Adverse events Participants (n) withdrew due to adverse effects			Withdrawals due to adverse events not measured or reported.
Adverse events Participants (n) reported serious adverse events			Serious adverse events not measured or reported.
Quality of life	Not measured or reported.		

*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; **OR:** Odds ratio.

GRADE Working Group grades of evidence
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] Diagnosis not consistent with ACR criteria. OA not distinguished from other causes of knee pain in older adults at baseline (presumptive diagnosis). Although OA is the most likely cause of knee pain in older adults, other arthritides are possible confounders.
[2] Exploratory study design; power, effect, and sample size not determined a priori.
[3] Placebo validity and blinding may be compromised by stinging effect of active intervention.
[4] Patients were follow up for pain and function measures at 4 and 16 weeks. In both intervention and control groups, further improvements in these domains were identified at follow up time points. These long term improvements suggest that short term changes in pain and function represent normal variation within individuals with OA, and are not of clinical importance.
[5] 1 week intervention, 15 weeks follow up.
[6] Urtica dioica stimulates pain receptors in the skin, which is part of the effect of this topical agent. "Stinging sensations" were not included in reported adverse events, probably because participants understood that this effect was likely with the the intervention. One participant in the control group reported stiffness in the knee as an adversse event. Stiffness is an expected outcome of untreated OA. These results suggest that insufficient blinding to the intervention may have confounded the reporting of adverse events.

APPENDICES

Appendix 1. Search Strategies

MEDLINE

1 exp osteoarthritis/

2 osteoarthr$.tw.

3 (degenerative adj2 arthritis).tw.

4 arthrosis.tw.

5 or/1-4

6 exp Medicine, Herbal/

7 exp Plants, Medicinal/

8 exp Medicine, Traditional/

9 exp Drugs, Chinese Herbal/

10 herb$.tw.

11 (plant or plants).tw.

12 phytomedicine.tw.

13 botanical.tw.

14 weed$.tw.

15 algae.tw.

16 (fungi or fungus).tw.

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

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

19 or/6-18

20 5 and 19

EMBASE

1 exp osteoarthritis/

2 osteoarthr$.tw.

3 (degenerative adj2 arthritis).tw.

4 arthrosis.tw.

5 or/1-4

6 exp Herbal Medicine/

7 exp Medicinal Plant/

8 exp Traditional Medicine/

9 exp Chinese Medicine/

10 herb$.tw.

11 (plant or plants).tw.

12 phytomedicine.tw.

13 botanical.tw.

14 weed$.tw.

15 algae.tw.

16 (fungi or fungus).tw.

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

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

19 or/6-18

20 5 and 19

CINAHL

1 exp OSTEOARTHRITIS/

2 osteoarthr$.tw.

3 (degenerative adj2 arthritis).tw.

4 arthrosis.tw.

5 or/1-4

6 exp Medicine, Herbal/

7 exp Plants, Medicinal/

8 Medicine, Traditional/

9 exp Plant Extracts/

10 herb$.tw.

11 (plant or plants).tw.

12 phytomedicine.tw.

13 botanical.tw.

14 weed$.tw.

15 algae.tw.

16 (fungi or fungus).tw.

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

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

19 or/6-18

20 5 and 19

Revised Strategy (EBSCOhost)

S24 S5 and S22
S23 S5 and S22

S22 S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21

S21 ti chinese tradition* or ab chinese tradition*

S20 ti oriental tradition* or ab oriental tradition*

S19 ti herbal medicine or ab herbal medicine
S18 ti chinese medicine or ab chinese medicine

S17 ti traditional medicine or ab traditional medicine

S16 ti fungi or ti fungus or ab fungi or ab fungus

S15 ti algae or ab algae

S14 ti weed* or ab weed*

S13 ti botanical or ab botanical

S12 ti phytomedicine or ab phytomedicine

S11 ti plant or ti plants or ab plant or ab plants

S10 ti herb* or ab herb*

S9 (MH "Plant Extracts+")

S8 (MH "Medicine, Traditional+")
S7 (MH "Plants, Medicinal+")

S6 (MH "Medicine, Herbal+")

S5 S1 or S2 or S3 or S4

S4 ti arthrosis or ab arthrosis

S3 ti degenerative N2 arthritis or ab degenerative N2 arthritis
S2 ti osteoarthr* or ab osteoarthr*

S1 (MH "Osteoarthritis+")

AMED

1 exp Osteoarthritis/

2 osteoarthr$.tw.

3 (degenerative adj2 arthritis).tw.

4 arthrosis.tw.

5 or/1-4

6 exp herbal drugs/

7 exp traditional medicine/

8 exp plant extracts/

9 exp plants medicinal/

10 herb$.tw.

11 (plant or plants).tw.

12 phytomedicine.tw.

13 botanical.tw.

14 weed$.tw.

15 algae.tw.

16 (fungi or fungus).tw.

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

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

19 or/6-18

20 5 and 19

The Cochrane Library 2008, Issue 4

#1 MeSH descriptor Osteoarthritis explode all trees

#2 osteoarthr*:ti,ab

#3 (degenerative near/2 arthritis):ti,ab

#4 arthrosis:ti,ab

#5 (#1 OR #2 OR #3 OR #4)

#6 MeSH descriptor Medicine, Herbal explode all trees

#7 MeSH descriptor Plants, Medicinal explode all trees

#8 MeSH descriptor Medicine, Traditional explode all trees

#9 MeSH descriptor Drugs, Chinese Herbal explode all trees

#10 herb*:ti,ab

#11 (plant or plants):ti,ab

#12 phytomedicine:ti,ab

#13 botanical:ti,ab

#14 weed*:ti,ab

#15 algae:ti,ab

#16 (fungi or fungus):ti,ab

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

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

#19 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)

#20 (#5 AND #19)

ISI Web of Science

#7 #4 AND #1

Refined by: Publication Years=(2009 OR 2007 OR 2004 OR 2001 OR 2010 OR 2005 OR 2003 OR 2000 OR 2008 OR 2006 OR 2002) AND Document Type=(PROCEEDINGS PAPER OR MEETING ABSTRACT)

#6 #4 AND #1

Refined by: Publication Years=(2009 OR 2007 OR 2004 OR 2001 OR 2010 OR 2005

#5 #4 AND #1

#4 #3 OR #2

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

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

#1 Topic=(arthrit* or arthrosis or osteoarthrit* or osteoarthrosis)

Dissertation Abstracts

arthrit* or arthrosis or osteoarthrit* or osteoarthrosis AND

herb* or plant or plants or phytomedicine or botanical or weed* or algae or fungi or fungus or ((oriental or chinese or traditional) and (medicin* or therap*))

World Health Organization International Clinical Trials Registry Platform

Osteoarthritis in Condition AND

herb* or plant or plants or phytomedicine or botanical or weed* or algae or fungi or fungus or oriental or chinese or traditional in Intervention

WHAT'S NEW

Date	Event	Description
28 May 2013	Amended	Minor changes to abstract

HISTORY

Review first published: Issue 5, 2013

Date	Event	Description
12 March 2013	New citation required and conclusions have changed	Substantive amendment; new authors.
27 February 2012	New search has been performed	This updated review is divided into two parts: topical herbal therapies and oral herbal therapies for treating osteoarthritis. The original review included only 5 studies, one of which investigated extracted capsaicin, which is by the WHO definition not herbal, so this study has been excluded (Deal 1991). This updated review covers topical herbal therapies only. A total of 7 new studies were identified for inclusion in this updated review (Grube 2007; Kosuwon 2010; Randall 2000; Randall 2008; Soltanian 2010; Wang 2012; Widrig 2007). The main distinguishing features of topical medicinal plant products are (a) the additional skin irritant mechanism of action for some products, and (b) for other products safety concerns when consumed orally. The inclusion criteria have been expanded such that language of publication is no longer a barrier to inclusion, studies using active as well as placebo controls are included. Changes to methods of quality assessment (risk of bias), and presentation of results are consistent with updated Cochrane methods introduced since the original review. The table of herbal interventions has been extensively revised so that it offers detailed information about the herbal medicines, including full botanical name, part of the plant used, details of extraction methods, drug:extract ra-

Date	Event	Description
		tio, and content of marker substances of the active principle if possible. This information is the minimum required to be able to repeat the study.

CONTRIBUTIONS OF AUTHORS

SC and MC, along with those people named in the 'Acknowledgements', contributed to the paper selection and data extraction. MC and SG completed the data analysis and interpretation then wrote, checked, proof-read, and approved the updated review.

DECLARATIONS OF INTEREST

None known

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Internal sources

- Victoria University, Australia.

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- University of Freiburg, Germany.

  University of Freiburg provided one author.
- Australian Catholic University, Australia.

  The Australian Catholic University provided one author with time (2010-2011). Librarians from the Australian Catholic University assisted with the acquisition of full manuscripts of studies included in this review.
- University of the Sunshine Coast, Australia.

  The University of the Sunshine Coast provided one author (2012-2013), and allowed time release from normal duties to complete this review.

External sources

- National Center for Complementary and Alternative Medicine, USA.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this revew update, we expanded the inclusion criteria so studies that included an active control as well as placebo controls, and unpublished reports of randomised controlled trials, were eligible for inclusion. Changes to the 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. We restricted the included studies to those investigations of interventions that strictly satisfy the WHO guidelines for herbal medicines. This updated review is limited to topical medicinal plant products only.

INDEX TERMS

Medical Subject Headings (MeSH)

Arnica; Capsaicin [therapeutic use]; Comfrey [chemistry]; Drugs, Chinese Herbal [administration & dosage]; Hand Joints; Osteoarthritis [*drug therapy]; Osteoarthritis, Knee [drug therapy]; Phytotherapy [*methods]; Plant Extracts [*administration & dosage]

MeSH check words

Humans