Efficacy and safety of plant-derived products for the treatment of osteoarthritis

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Background: Plant-derived therapies are traditionally used as medicines, but they have generally not been studied with the same rigor as pharmaceutical agents. This review summarizes the use of plant-derived products for osteoarthritis.

Methods: Sixty-three identified trials were summarized for pain, function, and safety outcomes using standardized mean differences (SMDs) and relative risks.

Results: Plant-derived therapies are effective for treating pain compared to placebo, as assessed using visual analog scores and numerical rating scales (SMD, 1.08; 95% confidence interval [CI]: 0.72–1.44), or Western Ontario and McMaster University Osteoarthritis Index (WOMAC)/Knee injury and Osteoarthritis Outcome Score (KOOS) pain scales (SMD, 0.98; 95% CI: 0.62–1.35). Classes demonstrating overall efficacy in more than one trial for either visual analog scores or WOMAC pain included Boswellia serrata, capsaicin, and ginger; there was single-trial evidence of the efficacy of another nine agents. Plant-derived therapies have similar efficacy to an active comparator (SMD, 0.32; \( P = 0.08 \); \( -0.08; \ P = 0.14 \)). Therapies are also effective for functional outcomes compared to placebo (SMD, 0.92; \( P < 0.001 \)). However, significant heterogeneity remains for all pain and function outcomes, indicating that the results need to be interpreted with caution. Risk of adverse events was similar to placebo (relative risk, 1.13; \( P = 0.1 \)), but reduced compared to an active comparator (relative risk, 0.75; \( P < 0.001 \)).

Conclusion: Plant-derived therapies may be efficacious in treating osteoarthritic pain and functional limitations, and they appear to be safer than other active therapies. However, quality trials and long-term data are lacking, and the number of trials for each therapy is limited. Comparisons would be assisted by trial standardization.

Keywords: phytotherapy, plant extract, herbal, review, meta-analysis, osteoarthritis

Introduction

Osteoarthritis (OA) is the most common joint disorder and it predominantly affects the knees, hips, and hands of older adults. It is a leading cause of pain, functional limitations and disability worldwide, with levels of disability among people with OA having increased globally by over 25% from 1990–2010. Despite the large disease burden, OA etiology is poorly understood, and treatment remains palliative. Commonly involved joint structures include subchondral bone, ligaments, menisci, periarticular muscles, peripheral nerves, and synovium.

OA is no longer considered to be a single disease entity, but a collection of heterogeneous pathologies that result in a common outcome. The lack of a common causal pathway has hampered the development of effective treatments for modifying the natural history of the disease. Most existing treatments focus on relieving pain and.
improving function, and there are few examples of therapies that modify disease. The pathogenesis of pain in OA is complex and multifactorial, involving local nociception, inflammatory mediators, and central sensitization.\(^5\)\(^-\)\(^8\)

Treatment of osteoarthritic pain includes a wide range of therapies, from: nonpharmacological treatments (eg, education, weight reduction, physiotherapy); pain medications (eg, paracetamol, nonsteroidal anti-inflammatory drugs, opioids); nutraceuticals (eg, glucosamine, chondroitin sulfate); and surgical therapies (eg, joint replacement). Additionally, the effect sizes (ES) of existing treatments vary, but they are typically small to moderate\(^9\) and fall short of the levels of pain relief desired by patients.\(^10\)

Medicinal plants form the basis of traditional medicinal systems around the world, and the number and type of botanically-based therapies and their mechanisms of action are similarly diverse. Given the limited efficacy of many existing treatments, there is considerable scope for alternative therapies, and plant-based therapies are well-placed to supplement this gap.

Additionally, controversy surrounding use of cyclooxygenase-2 inhibitors and heightened cardiovascular risk,\(^11\)\(^-\)\(^14\) highlights the importance of finding safer treatment options to minimize adverse side effects.\(^15\) Botanical treatments may play a role in treatment of OA even if they are only moderately effective if they also have favorable safety profiles compared to alternatives (eg, nonsteroidal anti-inflammatory drugs). Additionally, given the high proportion of persons with OA using complementary and alternative medicines of various types,\(^16\)\(^,\)\(^17\) assessment of treatment efficacy and the relative risk (RR) of side effects is warranted.

The efficacy and safety of plant-based therapies for OA have been the subject of several previous reviews.\(^18\)\(^-\)\(^21\) However, the number of studies trialing therapies is steadily increasing, necessitating more recent reviews; no previous reviews have summarized trials in such a way that efficacy and safety are directly comparable, either to placebo or to an active comparator.

Therefore, this review investigates the efficacy and safety of plant-derived products for the treatment of OA, as compared to placebo and active comparators, on OA pain and function.

Methods

Identification of clinical trials

Literature databases (PubMed and Embase) were searched for randomized controlled trials of botanical therapies as an intervention for pain or functional outcomes in OA, where the comparator was a placebo or an active comparator. The following keywords were used: “phytotherapy OR medicinal plants OR plant extract OR herbal”; “osteoarthritis” (both as a single phrase and as a topic) and “hip” or “knee” or “hand”; “randomized controlled trial [publication type]” or “controlled clinical trial [publication type]”; and “humans” that were published up to June 2013. This was supplemented by manually searching the bibliographies of relevant published reviews and papers.

Database searches identified a total of 144 studies: 92 in PubMed and 104 in Embase, and 52 in both. This yielded 58 studies after unsuitable trials were excluded. Supplemented papers included one notable plant-based treatment class, which did not appear in the original search (capsaicin) and an article using pine bark, which was not indexed under plant-based therapies.\(^22\)

Inclusion/exclusion criteria

The included studies were randomized controlled trials of at least one plant-based therapy conducted with humans, where at least a subpopulation of adult patients had OA, as long as this subpopulation was presented separately. Studies were excluded if they were observational studies, not in English, where the botanical therapy was not the subject of the trial, where the botanical therapy was in both active and control medications (but no additional botanical therapy was used as an intervention), and when insufficient data were reported to extract ES (eg, where medians rather than means were reported). Topical therapies were included. Studies on animal populations and in participants with back pain or spinal OA were excluded. Studies were read by one reviewer (LLL).

Definition of plant-derived products

Treatments were included if they were any type of plant-derived intervention (defined as any plant preparation, including whole, powder, extract, or standardized mixture), and they were excluded if there was any preparation of synthetic origin. These treatments could be used in any way, but they are typically ingested orally or applied topically on the skin (Table 1).

Treatments could be compared to an inert substance (placebo) or an active comparator. Botanical therapies used in conjunction with other treatments or combined with a nonbotanical substance were also included if the effect of the nonherbal intervention was consistent among all groups and was quantifiable. Treatment arms were omitted if they were additional to active versus placebo or active versus active comparator comparisons.
Table 1 Details of the herbal medicinal products used for the treatment of OA in randomized controlled double-blind studies

<table>
<thead>
<tr>
<th>Study, duration</th>
<th>n</th>
<th>Mean age (years)</th>
<th>OA site</th>
<th>Formulation (daily dose)</th>
<th>Comparator</th>
<th>Route</th>
<th>Pain and function outcomes</th>
<th>Adverse events</th>
<th>Comments</th>
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<td><strong>AIF</strong></td>
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<tr>
<td>Park et al[9]</td>
<td>57</td>
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<td>Knee</td>
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<td>Widrig et al[7]</td>
<td>198</td>
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<td>Ibuprofen</td>
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<td>Pain VAS, hand function (hand algofunctional index)</td>
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<td>48</td>
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<td>Oral</td>
<td>NRS pain</td>
<td>Dermatitis, abdominal pain, nausea</td>
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<tr>
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<td>22</td>
<td>62</td>
<td>Knee</td>
<td>Aquamin F (seaweed)</td>
<td>Placebo</td>
<td>Oral</td>
<td>WOMAC</td>
<td>Increased pain</td>
<td>Trial was 12 weeks, but only 4 weeks' pain data included</td>
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<td>Aquamin F (seaweed)</td>
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<td>Oral</td>
<td>WOMAC</td>
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<td>Chondroitin sulfate, 1,200 mg</td>
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<td>Allergic reactions, GI symptoms</td>
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<td>163</td>
<td>63</td>
<td>Hip</td>
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<td>Placebo</td>
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<td>Pengkhum et al[10]</td>
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<td>Knee</td>
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<td>Sengupta et al[20]</td>
<td>38</td>
<td>52</td>
<td>Knee</td>
<td>Boswellia serrata extract (S-Loxin®; Aflapin®)</td>
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<td>Oral</td>
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<td>Acidity</td>
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<td>75</td>
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<td>S-Loxin® (Boswellia serrata extract, 100 mg and 250 mg)</td>
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<td>WOMAC, VAS, Lequesne's index</td>
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<td>Formulation (daily dose)</td>
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<td>Route</td>
<td>Pain and function outcomes</td>
<td>Adverse events</td>
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<td>Sontakke et al</td>
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<td>Valdecoxib, 10 mg</td>
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<td>WOMAC</td>
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<td>Usha and Naidu</td>
<td>40</td>
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<td>EzMov Plus: Picrorhiza kurroa (270 mg); Boswellia serrata (200 mg); Cyperus</td>
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<td>GI symptoms</td>
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<td>Chopra et al</td>
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<td>RA-I I: Withania somnifera; Boswellia serrata; Zingiber officinalis; Curcuma</td>
<td>Placebo</td>
<td>Oral</td>
<td>VAS pain, WOMAC</td>
<td>Skin rash</td>
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<td>23 M:67 F</td>
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<td>longa; (amounts not stated); four capsules daily</td>
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<td>Kimmrakar et al</td>
<td>30</td>
<td>59</td>
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<td>GI symptoms</td>
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<td>Kosuwon et al</td>
<td>100</td>
<td>61</td>
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<td>Pain VAS, WOMAC</td>
<td>Application site burning</td>
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<td>McNee</td>
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<td>Topical</td>
<td>Pain VAS</td>
<td>No info on adverse events</td>
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<td>113</td>
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<td>Knee, ankle,</td>
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<td>Pain VAS</td>
<td>Application site burning</td>
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<td>Schnitzer et al</td>
<td>59</td>
<td>67</td>
<td>Hand</td>
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<td>60</td>
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<td>Likert pain scale (pain at rest)</td>
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<td>Madhu et al</td>
<td>42</td>
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<td>VAS pain</td>
<td>Body pain, cough, dyspepsia</td>
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<td><strong>Comfrey</strong></td>
<td>Laslett et al&lt;sup&gt;25&lt;/sup&gt; 12 weeks</td>
<td>Placebo</td>
<td>133</td>
<td>64.8</td>
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<td>Comfrey extract Sympyrum officinale (200 mg/g); tannic acid (100 mg/g); aloe vera</td>
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<td>Rash</td>
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<td>(300 mg/g); eucalyptus oil (40 mg/g); 64.8</td>
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<td>54 M:79 F</td>
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<td>Grube et al&lt;sup&gt;8&lt;/sup&gt;</td>
<td>3 weeks</td>
<td>Placebo</td>
<td>220</td>
<td>58</td>
<td>Knee</td>
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<tr>
<td></td>
<td>Kyetta-Salbe F (comfrey root liquid, Symphytum officinale, 35%) 6 cm</td>
<td>Topical Pain VAS</td>
<td>Not stated</td>
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<td>67 M:153 F</td>
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<tr>
<td><strong>Derris scandens</strong></td>
<td>Kuptniratsaikul et al&lt;sup&gt;8&lt;/sup&gt; 4 weeks</td>
<td>Naproxen, 500 mg</td>
<td>Oral WOMAC</td>
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<td></td>
<td>Comfrey root liquid, Symphytum officinale, 6 cm</td>
<td>Oral WOMAC, Lequesne’s functional index</td>
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<tr>
<td><strong>Duhuo Jisheng Wan</strong> (Radix Angelicae Pubescentsis, Loranthus parasiticus)</td>
<td>Teekachunhatean et al&lt;sup&gt;2&lt;/sup&gt; 4 weeks</td>
<td>Naproxen, 500 mg</td>
<td>Oral WOMAC</td>
<td>–</td>
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<td>Duhuo Jisheng Wan (DJW): 3 g</td>
<td>Oral WOMAC, Lequesne’s functional index</td>
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<td>200 62</td>
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<td><strong>E-OA-07</strong></td>
<td>Kulkarni et al&lt;sup&gt;44&lt;/sup&gt; 12 weeks</td>
<td>Placebo</td>
<td>16</td>
<td>55</td>
<td>Knee</td>
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<td>E-OA-07 (shyonak [Oroxylum indicum], ashwagandha [Withania somnifera], shunthi [Zingiber officinale], guggul [Commiphora wightii], chaphchini [Smilax china], rasana [Pluchea lanceolata], shalaki [Boswellia serrata]): amounts not stated</td>
<td>Oral VAS pain score, WOMAC</td>
<td>Fracture</td>
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<td><strong>Flavocoxid</strong></td>
<td>Levy et al&lt;sup&gt;46&lt;/sup&gt; 4 weeks</td>
<td>Naproxen, 1,000 mg</td>
<td>Oral Total WOMAC score</td>
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<td></td>
<td>Flavocoxid, 1,000 mg (Scutellaria baicalensis; Acacia catechu)</td>
<td>Oral WOMAC score</td>
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<td><strong>Fufang Nanxing Zhitong Gao, Shangshi Jietong Gao</strong></td>
<td>Wang&lt;sup&gt;11&lt;/sup&gt; 1 week</td>
<td>Placebo</td>
<td>150</td>
<td>59</td>
<td>Knee</td>
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<td>FNZG; SJG (see notes for ingredients)</td>
<td>Patch Pain VAS (walking on flat surface); WOMAC score (Likert scale)</td>
<td>Patch site reaction</td>
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<td>Patch Site reaction</td>
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<td><strong>GBT</strong></td>
<td>Tao et al&lt;sup&gt;62&lt;/sup&gt; 8 weeks</td>
<td>Glucosamine sulfate 1,500 mg</td>
<td>Oral VAS pain</td>
<td>Abdominal distension, mild diarrhea</td>
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<td>GBT, 400 mL drynaris rhizoma, 18–20 g eucommia bark, 20–30 g cibot rhizome (Rhizoma Cibotii) 25–30 g; psoralea fruit, 10–15 g tubeimu tuber (Boesemana paniculata) 15–20 g; orientvine (Caulis Sinomenii) 20–30 g; spatholobus stem (Spatholobus sub erectus), 20–30 g; epimedium herb, 10–15 g</td>
<td>Oral VAS pain</td>
<td>Abdominal distension, mild diarrhea</td>
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<td>90 63</td>
<td>Glucosamine sulfate 1,500 mg</td>
<td>Oral VAS pain</td>
<td>Abdominal distension, mild diarrhea</td>
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<td>Study, duration</td>
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<td>Mean age (years)</td>
<td>OA site</td>
<td>Formulation (daily dose)</td>
<td>Comparator</td>
<td>Route</td>
<td>Pain and function outcomes</td>
<td>Adverse events</td>
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<tr>
<td>Ginger</td>
<td>Drozdov et al27</td>
<td>43</td>
<td>55</td>
<td>Knee, hip</td>
<td>Ginger + glucosamine (Zinaxin® glucosamine: 200 mg, ginger extract; 1000 mg, glucosamine)</td>
<td>Diclofenac + glucosamine (100 mg diclofenac; 100 mg glucosamine)</td>
<td>Oral</td>
<td>VAS pain on standing (0–100)</td>
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<tr>
<td></td>
<td>Zahmatkash and Vafaee nasab33</td>
<td>92</td>
<td>52.2</td>
<td>Knee</td>
<td>Ginger (Zingiber officinale), mastic, sesame oil, 6 g</td>
<td>Salicylate (dose not stated) 6 g</td>
<td>Topical</td>
<td>VAS pain, stiffness</td>
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<tr>
<td></td>
<td>Zakeri et al27</td>
<td>37</td>
<td>204</td>
<td>Knee</td>
<td>Ginger (Zintoma: Zingiber officinale) 250 mg</td>
<td>Placebo</td>
<td>Oral</td>
<td>VAS pain (standing, walking), WOMAC</td>
<td>–</td>
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<tr>
<td></td>
<td>Yip and Tam53</td>
<td>59</td>
<td>74</td>
<td>Knee</td>
<td>Massage + 1% ginger essential oil, 0.5% orange essential oil</td>
<td>Massage + no essential oils; conventional treatment only</td>
<td>Topical, massage</td>
<td>WOMAC</td>
<td>–</td>
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<tr>
<td></td>
<td>Wigler et al67</td>
<td>29</td>
<td>62</td>
<td>Knee</td>
<td>Ginger extract (Zingiber officinale, Zintona EC) 1000 mg</td>
<td>Placebo</td>
<td>Oral</td>
<td>VAS pain on movement</td>
<td>Case-crossover trial</td>
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<td></td>
<td>Altman and Marcussen6</td>
<td>261</td>
<td>65</td>
<td>Knee</td>
<td>Ginger extract EV.EXT 77 (Zingiber officinale, Alpinia galanga) 255 mg</td>
<td>Placebo</td>
<td>Oral</td>
<td>VAS pain on standing (0–100), WOMAC</td>
<td>GI events</td>
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<td><strong>Harpagophytum procumbens</strong></td>
<td>Chantre et al77</td>
<td>122</td>
<td>61</td>
<td>Knee, hip</td>
<td>Devil’s claw, Harpadol, 2610 mg (Harpagophytum procumbens)</td>
<td>Diacerein, 100 mg</td>
<td>Oral</td>
<td>VAS pain, Lequesne’s functional index</td>
<td>–</td>
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<tr>
<td><strong>Individualized herbal treatment</strong></td>
<td>Hamblin et al11</td>
<td>20</td>
<td>67</td>
<td>Knee</td>
<td>Individualized herbal treatment + multivitamins</td>
<td>Placebo + multivitamins</td>
<td>Oral</td>
<td>WOMAC</td>
<td>Not reported</td>
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<tr>
<td><strong>Individualized traditional Chinese medicine</strong></td>
<td>Lechner et al82</td>
<td>102</td>
<td>59</td>
<td>Hip or knee</td>
<td>Individualized traditional Chinese medicine prescription</td>
<td>Nonspecific herbal treatment</td>
<td>Oral, as tea</td>
<td>WOMAC, SF-36</td>
<td>–</td>
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<tr>
<td><strong>Olive oil</strong></td>
<td>Bohlooli et al90</td>
<td>71</td>
<td>40–80</td>
<td>Knee</td>
<td>Virgin olive oil</td>
<td>0.5% piroxicam (amount not stated)</td>
<td>Topical</td>
<td>WOMAC</td>
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<td><strong>Passion fruit peel</strong></td>
<td>Farid et al90</td>
<td>33</td>
<td>53</td>
<td>Knee</td>
<td>Passion fruit peel extract (Passiflora edulis), 150 mg</td>
<td>Placebo</td>
<td>Oral</td>
<td>WOMAC</td>
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<td><strong>Phellodendron amurense</strong></td>
<td>Oben et al90</td>
<td>80</td>
<td>–</td>
<td>Knee</td>
<td>Phellodendron amurense tree bank, Citrus sinensis extract (NP 06–1, 1.5 g)</td>
<td>Placebo</td>
<td>Oral</td>
<td>Lequesne’s functional index</td>
<td>Hepatitis, nausea</td>
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<td><strong>Plant-derived therapies for osteoarthritis</strong></td>
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<td><strong>Phytalgic</strong></td>
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<td>Jacquet et al&lt;sup&gt;48&lt;/sup&gt;</td>
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<td>Knee or hip</td>
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<td>Placebo Oral</td>
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<td>WOMAC</td>
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<tr>
<td>Phytalgic (fish oils, <em>Urtica dioica</em>, zinc, vitamin E)</td>
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<td>Fishy belching, increased pain, infection, falls, muscle pains</td>
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<td>26 M:55 F</td>
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| **Pycnogenol**                               |
| Cisár et al<sup>52</sup>                    |
| 15 weeks                                    |
| Knee                                        |
| Placebo Oral                                |
| VAS, WOMAC                                  |
| Pycnogenol (French maritime pine *Pinus maritima*), 150 mg |
| 32 M:68 F                                   |
| 48 M:42 F                                   |

| **Reparagen**                                |
| Mehta et al<sup>55</sup>                     |
| 8 weeks                                      |
| Knee                                        |
| Placebo Oral                                |
| WOMAC, Pain VAS                             |
| Reparagen (*Uncaria guianensis*, 300 mg; *Lepidium meyenii*, 1,500 mg, 1,800 mg) |
| 24 M:71 F                                   |

| **Rosehip**                                  |
| Winther et al<sup>51</sup>                   |
| 3 months                                     |
| Knee or hip                                  |
| Placebo Oral                                |
| WOMAC                                       |
| Rosehip (*Rosa canina*), 5 g                 |
| 40 M:54 F                                   |

| **Scutellaria baikalensis**                  |
| Sampalis and Brownell<sup>28</sup>           |
| 12 weeks                                     |
| Knee or hip                                  |
| Placebo or celecoxib, 200 mg daily           |
| UP446 (extracts of *Scutellaria baikalensis* and *Acacia catechu*), 250 mg or 500 mg |
| 57.6 M:38 F                                 |

| **Shu Feng Huo Luo Pian**                    |
| Wu and Zhou<sup>50</sup>                     |
| 4 weeks                                      |
| Not stated                                   |
| Placebo Oral                                |
| WOMAC, SF-36                                 |
| Shu Feng Huo Luo Pian, 1.2 g                 |
| 63 M:37 F                                   |

| **SK1306X**                                  |
| Jung et al<sup>52</sup>                      |
| 4 weeks                                      |
| Knee                                        |
| Placebo or celecoxib, 200 mg daily           |
| SK1306X (600 mg); Clematis Radix; Trichosanthes root; Prunella spike |
| 18 M:231 F                                  |

| **Stinging nettle (Urtica dioica)**          |
| Randall et al<sup>50</sup>                   |
| 16 weeks                                     |
| Knee                                         |
| Placebo                                     |
| Topical VAS, WOMAC                          |
| Stinging nettle (Urtica dioica)              |
| Localized skin rash                         |
| 24 M:18 F                                   |

| **Stinging nettle (Urtica dioica)**          |
| Randall et al<sup>56</sup>                   |
| 1 week                                       |
| Base of thumb                                |
| Placebo                                     |
| Topical VAS, WOMAC                          |
| Stinging nettle (Urtica dioica)              |
| Localized skin rash                         |
| 4 M:23 F                                     |

(Continued)
Table 1 (Continued)

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<thead>
<tr>
<th>Study, duration</th>
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<th>Mean age (years)</th>
<th>OA site</th>
<th>Formulation (daily dose)</th>
<th>Comparator</th>
<th>Route</th>
<th>Pain and function outcomes</th>
<th>Adverse events</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Tipi tea (Petiveria alliacea)</strong></td>
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<td>Ferraz et al [9]</td>
<td>20</td>
<td>62</td>
<td>Knee, hip</td>
<td>Tipi tea (Petiveria alliacea), 9 g in 600 mL water</td>
<td>Placebo tea (Imperata exaltata [sape])</td>
<td>Oral, as tea</td>
<td>Pain subscales (pain at rest, pain on motion, pain at night)</td>
<td>Not reported</td>
<td>Case-crossover trial; AE not reported</td>
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<td><strong>Willow bark (Salix daphnoides)</strong></td>
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<td>Biegert et al [3]</td>
<td>127</td>
<td>62</td>
<td>Knee or hip</td>
<td>Willow bark (Salix daphnoides), 240 mg</td>
<td>Diclofenac 100 mg or placebo</td>
<td>Oral</td>
<td>WOMAC</td>
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<td>42 days</td>
<td>53</td>
<td>M:74 F</td>
<td>Knee or hip</td>
<td>Willow bark (Salix daphnoides), 340 mg</td>
<td>Placebo</td>
<td>Oral</td>
<td>WOMAC, VAS pain</td>
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<td>Schmid et al [3]</td>
<td>78</td>
<td>52</td>
<td>Knee or hip</td>
<td>Willow bark (Salix daphnoides), 340 mg</td>
<td>Placebo</td>
<td>Oral</td>
<td>WOMAC, VAS pain</td>
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<td>2 weeks</td>
<td>59</td>
<td>M:19 F</td>
<td>Knee or hip</td>
<td>Willow bark (Salix daphnoides), 340 mg</td>
<td>Placebo</td>
<td>Oral</td>
<td>WOMAC, VAS pain</td>
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Abbreviations: n, number of study participants; M, male; F, female; OA, osteoarthritis; AE, adverse event; AIF, anti-inflammatory factor; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; NRS, numeric rating scale; ASU, avocado/soybean unsaponifiables; GI, gastrointestinal; SD, standard deviation; KOOS, Knee injury and Osteoarthritis Outcome Score; FNZG, Fufang Nanxing Zhitong Gao; SJG, Shangshi Jietong Gao; GBT, Gubitong Recipe; BMI, body mass index; RA, rheumatoid arthritis; AS, ankylosing spondylitis.
Data extraction and quality assessment

Data relating to treatment duration, demographic information, OA site, route, intervention(s), the patient-rated outcomes of pain and function, ES, and adverse events were extracted into predefined tables by one author (LLL).

Methodological quality was assessed using The Cochrane Collaboration’s tool for assessing risk of bias by one author (XJ). Studies were assessed as having a low risk of bias, unclear risk of bias, or a high risk of bias. Included domains were: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias (scoring for individual items is shown in Table 2). Scores were summed to create a risk of bias score (possible range: 0–14), with higher scores indicating a greater risk of bias. Studies were also scored as to whether or not they required participants to cease pain medications prior to trial entry (yes/no).

Identified trials

Table 1 shows the 63 double-blind randomized controlled trials of therapies of botanical origin to treatment of pain in OA. The 63 studies include eight case-crossover clinical trials. Treatment duration ranged from 1 week–1 year. Inclusion and exclusion criteria varied between trials, but patients were typically required to have at least moderate pain and either radiological evidence of OA or to be clinically diagnosed as having OA, or both. Where a study was defined as a case-crossover trial, data were extracted only up to the point of crossover, so that the data could be compared with those derived from parallel trials.

Outcome assessment

Pain outcomes included individual pain intensity scores assessed using a visual analog scale ([VAS; continuous data ranging from 0–100]) or a numeric rating scale ([NRS]; integers), or a Likert scale (numbers representing descriptions, eg, “never”, “sometimes”, “often”), and data from the pain scales of pain and function questionnaires (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] and the Knee injury and Osteoarthritis Outcome Score [KOOS]). Data were used from total pain scores where possible.

Rasch analyses of the WOMAC pain subscale have previously suggested that it measures a combined function–pain construct. Function outcomes included the KOOS symptom score, the WOMAC function score, and the Lequesne’s functional index. Adverse events included the total number of patients with one or more adverse events. Trials that did not have data for any of the above categories did not contribute data to this review.

Statistics

Data were analyzed using the “metan” command in Stata 12.1 (StataCorp LP, College Station, TX, USA). Statistical significance was set as a P-value ≤0.05 (two-tailed).

The main analyses were performed using a random effects model that generated an estimate of ES (standardized mean difference [SMD]). This is calculated by dividing the mean difference between treatments by the standard deviation (SD) of the difference. It is, therefore, a number without units that can be used for cross-study comparisons. Clinically, ES =0.2 is considered small, ES =0.5 is moderate, and ES >0.8 is a large effect. These were pooled using the method of DerSimonian and Laird.

Subgroup analyses were analyzed using a random effects model if there was significant heterogeneity and fixed effects model if there was not. Fixed effects models were weighted using the inverse of the variance of the difference in means. All estimates of heterogeneity were taken from the Mantel–Haenszel model. Associations between the risk of bias score and ES were assessed using the Spearman’s rank correlation coefficients. Adverse event data were summarized using both fixed and random effects. The direction of the effect of KOOS outcome data was reversed to meaningfully pool it with WOMAC data.

A change in means was calculated using the final result minus the baseline result. Standard error or SD for the change in means was obtained from original papers where available. Where unavailable, the standard error of the difference was calculated using the following formula,

\[
\sqrt{(SE_{Baseline}^2 + SE_{Follow-up}^2 - 2 \times r \times SE_{Baseline} \times SE_{Follow-up})}
\]

where baseline and follow-up are the first and last time points, and \( r \) is the correlation between standard errors, conservatively assumed to be 0.7. Adverse event data were assessed using RR.

Results

Summaries of the 63 included trials are presented in Table 1. These studies encompass a wide range of botanical therapies administered orally, topically, and by other methods. Treatments were predominantly conducted on OA of the knee, but they also included OA of the hand and hip. Results are presented for pain outcomes (VAS, NRS pain scores, and WOMAC and KOOS pain scales), function, and adverse events data, and are presented separately by comparator (placebo or active control). Data were summarized by...
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(Continued)
year of publication and compared using SMDs as compared to placebo or an active comparator. An active comparator is typically a nonsteroidal anti-inflammatory agent, but it also includes any other osteoarthritic therapy.

**Efficacy**

**Pain efficacy compared to placebo**

There were sufficient numbers of studies to present data on five subgroups of plant-based therapies: comfrey and comfrey blends;\(^{1,24,58}\) *Boswellia serrata* extracts and blends;\(^{36,38,54,66,68,81}\) capsaicin;\(^{31,78,83,84}\) avocado/soybean unsaponifiables (ASUs);\(^{41,78,83,84}\) ginger;\(^{37,53,71}\) and pine bark\(^{52,22}\) (Figures 1 and 2).

For pain, as assessed by the VAS, NRS, and Likert pain scores (Figure 1), the SMDs (given using random effects) for subgroups are: comfrey, 1.70 (95% CI: −0.82 to 4.22; \(P=0.2\)); *Boswellia serrata*. 1.33 (95% CI: 0.74−1.92; \(P<0.001\)); capsaicin 0.48 (95% CI: 0.27−0.70; \(P=0.001\)); and ASUs, 1.09 (95% CI: −0.08 to 2.25; \(P=0.068\)). The SMD for the remaining botanical therapies is 0.94 (95% CI: 0.48−1.40; \(P<0.001\)). This would imply a large benefit from all classes of plant-based therapies (apart from capsaicin, which was moderate) on pain scores (as assessed by VAS and NRS) compared to placebo. Therefore, *Boswellia serrata*, capsaicin, and the ungrouped treatments as a whole are efficacious, but SMDs for comfrey and ASUs are not (SMD, 1.70; \(P=0.18\); SMD, 1.09; \(P=0.068\)). There was no association between ES and risk of bias (\(ρ=0.01\); \(P=0.94\)). Heterogeneity existed for plant-based therapies as a whole (\(I^2=93.5\%\)) and for all subgroups except capsaicin, with \(F\) values of 98.9% for comfrey, 85.2% for *Boswellia serrata*, and 97.9% for ASUs. Individual trials of plant-based therapies demonstrating significant benefit over placebo include: NR-INF-02 (Turmacin™, *Curcuma longa*);\(^{24}\) pine bark extract (Pycnogenol\(^{19}\));\(^{52}\) SK1306X (extract of Clematis Mandarinshurica, *Trichosanthes kirilowii*, and *Prunella vulgaris*);\(^{74}\) E-OA-O7 (Lanconone™, extract of shyonaka *Oroxylum indicum*); ashwagandha (*Withania somnifera*); shunti (*Zingiber officinale*); guggul (*Commiphora wightii*); chopchini (*Smilax china*); rasana (*Phlucent lanceolata*); shallaki (*Boswellia serrata*);\(^{34}\) and willow bark (*Salix purpurea x daphnoides*).\(^{75}\)

Studies using anti-inflammatory factor (AIF); extract of *Panax notoginseng* [Burk] F H Chen, *Rehmannia glutinosa* *Libosch*, and *Eleutherococcus senticosus*,\(^{49}\) roshope (*Rosa canina*)\(^{44}\) and stinging nettle (*Urtica dioica*) did not reach statistical significance. These results are also summarized in Table 3.

For WOMAC and KOOS pain scores (Figure 2), the SMD for *Boswellia serrata* extracts and blends is 4.21 (95% CI: 1.85−6.57; \(P<0.001\)), with considerable heterogeneity. All trials required patients to cease pain medications. Later trials had substantially smaller ES, though all are large. The SMD for ginger-based therapies is 0.28 (95% CI: 0.10−0.46; \(P=0.002\)), without significant heterogeneity. However, the two trials, not including massage, had much

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<td>Stinging nettle</td>
<td>Low risk</td>
<td>Risk unclear</td>
<td>Risk unclear</td>
<td>Risk unclear</td>
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<td>Capsaicin</td>
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<td>Meheu et al(^{77})</td>
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<tr>
<td>Altman et al(^{71})</td>
<td>Capsaicin</td>
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<td>Risk unclear</td>
<td>Risk unclear</td>
<td>Risk unclear</td>
<td>High risk</td>
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<tr>
<td>Schnitzer et al(^{78})</td>
<td>Capsaicin</td>
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<td>Risk unclear</td>
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<td>Low risk</td>
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<td>Ferraz et al(^{82})</td>
<td>Tigli tea</td>
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<tr>
<td>Kulkarni et al(^{83})</td>
<td>Articular-F</td>
<td>Risk unclear</td>
<td>Risk unclear</td>
<td>Risk unclear</td>
<td>Risk unclear</td>
<td>Risk unclear</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**Abbreviations:** FNZG, Fufang Nanxing Zhitong Gao; SJG, Shangshi Jietong Gao; TCM, traditional Chinese medicine; ASU, avocado/soybean unsaponifiables; AIF, anti-inflammatory factor; GBT, Gubitong Recipe; DJW, Duhuo Jisheng Wan.
higher SMDs, both of which required participants to cease pain medications prior to study commencement and, therefore, might inflate the ES – one of which had a high risk of bias due to the incomplete assessment of outcomes. The SMD for pine bark was 0.74 (95% CI: −1.03 to 2.50; $P=0.41$), with significant heterogeneity ($I^2=94.2\%$). There was no association between risk of bias and ES ($P=0.01$; $P=0.95$). The overall SMD for the unclassified therapies was 0.40 (95% CI: 0.11–0.70; $P=0.007$), but with significant heterogeneity between studies ($I^2=79.6\%$). Individual agents that demonstrated significant benefit over placebo included the following: capsaicin,41 UP446 (a blend of extracts of Scutellaria baicalensis and Acacia catechu);28 E-OA-O7 (extract of shyonak (Oroxylum indicum); ashwagandha (Withania somnifera); shunthi (Zingiber officinalis); guggul (Commiphora wightii); chopchini (Smilax china); rasana (Pluchea lanceolata); shalalka (Boswellia serrata);14 passion fruit peel (Passiflora edulis);39 and Phytalgic® (a combination of a trial of stinging nettle Urtica dioica and fish oil).48

Randomized controlled trials of compounds containing traditional Chinese ingredients,31,32 individualized herbal treatment or mineral supplements,47,55 comfrey (Symphytum officinale),23 AIF (Panax notoginseng, Rehmannia glutinosa),49 a trial of stinging nettle (Urtica dioica) alone,30 and rosehip (Rosa canina) did not demonstrate efficacy on WOMAC or KOOS pain scales when compared to placebo.

Overall, plant-based therapies including Boswellia serrata, capsaicin, and ginger conferred large benefit for pain scores (as assessed by WOMAC and KOOS pain scales) when compared to placebo.

### Pain efficacy compared to active comparator

For pain, as assessed by VAS, NRS, and Likert pain scores, the overall SMD was 0.32 (95% CI: −0.04 to 0.67; $P=0.08$), indicating no significant benefit for botanical therapies on pain scores (as assessed by VAS and NRS pain scales) when compared to an active comparator (Figure 3), and −0.08 (95% CI: −0.42 to 0.25; $P=0.6$) for WOMAC/KOOS pain scores. There was significant heterogeneity between studies ($I=90.1\%, P<0.001$ [Figure 3]; $I=85.9\%$ [Figure 4]) There was no association between the risk of bias and ES for either

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>Study duration (days)</th>
<th>Botanical treatment</th>
<th>Pain medications ceased</th>
<th>Risk of bias score</th>
<th>SMD (95% CI)</th>
<th>% weight</th>
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<tbody>
<tr>
<td>Madhu 2013</td>
<td>27</td>
<td>42</td>
<td>NR-INF-02</td>
<td>No</td>
<td>0</td>
<td>2.08 (1.45, 2.72)</td>
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<td></td>
</tr>
<tr>
<td>Kulkarni 2011</td>
<td>31</td>
<td>84</td>
<td>E-OA-O7</td>
<td>Yes</td>
<td>5</td>
<td>2.63 (1.20, 4.07)</td>
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<tr>
<td>Park 2009</td>
<td>30</td>
<td>42</td>
<td>AI</td>
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<td>0.33 (−0.22, 0.87)</td>
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<tr>
<td>Osler 2008</td>
<td>44</td>
<td>105</td>
<td>Fycnogenol</td>
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<td>1</td>
<td>1.96 (0.64, 1.48)</td>
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<td>Rosehip</td>
<td>No</td>
<td>0</td>
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<tr>
<td>Schmid 2001</td>
<td>99</td>
<td>28</td>
<td>SKO/SX/600 mg</td>
<td>Yes</td>
<td>3</td>
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<tr>
<td>Jung 2001</td>
<td>113</td>
<td>78</td>
<td>Willow bark</td>
<td>Yes</td>
<td>2</td>
<td>0.47 (0.02, 0.92)</td>
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<tr>
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<td>54</td>
<td>Stinging nettle</td>
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<td>2</td>
<td>0.36 (−0.17, 0.80)</td>
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<tr>
<td>Comfrey</td>
<td>Laslett 2012</td>
<td>315</td>
<td>34</td>
<td>Jointz (comfrey, tannic acid)</td>
<td>Yes</td>
<td>5</td>
<td>0.42 (0.70, 0.76)</td>
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<tr>
<td>Grube 2007</td>
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<td>220</td>
<td>Comfrey</td>
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<td>5</td>
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<td>1.70 (0.62, 4.22)</td>
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<tr>
<td>Boswellia serrata</td>
<td>Visal 2011</td>
<td>317</td>
<td>59</td>
<td>Alfapain</td>
<td>Yes</td>
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<td>1.86 (1.25, 2.48)</td>
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<td>38</td>
<td>5-Lisin</td>
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<td>1.23 (0.53, 1.93)</td>
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<td>38</td>
<td>Alfapain</td>
<td>Yes</td>
<td>0</td>
<td>2.33 (1.50, 3.17)</td>
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<tr>
<td>Sengupta 2009</td>
<td>320</td>
<td>47</td>
<td>5-Lisin 100 g</td>
<td>Yes</td>
<td>0</td>
<td>2.24 (1.50, 2.97)</td>
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<td>Chopra 2008</td>
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<td>90</td>
<td>RA-11</td>
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<td>1</td>
<td>0.41 (0.00, 0.83)</td>
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<tr>
<td>Kinnaird 2003</td>
<td>322</td>
<td>30</td>
<td>Boswellia serrata</td>
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<td>2</td>
<td>1.00 (0.24, 1.76)</td>
<td>3.69</td>
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<td>Kulkarni 1991</td>
<td>323</td>
<td>84</td>
<td>Articulin F</td>
<td>Yes</td>
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<td>0.53 (0.10, 0.97)</td>
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<td>1.33 (0.74, 1.92)</td>
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<td>324</td>
<td>99</td>
<td>Capsaicin</td>
<td>No</td>
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<td>Capsaicin</td>
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<td>0.41 (−0.04, 0.85)</td>
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<td>113</td>
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<td>8</td>
<td>0.47 (0.10, 0.84)</td>
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<td>Schnitler 1994</td>
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<td>59</td>
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<td>0.48 (0.27, 0.70)</td>
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<td>Avocado/soybean unsaponifiables</td>
<td>Leucene 2002</td>
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<td>163</td>
<td>ASU 300 mg</td>
<td>No</td>
<td>1</td>
<td>−0.09 (−0.40, 0.22)</td>
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<td>Appleboom 2001</td>
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<td>173</td>
<td>ASU 300 mg</td>
<td>No</td>
<td>4</td>
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<td>102</td>
<td>ASU 300 mg</td>
<td>Yes</td>
<td>8</td>
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<td>163</td>
<td>ASU 300 mg</td>
<td>No</td>
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<td>Subtotal (P=97.9%, P=0.000)</td>
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<td></td>
<td></td>
<td>1.09 (−0.08, 2.25)</td>
<td>16.98</td>
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<tr>
<td>Overall (P=93.4%, P=0.000)</td>
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<td></td>
<td></td>
<td>1.08 (0.72, 1.44)</td>
<td>100.00</td>
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</tbody>
</table>

**Figure 1.** Efficacy of plant-derived therapies compared to placebo on VAS and NRS pain scores.

**Note:** Weights are from random effects analysis.

**Abbreviations:** n, number of study participants; SMD, standardized mean difference; CI, confidence interval; VAS, visual analog scale; NRS, numeric rating scale; AIF, anti-inflammatory factor; ASU, avocado/soybean unsaponifiables.
the VAS and NRS pain scores or WOMAC/KOOS pain scores ($\rho=-0.22; P=0.5; \rho=+0.30; P=0.4$).

Only two trials demonstrated efficacy when compared to an active comparator: NR-INF-02 (containing curcumin)$^{24}$ compared to glucosamine sulfate, 1,500 mg; and Harpadol$^\text{®}$ (Devil’s claw), containing Harpagophytum procumbens, compared to dicearin, 100 mg$^{77}$ (Figure 3). Two therapies demonstrated significantly worse efficacy than active control: a Chinese herbal recipe (Duhuo Jisheng Wan) over 4 weeks$^{62}$ and willow bark extract (Salix daphnoides) over 42 days$^{63}$ of treatment. Both studies used the same active control (diclofenac, 75 mg/day or 100 mg/day) (Figure 4).

### Function efficacy

Function efficacy (when compared to placebo) was similar to that of the WOMAC/KOOS pain scores, with overall SMDs for function in plant-based therapies of 0.92 (95% CI: 0.62–1.23; $P=0.001$). The Boswellia trials demonstrated SMD of 1.66 (95% CI: 0.77–2.55; $P<0.001$), ginger at 0.73 (95% CI: –0.23 to 1.69; $P=0.14$), and ASUs at 1.10 (95% CI: 0.17–1.21; $P=0.021$), with significant heterogeneity observed in all subgroups and for the therapies as a whole. There was no association between ES and risk of bias ($\rho=0.01; P=0.96$).

Agents demonstrating significant benefit over placebo include UP446 (250 mg/day and 500 mg/day formulations),$^{28}$ E-OA-07 (extract of shyonak, ashwagandha, shunthi, guggal, chopchini, rasana, and shallaki),$^{34}$ passion fruit peel,$^{39}$ SKI306X (extract of Clematis mandshurica, Trichosanthes kirilowii, and Prunella vulgaris),$^{74}$ and NP 06-1 (Phellodendron amurense), but the effect was present only for overweight patients and absent in obese patients$^{44}$ (data not shown).

Compounds containing Urtica dioica demonstrated benefit in one study,$^{48}$ but not in another.$^{78}$ Studies investigating the effect of 4Joint$^{75}$, seaweed,$^{47,55}$ willow bark,$^{61,73}$ AIF,$^{69}$ pine bark,$^{22}$ and individualized herbal treatment$^{61}$ did not demonstrate efficacy on function.

Overall, plant-based therapies demonstrated efficacy compared to placebo for OA function. Compared to the active comparator, the overall SMD was similar to that for WOMAC/ KOOS pain scores, at $–0.04$ (95% CI: $–0.40$ to $0.32; P=0.99$), indicating no difference between the efficacy of botanical therapies and active comparator on function scores, but
there is significant heterogeneity between studies \((F=92.7\%\); 
\(P<0.001)\). Botanical therapies that demonstrate efficacy when compared to an active comparator are olive oil\(^{29}\) and UP446\(^{28}\)
(both low and high doses). Du huo ji sheng wan\(^{42}\) and willow bark\(^{43}\) favored the active comparator. There was no association between ES and risk of bias \((\rho=0.2\); 
\(P=0.44)\).

### Safety

Figure 5 shows that the RR of one or more adverse events was not increased among patients receiving botanical therapies compared to placebo \((RR=1.13\); 
95% CI: 0.98–1.31; 
\(P=0.10)\) using a random effects model, with significant heterogeneity \((P=0.050)\), and \(P=28.0\%.\) Ginger and capsaicin were associated with increase risk of adverse events: the RR for ginger is 1.40 \((95\% \text{ CI}: 1.09–1.80, \ P=0.009)\), and the RR for capsaicin is 5.59 \((95\% \text{ CI} 2.92–10.69, \ P<0.001)\). This is attributable to gastrointestinal events in the largest ginger trial\(^{77}\) and a localized burning sensation at the site of application for capsaicin. No trials other than those using capsaicin demonstrated an increased risk of adverse events compared to placebo. Reporting was often inadequate, with underreporting of adverse events common, particularly for adverse events that the investigators considered as not related to the study drug.

Figure 6 shows that the RR of one or more adverse events was reduced among patients receiving botanical therapies compared to an active comparator \((RR=0.75; 
95\% \text{ CI}: 0.65–0.85; \ P<0.001)\) using a fixed effects model, with no heterogeneity \((P=0.4)\), and \(P=3.3\%.\) Only one individual trial demonstrated reduced risk of adverse events compared to the active comparator;\(^{77}\) where Harpadol \((Harpagophytum procumbens)\) reduced the risk of adverse events when compared to diacerein 100 mg/day over 4 months of treatment. A reduction in adverse events was primarily found to be the reduction in gastrointestinal side effects when compared to nonsteroidal anti-inflammatory medications.

### Discussion

This review compared the effects of plant-derived therapies from randomized controlled trials, when compared to placebo or an active comparator, on osteoarthritic pain and function. The efficacy of plant-derived therapies is superior to placebo and comparable to active comparators for treating

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**Table 3** Summary of efficacy findings of plant-based therapy compared to placebo, by therapy class

<table>
<thead>
<tr>
<th>Class of plant-based therapy</th>
<th>VAS/NRS pain score</th>
<th>WOMAC/KOOS pain</th>
<th>WOMAC/KOOS function</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASU(^{37,55,79,80})</td>
<td>No</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>Boswellia serrata(^{26,36,38,54,59,60,66,68,81})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Capsaicin(^{41,70,83,84})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Comfrey(^{27,58})</td>
<td>No</td>
<td>(No)</td>
<td>(No)</td>
</tr>
<tr>
<td>Ginger(^{37,53,71})</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pycnogenol(^{22,52})</td>
<td>(Yes)</td>
<td>No</td>
<td>(Yes)</td>
</tr>
</tbody>
</table>

**Other treatments**

| Rosehip\(^{41,44}\)        | (No)               | –               | –                   |
| Stinging nettle\(^{0,76}\) | (No)               | (No)            | (No)                |
| Willow bark\(^{62,73}\)   | (Yes)              | (No)            | No                  |
| NR-INF-02\(^{24}\)        | Yes                | –               | –                   |
| UP446 250 mg\(^{28}\)      | –                  | No              | Yes                 |
| UP446 500 mg\(^{28}\)      | –                  | Yes             | Yes                 |
| FNZG/SJG\(^{31}\)         | –                  | No              | –                   |
| Individualized TCM/nonspecific herbal treatment\(^{32}\) | – | No | – |
| E-OA-07\(^{44}\)          | Yes                | Yes             | Yes                 |
| Passion fruit peel\(^{39}\) | –                  | Yes             | Yes                 |
| Phellodendron and citrus extracts \((NP 06-1)\)^{44} | – | – | No |
| Phytalgic\(^{48}\)         | –                  | Yes             | Yes                 |
| AIF\(^{49}\)              | No                 | –               | No                  |
| Individualized herbal treatment\(^{41}\) | – | No | No |
| Aquamin F\(^{50}\)        | –                  | Yes             | Yes                 |
| SK1306X\(^{45}\)          | –                  | Yes             | –                   |

**Notes:** Status in brackets indicates that data are only available for one trial within the class. Rosehip, stinging nettle, and willow bark were all trialed in two studies, but they are not directly comparable on the same outcome measure.

**Abbreviations:** VAS, visual analog scale; NRS, numeric rating scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KOOS, Knee injury and Osteoarthritis Outcome Score; ASU, avocado/soybean unsaponifiables; FNZG, Fufang Nanxing Zhitong Gao; SJG, Shangshi Jietong Gao; TCM, traditional Chinese medicine; AIF, anti-inflammatory factor.
ostearthritic pain and functional limitations. Risk of one or more adverse events is not increased with the use of plant-based therapies when compared to placebo, but the risk is decreased by 25% when compared to an active comparator. Therefore, plant-derived therapies have a favorable risk profile compared to standard osteoarthritic therapies.

We observed significant heterogeneity for both pain and functional outcomes. This is expected, as these plant-derived therapies contain a wide variety of active ingredients and, therefore, potentially therapeutically active molecules.28 However, heterogeneity exists within classes, which is not explained by differences in the chemical components of treatments. The trials of ASUs69,73,79,80 have SMDs with a very wide range. The trial by Lequesne et al69 is the longest at 12 months’ duration, with others trialed over 3 months75,80 or 6 months’ durations.79 This may indicate that ASU is not efficacious over longer periods of time for osteoarthritic knee pain. Several trials of Boswellia serrata36,38,54,59,60,66,68,81 have

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>Study duration (days)</th>
<th>Botanical treatment</th>
<th>Active comparator</th>
<th>Pain medications ceased</th>
<th>Risk of bias score</th>
<th>SMD (95% CI)</th>
<th>% weight</th>
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<tbody>
<tr>
<td>Niempoog 2012a</td>
<td>2012</td>
<td>100</td>
<td>42</td>
<td>Phytagel (Phai and ginger gel)</td>
<td>Diclofenac gel 1%</td>
<td>Yes</td>
<td>3</td>
<td>0.11 (0.28, 0.50)</td>
<td>10.52</td>
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<td>Sampalis 2012a</td>
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<td>30</td>
<td>90</td>
<td>UP446 500 mg/day</td>
<td>Celecoxib 200 mg</td>
<td>Yes</td>
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<td>0.55 (0.18, 1.28)</td>
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<td>Sampalis 2012a</td>
<td>2012</td>
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<td>90</td>
<td>UP446 250 mg/day</td>
<td>Celecoxib 200 mg/day</td>
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<td>0.71 (0.03, 1.45)</td>
<td>7.66</td>
</tr>
<tr>
<td>Bahkti 2012b</td>
<td>2012</td>
<td>71</td>
<td>28</td>
<td>Virgin olive oil</td>
<td>Phentermine 0.5%</td>
<td>Yes</td>
<td>2</td>
<td>0.20 (0.27, 0.86)</td>
<td>9.92</td>
</tr>
<tr>
<td>Kuphirinabiku 2011b</td>
<td>2011</td>
<td>125</td>
<td>28</td>
<td>Denis acadenlo</td>
<td>Naproxen 500 mg</td>
<td>Yes</td>
<td>4</td>
<td>~0.25 (~0.60, 0.10)</td>
<td>10.83</td>
</tr>
<tr>
<td>Pavalka 2010a</td>
<td>2010</td>
<td>361</td>
<td>183</td>
<td>ASU 300 mg</td>
<td>Chondroitin sulfate 1,200 mg</td>
<td>No</td>
<td>1</td>
<td>~0.21 (~0.42, ~0.00)</td>
<td>11.76</td>
</tr>
<tr>
<td>Mehra 2007a</td>
<td>2007</td>
<td>95</td>
<td>56</td>
<td>Reparaneg 1,800 mg</td>
<td>Glucosamine sulfate 1,500 mg</td>
<td>No</td>
<td>1</td>
<td>0.33 (~0.77, 0.74)</td>
<td>10.42</td>
</tr>
<tr>
<td>Sonakkie 2007a</td>
<td>2007</td>
<td>66</td>
<td>183</td>
<td>Boswellia serrata 1 g</td>
<td>Valdecoxib 10 mg</td>
<td>Unclear</td>
<td>7</td>
<td>0.03 (~0.45, 0.52)</td>
<td>9.79</td>
</tr>
<tr>
<td>Teekachunhatean 2004a</td>
<td>2004</td>
<td>200</td>
<td>28</td>
<td>Duhno Jiheng Wan 3 g</td>
<td>Diclofenac 75 mg</td>
<td>Yes</td>
<td>3</td>
<td>~1.11 (~1.41, ~0.81)</td>
<td>11.22</td>
</tr>
<tr>
<td>Bisgert 2004b</td>
<td>2004</td>
<td>86</td>
<td>42</td>
<td>Willow bark 240 mg</td>
<td>Diclofenac 100 mg</td>
<td>Yes</td>
<td>1</td>
<td>~0.73 (~1.17, ~0.29)</td>
<td>10.16</td>
</tr>
<tr>
<td>Overall (P=0.85 %, P=0.000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>~0.08 (~0.42, 0.25)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 3 Efficacy of plant-derived therapies compared to active comparator on VAS and NRS pain scores. Note: Weights are from random effects analysis. Abbreviations: ASU, avocado/soybean unsaponifiables; n, number of study participants; SMD, standardized mean differences; CI, confidence interval; VAS, visual analog scale; NRS, numeric rating scale.
### Figure 5: Safety of plant-derived therapies compared to placebo: incidence of one or more adverse events.

**Abbreviations:** n, number of study participants; FNZGC, Fung Nanning Zhong Gao; SJG, Shangshi Jietong Gao; RR, relative risk; CI, confidence interval; AIF, anti-inflammatory factor; TCM, traditional Chinese medicine; M-H, effect size for the risk ratio using a fixed effect model using the method of Mantel and Haenszel; D+L, effect size for the risk ratio using a random effects model using the method of DerSimonian and Laird.

#### Study, Year, n
<table>
<thead>
<tr>
<th>General botanical therapies</th>
<th>Botanical treatment</th>
<th>RR (95% CI)</th>
<th>Events, treatment</th>
<th>Events, control</th>
<th>% weight (M-H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metha 2013b</td>
<td>60</td>
<td>NR-INV-G2</td>
<td>100 mg</td>
<td>1.00 (0.15, 6.64)</td>
<td>230</td>
</tr>
<tr>
<td>Sampols 2012a</td>
<td>30</td>
<td>L passionate</td>
<td>250 mg</td>
<td>1.17 (0.71, 2.00)</td>
<td>715</td>
</tr>
<tr>
<td>Sampols 2012a</td>
<td>30</td>
<td>UPA66</td>
<td>300 mg</td>
<td>1.00 (0.42, 2.45)</td>
<td>615</td>
</tr>
<tr>
<td>Wang 2012</td>
<td>60</td>
<td>PNZG</td>
<td>0.50 mg</td>
<td>4.57 (0.25, 8.26)</td>
<td>480</td>
</tr>
<tr>
<td>Wang 2012</td>
<td>88</td>
<td>SLG</td>
<td>0.50 mg</td>
<td>4.69 (0.28, 0.83)</td>
<td>459</td>
</tr>
<tr>
<td>Kulkarni 2011b</td>
<td>16</td>
<td>E-DAOT</td>
<td>0.50 mg</td>
<td>0.33 (0.04, 2.92)</td>
<td>14</td>
</tr>
<tr>
<td>Laschke 2011b</td>
<td>102</td>
<td>Individualized TCM</td>
<td>250 mg</td>
<td>0.91 (0.71, 1.19)</td>
<td>1441</td>
</tr>
<tr>
<td>Jawson 1977a</td>
<td>61</td>
<td>Phytotherapy (inulin, dandelion)</td>
<td>250 mg</td>
<td>1.00 (0.77, 1.29)</td>
<td>220</td>
</tr>
<tr>
<td>Dean 2009a</td>
<td>49</td>
<td>Pfluegeltherapie and cholin extracts</td>
<td>250 mg</td>
<td>2.00 (0.24, 24.5)</td>
<td>200</td>
</tr>
<tr>
<td>Perret 2008</td>
<td>50</td>
<td>AF</td>
<td>250 mg</td>
<td>1.00 (0.90, 1.00)</td>
<td>1131</td>
</tr>
<tr>
<td>Tse 2008a</td>
<td>0</td>
<td>Gaoling recipe</td>
<td>250 mg</td>
<td>2.20 (0.82, 5.92)</td>
<td>245</td>
</tr>
<tr>
<td>Lequesne 2002</td>
<td>43</td>
<td>SEUKX9 600 mg</td>
<td>250 mg</td>
<td>4.04 (1.03, 10.4)</td>
<td>523</td>
</tr>
<tr>
<td>Protic 2001a</td>
<td>45</td>
<td>Cat’s claw</td>
<td>250 mg</td>
<td>0.30 (0.01, 6.91)</td>
<td>0</td>
</tr>
<tr>
<td>Catlin 2004b</td>
<td>64</td>
<td>Astaxanthin</td>
<td>250 mg</td>
<td>7.16 (0.01, 0.49)</td>
<td>0</td>
</tr>
<tr>
<td>Fildes 2005a</td>
<td>32</td>
<td>Passion fruit peel extract</td>
<td>250 mg</td>
<td>1.20 (0.94, 1.54)</td>
<td>1520</td>
</tr>
</tbody>
</table>

### Extensively Large ES. All Trials in this Class Required Study Participants to Cease Pain Medications Before the Trials Commenced, Possibly Increasing the Likelihood of Demonstrating an Effect of the Plant Therapy. None of the Trials in this Class was Classified as Being at High Risk of Bias in any Category, although the risk of bias was unclear in numerous domains in several trials.

Among the four included trials of topical capsaicin, 41,78,83,84 all had high risk of bias in one subgroup, three had incomplete outcome data (attrition bias), and one exhibited allocation concealment. The use of capsaicin is associated with an increased risk of adverse events (RR = 5.6), primarily a burning sensation at the site of application, which is of mild intensity and...
diminishes with continued use.83,92 However, this common adverse event makes allocation concealment of capsaicin trials challenging.

The ES (in SMDs) of many of the trials is very large, exceeding 1. While this is technically and methodologically possible, some of the exceedingly large ES are unexpectedly and implausibly large. Statistically significant correlations between study quality and ES have been reported in other settings, but we did not observe that in this review. Most studies included estimates of variation (either SD or standard errors) of baseline and follow-up measurements, but not change scores, with over 60% of studies not having SD or standard errors for change scores. Therefore, correlations between baseline and the last follow-up have been estimated conservatively at \( r = 0.7 \). This underestimates the ES if the true correlation is larger than this and overestimates it if the true correlation is smaller. For example, the SMD for VAS/NRS pain scores for the *Boswellia* class is 1.33 with the existing assumption (\( r = 0.7 \)), 2.03 (95% CI: 1.01–3.06) with a higher correlation (\( r = 0.95 \)), and 1.13 (95% CI: 0.67–1.59) with a lower correlation (\( r = 0.5 \)) – though botanical therapy is favored over placebo in all three scenarios. In these scenarios, SMD for VAS/NRS pain scores overall are 1.62 (95% CI: 1.10–2.14; \( r = 0.95 \)), 0.94 (95% CI: 0.62–1.26; \( r = 0.5 \)), and 0.86 (95% CI: 0.57–1.15; \( r = 0.3 \)). Correlations are also likely to vary between treatment, placebo, and active control groups and they may be different depending on the intervention studies. Overall, estimates in this review may be underestimates of efficacy if the correlation is greater than this and they may be overestimates if the correlation is less.

Reporting of the SD or standard error of the mean of the change in outcomes is required for more precise pooling of study data in future reviews.

Many therapies are only trialed in one clinical trial, or in only one trial for an individual outcome. First, this suggests that additional studies are required to validate the findings, and second, this makes pooling therapies difficult or impossible. This is especially so when treatments are compared to an active comparator but this is more broadly applicable. Numerous studies were poorly described, with only 12 studies having a low risk of bias in all dimensions, and only a further 12 studies scored as having a risk of bias that was unclear in only one dimension. Conduct of the trial (or reporting of the conduct of the trial) in the remaining studies was unclear regarding the risk of bias in more than one domain, and 31% were at high risk of bias in one or more domains. Use of the Consolidated Standards of Reporting Trials statement for the reporting of new clinical trials will be a welcome development.

**Conclusion**

Plant-derived therapies may be efficacious in treating osteoarthritis pain and functional limitation when compared to placebo, and similarly effective when compared to active comparators. The safety profile is similar to placebo and better than active comparators. However, quality trials and...
long-term data are lacking, and the number of trials for each therapy is limited. A comparison of efficacy would be assisted by trial standardization.

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References


