Botanics: Targets and Therapy

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REVIEW

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,[1] with levels of disability among people with OA having increased globally by over 25% from 1990–2010.[2] 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.[3,4]

OA is no longer considered to be a single disease entity, but a collection of heterogeneous pathologies that result in a common outcome.[5,6] 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

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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

Study, duration	n	Mean age (years) Sex (M:F)	OA site	Formulation (daily dose)	Comparator	Route	Pain and function outcomes	Adverse events#	Comments
AIF									
Park et al[49] 6 weeks	57	69 5 M:52 F	Knee	AIF (*Panax notoginseng, Rehmannia glutinosa Libosch, Eleutherococcus senticosus*), 200 mg	Placebo	Oral	VAS pain, WOMAC	Dyspepsia	
Arnica									
Widrig et al[57] 3 weeks	198	64 51 M:147 F	Hand	Arnica gel (*Arnica montana*, 50 g/100 g gel)	Ibuprofen gel 5%	Topical	Pain VAS, hand function (hand algofunctional index)	–	
Articulin-F									
Kulkarni et al[81] 12 weeks	42	48 10 M:32 F	Knee, hip	Articulin-F (*Withania somnifera*, 900 mg; *Boswellia serrata*, 200 mg; *Curcuma longa*, 100 mg; zinc, 50 mg)	Placebo	Oral	NRS pain	Dermatitis, abdominal pain, nausea	Case-crossover trial
Aquamin F									
Frestedt et al[47] 4 weeks	22	62 7 M: 5 F	Knee	Aquamin F (seaweed)	Placebo	Oral	WOMAC	Increased pain	Trial was 12 weeks, but only 4 weeks' pain data included
Frestedt et al[55] 12 weeks	39	58 17 M:19 F	Knee	Aquamin F (seaweed)	Placebo	Oral	WOMAC	Musculoskeletal complaints	
ASU									
Pavelka et al[40] 6 months	364	62 62 M:299 F	Knee	ASU, 300 mg	Chondroitin sulfate, 1,200 mg	Oral	WOMAC, Lequesne's functional index, VAS pain	Allergic reactions, GI symptoms	
Lequesne et al[69] 1 year	163	63 102 M:61 F	Hip	ASU, 300 mg	Placebo	Oral	VAS pain, Lequesne's functional index	GI symptoms, neurologic, cutaneous, epigastric	
Appelboom et al[75] 3 months	260	65 55 M:205 F	Knee	ASU, 300 mg or 600 mg	Placebo	Oral	VAS pain, Lequesne's functional index	–	Dose-finding study
Maheu et al[79] 6 months	164	64 46 M:118 F	Knee, hip	ASU, 300 mg	Placebo	Oral	VAS pain, Lequesne's functional index	–	
Blotman et al[80] 3 months	163	64 55 M:108 F	Knee, hip	ASU, 300 mg	Placebo	Oral	VAS pain, Lequesne's functional index	–	
Ayurved Siriraj Wattana recipe									
Pengkhum et al[30] 12 weeks	60	63 8 M:52 F	Knee	Ayurved Siriraj Wattana recipe, 900 mg (see Notes for ingredients)	Diclofenac, 75 mg	Oral	VAS pain (0–100), Oxford knee scores	Edema, diarrhea	Open label
Boswellia serrata									
Sengupta et al[38] 12 weeks	38	52 12 M:26 F	Knee	*Boswellia serrata* extract (5-Loxin®; Aflapin®)	Placebo	Oral	WOMAC, Lequesne's functional index, VAS pain	Acidity	
Sengupta et al[54] 90 days	75	53 20 M:50 F	Knee	5-Loxin® (*Boswellia serrata* extract, 100 mg and 250 mg)	Placebo	Oral	WOMAC, VAS, Lequesne's index	–	Only total n of adverse events reported

(*Continued*)

Table 1 (*Continued*)

Study, duration	n	Mean age (years) Sex (M:F)	OA site	Formulation (daily dose)	Comparator	Route	Pain and function outcomes	Adverse events#	Comments
Sontakke et al[59] 6 months	66	Not stated	Knee	*Boswellia serrata*, 1 g	Valdecoxib, 10 mg	Oral	WOMAC	GI symptoms, inadequate pain control	Open label; dropouts reported, not adverse events
Usha and Naidu[60] 6 weeks	40	55 13 M:F 27	Knee	EazMov Plus: *Picrorhiza kurroa* (270 mg); *Boswellia serrata* (200 mg); *Cyperus rotundus* (100 mg); *Tinospora cordifolia* (100 mg); *Glycyrrhiza glabra* (60 mg); *Zingiber officinale* (50 mg); *Trachyspermum ammi* (100 mg)	Ibuprofen, 1,200 mg	Oral	Likert pain, VAS pain, Lequesne's index	GI symptoms	Total n of patients with adverse events not reported
Chopra et al[66] 32 weeks	90	57 23 M:67 F	Knee	RA-11: *Withania somnifera; Boswellia serrata; Zingiber officinale; Curcuma longa*; (amounts not stated); four capsules daily	Placebo	Oral	VAS pain, WOMAC	Skin rash	
Kimmatkar et al[68] 8 weeks	30	59 12 M:18 F	Knee	*Boswellia serrata* extract (333 mg)	Placebo	Oral		GI symptoms	Case-crossover trial
Capsaicin									
Kosuwon et al[41] 4 weeks	100	61 0 M:99 F	Knee	Capsaicin, 0.0125%	Placebo	Topical	Pain VAS, WOMAC	Application site burning	Case-crossover
McCleane[78] 5 weeks	80	48 39 M:41 F	Knee, hip, shoulder, hand	Capsaicin, 0.025%	Placebo	Topical	Pain VAS		No info on adverse events
Altman et al[83] 12 weeks	113	62 41 M:72 F	Knee, ankle, elbow, wrist, shoulder	Capsaicin, 0.025%	Placebo	Topical	Pain VAS	Application site burning	
Schnitzer et al[84] 3 weeks + extension to 9 weeks	59	67 29 M:40 F	Hand	Capsaicin, 0.025%	Placebo	Topical	Pain VAS	Application site burning	Total n of adverse events not given
Cat's claw (*Uncaria tomentosa, Uncaria guianensis*)									
Piscoya et al[72] 4 weeks	45	60 45 M:0 F	Knee	Cat's claw (*Uncaria tomentosa, Uncaria guianensis*), 100 mg	Placebo	Oral	Likert pain scale (pain at rest)	Headache	
Curcumin *(Curcuma domestica)*									
Madhu et al[24]	42	120 56 37 M:83 F	Knee	*Curcuma domestica* extract, 1000 g (NR-INF-02)	Placebo, glucosamine	Oral	VAS pain	Body pain, cough, dyspepsia	
Kuptniratsaikul et al[45] 6 weeks	107	61 21 M:86 F	Knee	*Curcuma domestica* extract, 2 g	Ibuprofen, 800 mg	Oral	WOMAC pain subscales	–	
Castor oil									
Medhi et al[43] 4 weeks	100	55 32 M:68 F	Knee	Castor oil, 2.7 mL	Diclofenac sodium, 150 mg	Oral	VAS pain	–	No info on SD

Comfrey								
Laslett et al[25] 12 weeks	133	64.8 54 M:79 F	Knee	4Jointz, 3.5 mg: Comfrey extract *Symphytum officinale* (200 mg/g); tannic acid (100 mg/g); aloe vera (300 mg/g); eucalyptus oil (40 mg/g); frankincense oil (1.0 mg/g)	Placebo	Topical	VAS pain, KOOS pain and stiffness	Rash
Grube et al[58] 3 weeks	220	58 67 M:153 F	Knee	Kytta-Salbe F (comfrey root liquid, *Symphytum officinale*, 35%) 6 cm	Placebo	Topical	Pain VAS	Not stated
Derris scandens								
Kuptniratsaikul et al[35] 4 weeks	125	60 18 M:89 F	Knee	*Derris scandens*	Naproxen, 500 mg	Oral	WOMAC	–
Duhuo Jisheng Wan (*Radix Angelicae Pubescentis, Loranthus parasiticus*)								
Teekachunhatean et al[62] 4 weeks	200	62 41 M:159 F	Knee	Duhuo Jisheng Wan (DJW)[a] 3 g	Diclofenac, 75 mg	Oral	WOMAC, Lequesne's functional index	–
E-OA-07								
Kulkarni et al[34] 12 weeks	16	55 3 M:13 F	Knee	E-OA-07 (shyonak [*Oroxylum indicum*], ashwagandha [*Withania somnifera*], shunthi [*Zingiber officinale*], guggul [*Commiphora wightii*], chopchini [*Smilax china*], rasana [*Pluchea lanceolata*], shallaki [*Boswellia serrata*]); amounts not stated	Placebo	Oral	VAS pain score, WOMAC	Fracture
Flavocoxid								
Levy et al[46] 4 weeks	103	58 13 M:90 F	Knee	Flavocoxid, 1,000 mg (*Scutellaria baicalensis; Acacia catechu)*	Naproxen, 1,000 mg	Oral	Total WOMAC score	–
Fufang Nanxing Zhitong Gao, Shangshi Jietong Gao								
Wang[31] 1 week	150	59 13 M:136 F	Knee	FNZG; SJG (see notes for ingredients)	Placebo	Patch	Pain VAS (walking on flat surface); WOMAC score (Likert scale)	Patch site reaction
GBT								
Tao et al[42] 8 weeks	90	63 52 M:38 F	Knee	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 (*Bolbostemma paniculatum*) 15–20 g; orientvine (*Caulis Sinomenii*) 20–30 g; spatholobus stem (*Spatholobus suberectus*), 20–30 g; epimedium herb, 10–15 g	Glucosamine sulfate 1,500 mg	Oral	VAS pain	Abdominal distension, mild diarrhea

(*Continued*)

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Table 1 (*Continued*)

Study, duration	n	Mean age (years) Sex (M:F)	OA site	Formulation (daily dose)	Comparator	Route	Pain and function outcomes	Adverse events#	Comments
Ginger¥									
Drozdov et al[27] 4 weeks	43	55 8 M:35 F	Knee, hip	Ginger + glucosamine (Zinaxin® glucosamine: 200 mg, ginger extract; 1,000 mg, glucosamine)	Diclofenac + glucosamine (100 mg diclofenac; 100 mg glucosamine)	Oral	VAS pain on standing (0–100)	–	
Zahmatkash and Vafaeenasab[33] 6 weeks	92	52.2 2 M:90 F	Knee	Ginger (*Zingiber officinale*), mastic, sesame oil, 6 g	Salicylate (dose not stated) 6 g	Topical	VAS pain, stiffness	–	Adverse events not reported
Zakeri et al[37] 6 weeks	204	47 40 M:164 F	Knee	Ginger (Zintoma: *Zingiber officinale*) 250 mg	Placebo	Oral	VAS pain (standing, walking), WOMAC	–	
Yip and Tam[53] 4 weeks	59	74 11 M:42 F	Knee	Massage + 1% ginger essential oil, 0.5% orange essential oil	Massage + no essential oils; conventional treatment only	Topical, massage	WOMAC	–	
Wigler et al[67] 12 weeks	29	62 6 M:23 F	Knee	Ginger extract (*Zingiber officinale*, Zintona EC) 1,000 mg	Placebo	Oral	VAS pain on movement	–	Case-crossover trial
Altman and Marcussen[71] 6 weeks	261	65 98 M:163 F	Knee	Ginger extract EV.EXT 77 (*Zingiber officinale, Alpinia galanga*) 255 mg	Placebo	Oral	VAS pain on standing (0–100), WOMAC	GI events	
Harpagophytum procumbens									
Chantre et al[77] 16 weeks	122	61 45 M:77 F	Knee, hip	Devil's claw, Harpadol, 2,610 mg (*Harpagophytum procumbens*)	Diacerein, 100 mg	Oral	VAS pain, Lequesne's functional index	–	
Individualized herbal treatment									
Hamblin et al[51] 10 weeks	20	67 6 M:14 F	Knee	Individualized herbal treatment + multivitamins	Placebo + multivitamins	Oral	WOMAC	Not reported	Adverse events not reported
Individualized traditional Chinese medicine									
Lechner et al[32] 20 weeks	102	59 29 M:63 F	Hip or knee	Individualized traditional Chinese medicine prescription	Nonspecific herbal treatment	Oral, as tea	WOMAC, SF-36	–	
Olive oil									
Bohlooli et al[29] 4 weeks	71	40–80 0 M:71 F	Knee	Virgin olive oil	0.5% piroxicam (amount not stated)	Topical	WOMAC	–	
Passion fruit peel									
Farid et al[39] 90 days	33	53 8 M:25 F	Knee	Passion fruit peel extract (*Passiflora edulis*), 150 mg	Placebo	Oral	WOMAC	–	
Phellodendron amurense									
Oben et al[44] 8 weeks	80	–	Knee	*Phellodendron amurense* tree bank, *Citrus sinensis* extract (NP 06–1, 1.5 g)	Placebo	Oral	Lequesne's functional index	Hepatitis, nausea	Limited demographic information, stratified by BMI

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Phytalgic									
Jacquet et al[48] 4 weeks	81	57 26 M:55 F	Knee or hip	Phytalgic (fish oils, *Urtica dioica*, zinc, vitamin E)	Placebo	Oral	WOMAC	Fishy belching, increased pain, infection, falls, muscle pains	
Pycnogenol									
Cisár et al[52] 15 weeks	100	54 32 M:68 F	Knee	Pycnogenol (French maritime pine *Pinus maritima*), 150 mg	Placebo	Oral	VAS, WOMAC		
Farid et al[22] 90 days	37	48 3 M:35 F	Knee	Pycnogenol (French maritime pine, *Pinus maritima*), 150 mg	Placebo	Oral	WOMAC	–	
Reparagen									
Mehta et al[56] 8 weeks	95	53 24 M:71 F	Knee	Reparagen (*Uncaria guianensis,* 300 mg; *Lepidium meyenii,* 1,500 mg), 1,800 mg	Glucosamine sulfate, 1,500 mg	Oral	WOMAC, Pain VAS	–	
Rosehip									
Winther et al[61] 3 months	94	65 40 M:54 F	Knee or hip	Rosehip (*Rosa canina*), 5 g	Placebo	Oral	WOMAC	–	Case-crossover trial
Rein et al[64] 3 months	112	67 41 M:71 F	Various	Hyben Vita *(Rosa canina* fruits), 5 g	Placebo	Oral	Likert pain	Micturition, waterbrash, diarrhea, cancer	Case-crossover trial
Warholm et al[85] 4 months	100	65 35 M:65 F	Knee or hip	Standardized rosehip powder (*Rosa canina*), 5 mg	Placebo	Oral	Likert pain score for symptom improvement (0–4)	–	
Scutellaria baicalensis									
Sampalis and Brownell[28] 12 weeks	60	57.6 22 M:38 F	Knee or hip	UP446 (extracts of *Scutellaria baicalensis* and *Acacia catechu*), 250 mg or 500 mg	Placebo or celecoxib, 200 mg daily	Oral	WOMAC, SF-36	–	
Shu Feng Huo Luo Pian									
Wu and Zhou[70] 4 weeks	50	63 13 M:37 F	Not stated	Shu Feng Huo Luo Pian, 1.2 g	Sulindac, 0.4 g	Oral	Arthralgia and joint dysfunction indexes	Feverish sensation in limbs, stomach burning	Open label
SKI306X									
Jung et al[65] 4 weeks	249	63 18 M:231 F	Knee	SKI306X (600 mg): *Clematis Radix; Trichosanthes root; Prunella spike*	Diclofenac, 100 mg	Oral	Pain VAS, Lequesne's functional index	–	
Jung et al[74] 4 weeks	72	59 9 M:84 F	Knee	SKI306X (600 mg, 1,200 mg, 1,800 mg); *Clematis mandshurica; Trichosanthes kirilowii; Prunella vulgaris*	Placebo	Oral	VAS pain, Lequesne index	–	Dose-finding study
Stinging nettle (*Urtica dioica*)[f]									
Randall et al[50] 16 weeks	42	66 24 M:18 F	Knee	Stinging nettle (*Urtica dioica*)	Placebo (*Urtica galeopsifolia*)	Topical	VAS pain, WOMAC	Localized skin rash	
Randall et al[76] 1 week	27	60 4 M:23 F	Base of thumb	Stinging nettle (*Urtica dioica*)	Placebo	Topical	VAS pain	Localized skin rash	Case-crossover trial; some patients with RA and AS

(*Continued*)

Table 1 (*Continued*)

Study, duration	n	Mean age (years) Sex (M:F)	OA site	Formulation (daily dose)	Comparator	Route	Pain and function outcomes	Adverse events[#]	Comments
Tipi tea *(Petiveria alliacea)*									
Ferraz et al[82] 1 week	20	62 2 M: 20 F	Knee, hip	Tipi tea (*Petiveria alliacea*), 9 g in 600 mL water	Placebo tea (*Imperata exaltata* [sape])	Oral, as tea	Pain subscales (pain at rest, pain on motion, pain at night)	Not reported	Case-crossover trial; AE not reported
Willow bark *(Salix daphnoides)*									
Biegert et al[63] 42 days	127	62 53 M:74 F	Knee or hip	Willow bark (*Salix daphnoides*), 240 mg	Diclofenac 100 mg or placebo	Oral	WOMAC	–	
Schmid et al[73] 2 weeks	78	52 59 M:19 F	Knee or hip	Willow bark (*Salix daphnoides*), 340 mg	Placebo	Oral	WOMAC, VAS pain	–	

Notes: [a]Duhuo Jisheng Wan (DJW): 7.75% each of *Radix Angelicae Pubescentis* (Duhuo), *Radix Gentianae Macrophyllae* (Qinjiao), *Cortex Eucommiae* (Duzhong), *Radix Achyranthis Bidentatae* (Niuxi), *Radix Angelicae Sinensis* (Danggui), *Herba Taxilli* (Sangjisheng), *Radix Rehmanniae Preparata* (Shudihuang), *Rhizoma Chuanxiong* (Chuanxiong), *Cortex Cinnamomi* (Rougui) and *Radix Ledebouriellae* (Fangfeng), 5% each of *Radix Paeoniae Alba* (Baishao), *Radix Codonopsis* (Dangshen), *Radix Glycyrrhizae* (Gancao) and Poria (Fuling), as well as 2.5% of *Herba Asari* (Xixin). FNZG, hypaconitine and eugenol (*Rhizoma Arisaematis, Radix Aconiti, Flos Caryophylli), Cortex Cinnamomi, Radix Angelicae Dahuricae, Herba Asari, Rhizoma Chuanxiong, Radix Cynanchi Paniculati, Olibanum, myrrah, camphora, Borneolum Syntheticum*). SJG, 17 different herbs, including *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 Pinelliae, Semen Sinapis, Semen Vaccariae, Radix Aconiti Kusnezoffi*, and *Herba Menthae*. [#]Adverse events listed are events that are more frequent in participants receiving plant-based therapy. Adverse events of active comparators are not listed. Adverse events are not listed if similar patterns were observed in both groups. Ayurved Siriraj Wattana recipe: *Piper nigrum, Boesenbergia pandurata, Tinospora cordifolia, Terminalia chebula, Cladogynos orientalis, Ferula asafoetida, Saussurea lappa, Cyperus rotundus, Derris scandens, Anamirta cocculus, Drypetes roxburghii, Cinnamomum siamense, Aegle marmelos, Conioselinum univitatum*, and *Cryptolepis buchanani*. Individual amounts not stated;[30] [β]*Boswellia serrata*: also see Kulkarni[81] and Kulkarni (E-OA-07);[34] [¥]Ginger (*Zingiber officinale*): also see EazMov Plus,[60] E-OA-07,[34] and RA–11, Chopra;[66] [f]Stinging nettle, see also Phytalgic (Jacquet).[48]

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).[23] 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.[22,24–85] The 63 studies include eight case-crossover clinical trials.[41,61,64,67,68,76,81,82] 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][86] and the Knee injury and Osteoarthritis Outcome Score [KOOS][87]). 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.[88,89] Function outcomes included the KOOS symptom score,[87] the WOMAC function score,[86] and the Lequesne's functional index.[90] 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.[9] These were pooled using the method of DerSimonian and Laird.[91]

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,

$$\sqrt{(SE_{Baseline}{}^2 + SE_{Follow\text{-}up}{}^2 - 2 \times r \times SE_{Baseline} \times SE_{Follow\text{-}up})} \quad (1)$$

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.[24–84] 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

Table 2 Risk of bias assessment for individual randomized controlled trials of botanical therapy versus placebo or active comparator

Study	Treatment	Random sequence generation	Allocation concealment	Blinding: participants	Blinding: outcome assessment	Incomplete outcome data	Selective reporting	Other
Madhu et al[24]	Curcumin	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bohlooli et al[29]	Olive oil	Low risk	Low risk	Low risk	Low risk	Risk unclear	Low risk	Risk unclear
Drozdov et al[27]	Ginger	High risk	Risk unclear	Risk unclear	Risk unclear	Low risk	Low risk	Low risk
Laslett et al[25]	4Jointz	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Niempoog et al[26]	Ginger	Risk unclear	Risk unclear	Low risk	Low risk	Risk unclear	Low risk	Low risk
Pengkhum et al[30]	Ayurved Siriraj Wattana	Low risk	Risk unclear	High risk	High risk	Low risk	Low risk	Low risk
Sampalis and Brownell[28]	UP446	Risk unclear	Risk unclear	Risk unclear	Risk unclear	Risk unclear	Low risk	Low risk
Wang et al[31]	FNZG, SJG	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kosuwon et al[41]	Capsaicin	Low risk	High risk	Risk unclear	Risk unclear	Low risk	Low risk	Low risk
Kulkarni, 2011[34]	E-OA-07	Risk unclear	Low risk	Risk unclear	Risk unclear	High risk	Low risk	Low risk
Kuptniratsaikul et al[35]	Derris scandens	Low risk	Low risk	High risk	Risk unclear	Risk unclear	Low risk	Low risk
Lechner et al[32]	TCM	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Vishal et al[36]	*Boswellia serrata*	Low risk	Low risk	Low risk	Low risk	Risk unclear	Low risk	Low risk
Zahmatkash and Vafaeenasab[33]	Ginger	Low risk	Risk unclear	Risk unclear	Risk unclear	Risk unclear	Low risk	Low risk
Zakeri et al[37]	Ginger	Risk unclear	Risk unclear	Low risk	Low risk	Risk unclear	Low risk	Low risk
Farid et al[39]	Passion fruit peel	Risk unclear	Risk unclear	Low risk	Low risk	Risk unclear	Low risk	Low risk
Pavelka et al[40]	ASU	Low risk	Risk unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Sengupta et al[38]	*Boswellia serrata*	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Frestedt et al[47]	Aquamin F	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Risk unclear
Jacquet et al[48]	Phytalgic	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kuptniratsaikul et al[45]	Curcumin	Low risk	Low risk	High risk	High risk	Risk unclear	Low risk	Low risk
Levy et al[46]	Flavocoxid	Risk unclear	Risk unclear	Risk unclear	Risk unclear	Low risk	Low risk	Low risk
Medhi et al[43]	Castor oil	Risk unclear	Risk unclear	Risk unclear	Risk unclear	Risk unclear	Low risk	Low risk
Oben et al[44]	Phellodendron amurense	Low risk	Risk unclear	Low risk	Low risk	Risk unclear	Low risk	Low risk
Park et al[49]	AIF	Risk unclear	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Tao et al[42]	GBT	High risk	Risk unclear	High risk	High risk	Low risk	Low risk	Low risk
Cisár et al[52]	Pycnogenol	Risk unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Frestedt et al[55]	Aquamin F	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Hamblin et al[51]	Individualized herbal treatment	Risk unclear	Low risk	Risk unclear	Risk unclear	Low risk	Low risk	Low risk
Randall et al[50]	Stinging nettle	Low risk	Low risk	Low risk	Low risk	Risk unclear	Low risk	Low risk
Sengupta et al[54]	*Boswellia serrata*	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Yip and Tam[53]	Massage + essential oils	High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Grube et al[58]	Comfrey	Risk unclear	Risk unclear	Risk unclear	Risk unclear	Risk unclear	Low risk	Low risk
Mehta et al[56]	Reparagen	Low risk	Low risk	Low risk	Low risk	Risk unclear	Low risk	Low risk
Sontakke et al[59]	*Boswellia serrata*	Low risk	Risk unclear	High risk	High risk	Risk unclear	Risk unclear	Low risk
Widrig et al[57]	Arnica gel	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Farid et al[22]	Pine bark	Risk unclear	Risk unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Usha and Naidu[60]	EazMov Plus	Low risk	Risk unclear	High risk	High risk	Low risk	Low risk	Low risk
Winther et al[61]	Rosehip	Low risk	Low risk	Low risk	Low risk	Risk unclear	Low risk	Low risk
Biegert et al[63]	Willow bark	Low risk	Low risk	Low risk	Low risk	Risk unclear	Low risk	Low risk
Chopra et al[66]	RA-11	Low risk	Low risk	Low risk	Low risk	Risk unclear	Low risk	Low risk
Jung et al[65]	SKI306X	Low risk	Low risk	High risk	High risk	Risk unclear	Low risk	Low risk
Rein et al[64]	Rosehip	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Teekachunhatean et al[62]	DJW	Risk unclear	Risk unclear	Low risk	Low risk	Risk unclear	Low risk	Low risk
Kimmatkar et al[68]	*Boswellia serrata*	Low risk	Risk unclear	Low risk	Low risk	Risk unclear	Low risk	Low risk
Wigler et al[67]	Ginger	Low risk	Low risk	Low risk	Low risk	Risk unclear	Low risk	Low risk
Lequesne et al[69]	ASU	Low risk	Low risk	Low risk	Low risk	Risk unclear	Low risk	Low risk

(*Continued*)

Table 2 (*Continued*)

Study	Treatment	Random sequence generation	Allocation concealment	Blinding: participants	Blinding: outcome assessment	Incomplete outcome data	Selective reporting	Other
Wu and Zhou[70]	Shu Feng Huo Luo Pian	Risk unclear	Risk unclear	Risk unclear	Risk unclear	High risk	Risk unclear	Risk unclear
Altman and Marcussen[71]	Ginger	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Appelboom et al[75]	ASU	Risk unclear	Risk unclear	Risk unclear	Risk unclear	Low risk	Low risk	Low risk
Jung and Roh[74]	SKI306X	Risk unclear	Risk unclear	Low risk	Low risk	Risk unclear	Low risk	Low risk
Piscoya et al[72]	Cat's claw	Risk unclear	Risk unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Schmid et al[73]	Willow bark	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chantre et al[77]	Devil's claw	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Randall et al[76]	Stinging nettle	Risk unclear	Risk unclear	Low risk	Low risk	Low risk	Low risk	Low risk
McCleane[78]	Capsaicin	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Maheu et al[79]	ASU	Low risk	Low risk	Low risk	Low risk	Risk unclear	Low risk	Low risk
Blotman et al[80]	ASU	Risk unclear	Risk unclear	Low risk	Low risk	Risk unclear	Low risk	Low risk
Altman et al[83]	Capsaicin	Risk unclear	Risk unclear	Risk unclear	Risk unclear	High risk	Low risk	Low risk
Schnitzer et al[84]	Capsaicin	Risk unclear	Risk unclear	Risk unclear	Low risk	High risk	Low risk	Low risk
Ferraz et al[82]	Tipi tea	Risk unclear	High risk	Risk unclear	Risk unclear	Risk unclear	Risk unclear	Risk unclear
Kulkarni et al[81]	Articulin-F	Risk unclear	Risk unclear	Low risk	Low risk	Risk unclear	Low risk	Low risk

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.

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;[25,58] *Boswellia serrata* extracts and blends;[36,38,54,66,68,81] capsaicin;[41,78,83,84] avocado/soybean unsaponifiables (ASUs);[69,75,79,80] ginger;[37,53,71] and pine bark[22,52] (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; $P\leq0.001$); 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 I^2 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®);[52] SKI306X (extract of *Clematis mandshurica*, *Trichosanthes kirilowii,* and *Prunella vulgaris*);[74] E-OA-O7 (Lanconone™, extract of shyonaka [*Oroxylum indicum*]; ashwagandha [*Withania somnifera*]; shunthi [*Zingiber officinale*]; guggul [*Commiphora wightii*]; chopchini [*Smilax china*]; rasana [*Pluchea lanceolata*]; shallaki [*Boswellia serrata*]);[34] and willow bark (*Salix purpurea x daphnoides*).[73]

Studies using anti-inflammatory factor ([AIF]; extract of *Panax notoginseng* [Burk] F H Chen, *Rehmannia glutinosa Libosch,* and *Eleutherococcus senticosus*),[49] rosehip (R*osa canbina*)[64] and stinging nettle (*Urtica dioica*)[76] 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

higher SMDs, both of which required participants to cease pain medications prior to study commencement[37,71] and, therefore, might inflate the ES – one of which[71] 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 (ρ=−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 officinale*); guggul (*Commiphora wightii*); chopchini (*Smilax china*); rasana (*Pluchea lanceolata*); shallaki (*Boswellia serrata*);[34] passion fruit peel (*Passiflora edulis*);[39] and Phytalgic® (a combination of stinging nettle *Urtica dioica* and fish oil).[48]

Randomized controlled trials of compounds containing traditional Chinese ingredients,[31,32] individualized herbal treatment[51] or mineral supplements,[47,55] comfrey (*Symphytum officinale*),[25] AIF (*Panax notoginseng, Rehmannia glutinosa Libosch, Eleutherococcus senticosus*),[49] a trial of stinging nettle (*Urtica dioica)* alone,[50] and rosehip (*Rosa canina*)[61] did not demonstrate efficacy on WOMAC or KOOS pain scales when compared to placebo.

Overall, plant-based therapies including *Boswellia serrata*, capsaicin, and ginger confered 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^2=90.1%, P<0.001 [Figure 3]; I^2=85.9% [Figure 4]) There was no association between the risk of bias and ES for either

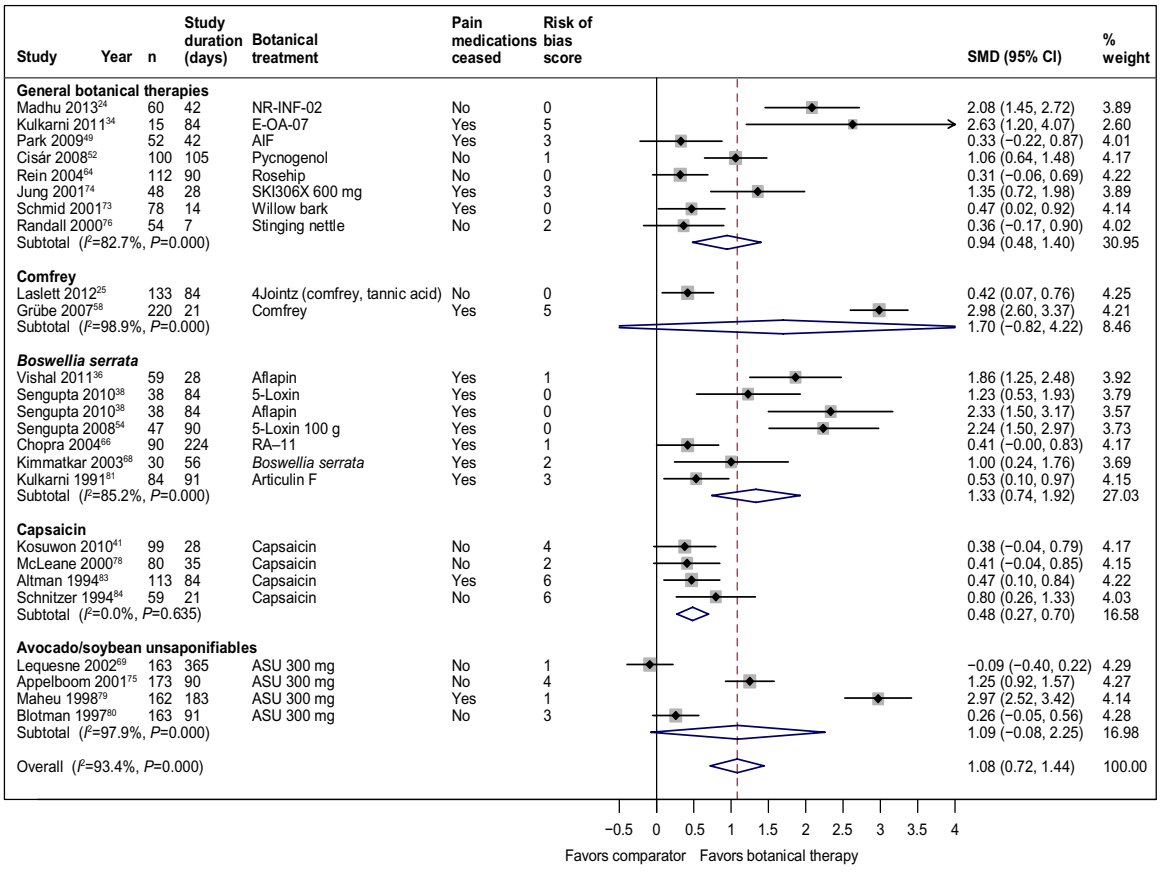

Figure 1 Efficacy of plant-derived therapies compared to placebo on VAS and NRS pain scores.
Note: Weights are from random effects analysis.
Abbreviations: n, number of study participants; SMD, standardized mean difference; CI, confidence interval; VAS, visual analog scale; NRS, numeric rating scale; AIF, anti-inflammatory factor; ASU, avocado/soybean unsaponifiables.

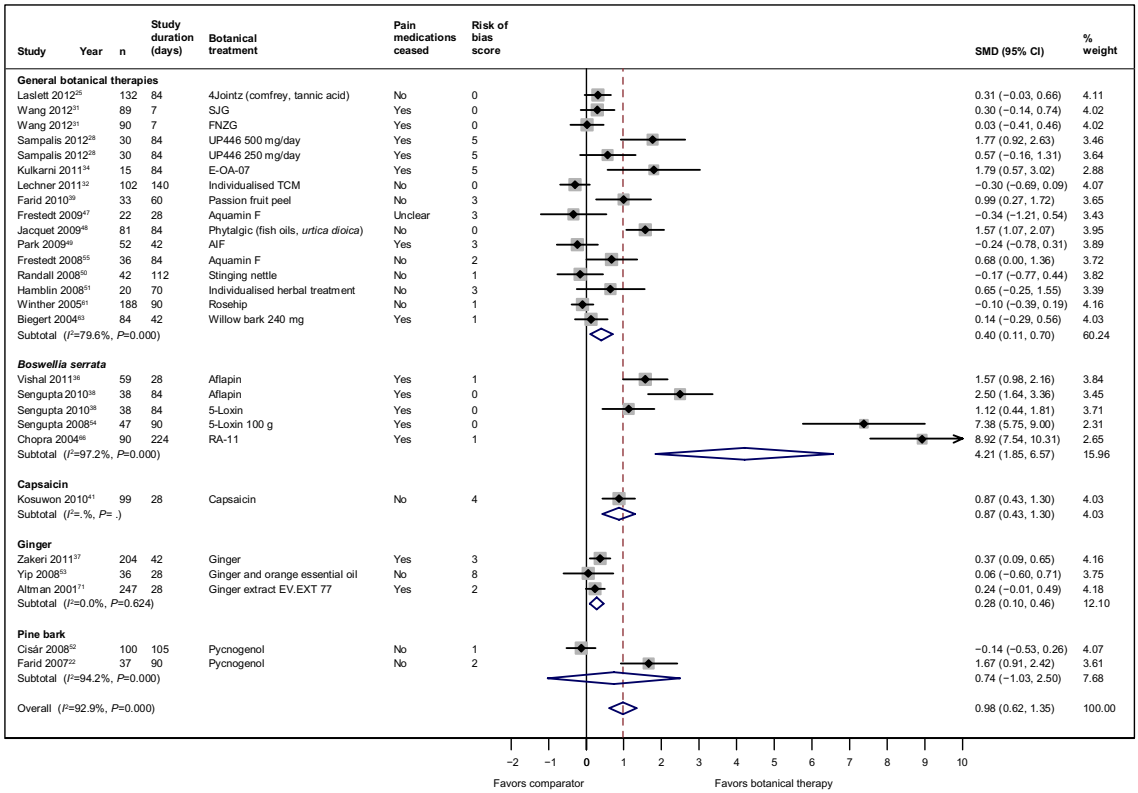

Figure 2 Efficacy of plant-derived therapies compared to placebo on pain WOMAC and KOOS pain scores.
Note: Weights are from random effects analysis.
Abbreviations: AIF, anti-inflammatory factor; n, number of study participants; SMD, standardized mean difference; CI, confidence interval; FNZG, Fufang Nanxing Zhitong Gao; SJG, Shangshi Jietong Gao; AIF, anti-inflammatory factor; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KOOS, Knee injury and Osteoarthritis Outcome Score; TCM, traditional Chinese medicine.

the VAS and NRS pain scores or WOMAC/KOOS pain scores (ρ=–0.22; P=0.5; ρ=+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® (Devil's claw), containing *Harpagophytum procumbens*, compared to diacerein, 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; $P \leq 0.001$). 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 (ρ=+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.[76] Studies investigating the effect of 4Jointz®,[25] seaweed,[47,55] willow bark,[63,73] AIF,[49] pine bark,[22] and individualized herbal treatment[51] 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

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

Class of plant-based therapy	VAS/NRS pain score	WOMAC/ KOOS pain	WOMAC/ KOOS function
ASU[69,75,79,80]	No	–	Yes
Boswellia serrata[36,38,54,59,60,66,68,81]	Yes	Yes	Yes
Capsaicin[41,78,83,84]	Yes	Yes	Yes
Comfrey[25,58]	No	(No)	(No)
Ginger[37,53,71]	–	Yes	No
Pycnogenol[22,52]	(Yes)	No	(Yes)
Other treatments			
Rosehip[61,64]	(No)	(No)	–
Stinging nettle[50,76]	(No)	(No)	(No)
Willow bark[63,73]	(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[34]	Yes	Yes	Yes
Passion fruit peel[39]	–	Yes	
Phellodendron and citrus extracts (NP 06-1)[44]	–	–	No
Phytalgic[48]	–	Yes	Yes
AIF[49]	No	–	No
Individualized herbal treatment[51]	–	No	No
Aquamin F[47,55]	–	Yes	No
SKI306X[74]	Yes	–	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.

there is significant heterogeneity between studies (I^2=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[62] and willow bark[63] favored the active comparator. There was no association between ES and risk of bias (ρ=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 I^2 of 28.0%. Ginger and capsaicin were associated with increase risk of adverse events: the RR for ginger is 1.40 (95% CI: 1.09–1.80, P=0.009), and the RR for capsaicin is 5.59 (95% CI 2.92–10.69; $P<0.001$). This is attributable to gastrointestinal events in the largest ginger trial[71] 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% CI: 0.65–0.85; $P<0.001$) using a fixed effects model, with no heterogeneity (P=0.4), and I^2 of 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

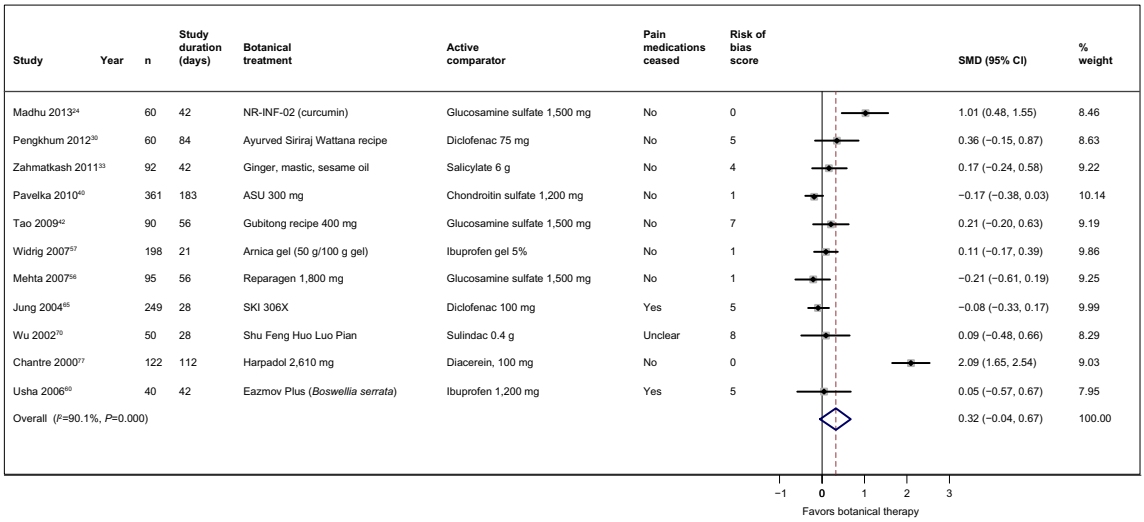

Figure 3 Efficacy of plant-derived therapies compared to active comparator on VAS and NRS pain scores.
Note: Weights are from random effects analysis.
Abbreviations: ASU, avocado/soybean unsaponifiables; n, number of study participants; SMD, standardized mean differences; CI, confidence interval; VAS,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

osteoarthritic 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.[20] However, heterogeneity exists within classes, which is not explained by differences in the chemical components of treatments. The trials of ASUs[69,75,79,80] have SMDs with a very wide range. The trial by Lequesne et al[69] is the longest at 12 months' duration, with others trialed over 3 months[75,80] 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 serrata*[36,38,54,59,60,66,68,81] have

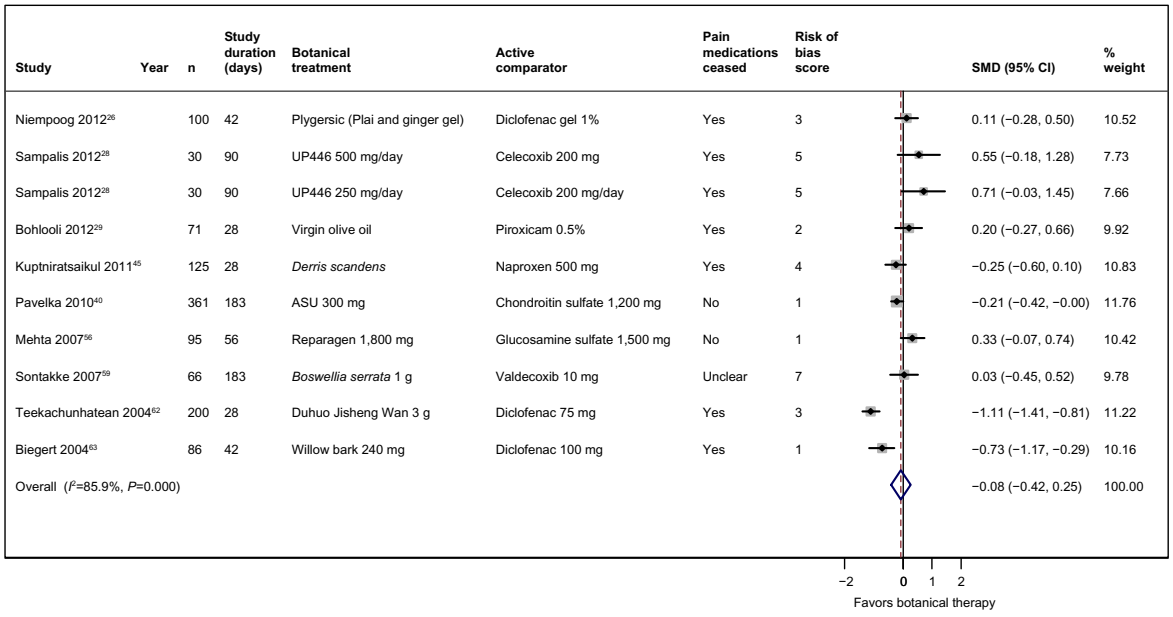

Figure 4 Efficacy of plant-derived therapies compared to active comparator on WOMAC and KOOS pain scores.
Note: Weights are from random effects analysis.
Abbreviations: ASU, avocado/soybean unsaponifiables; n, number of study participants; SMD, standardized mean differences; CI, confidence interval; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KOOS, Knee injury and Osteoarthritis Outcome Score.

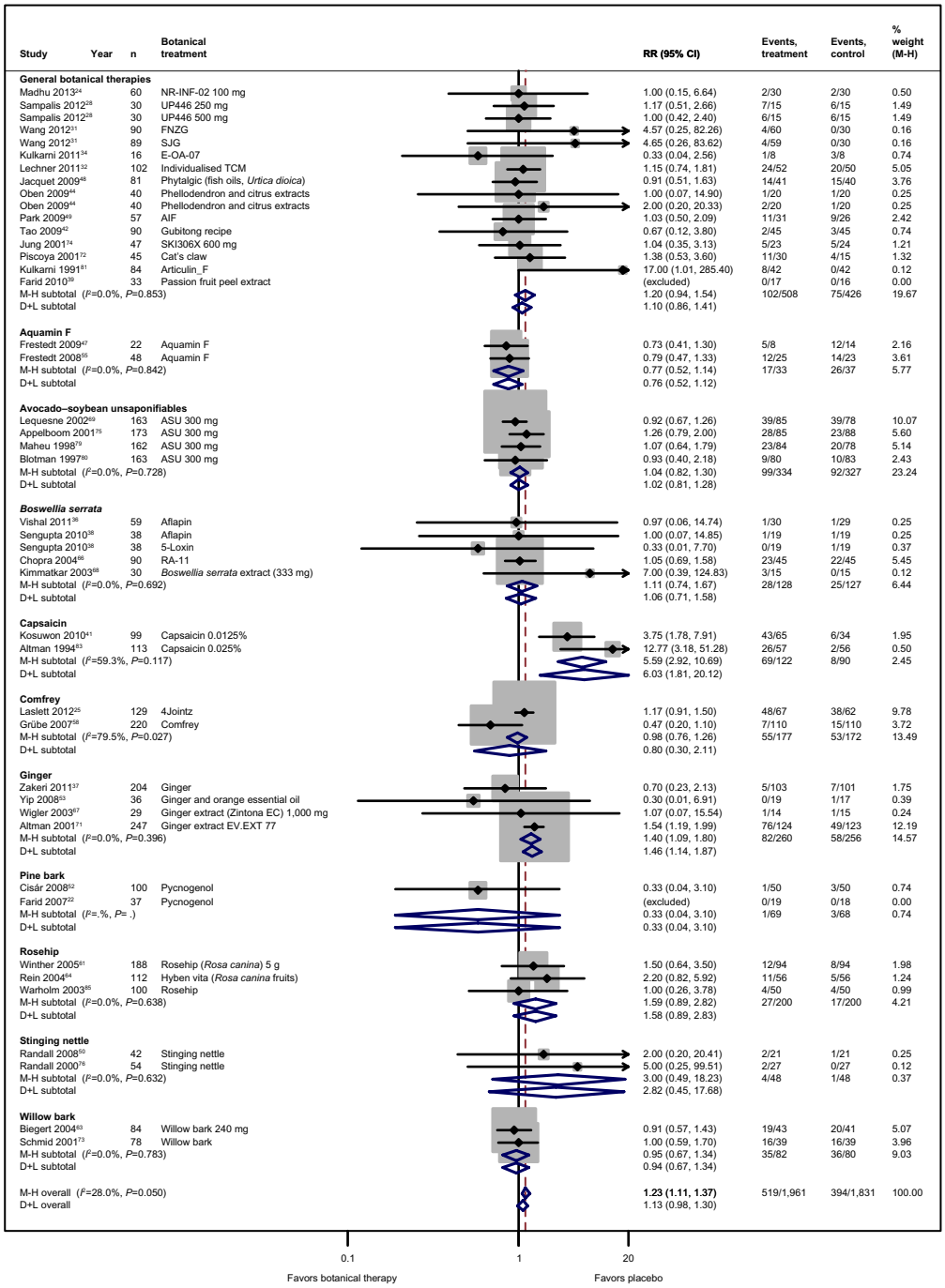

Figure 5 Safety of plant-derived therapies compared to placebo: incidence of one or more adverse events.

Abbreviations: n, number of study participants; FNZG, Fufang Nanxing Zhitong 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.

extremely 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

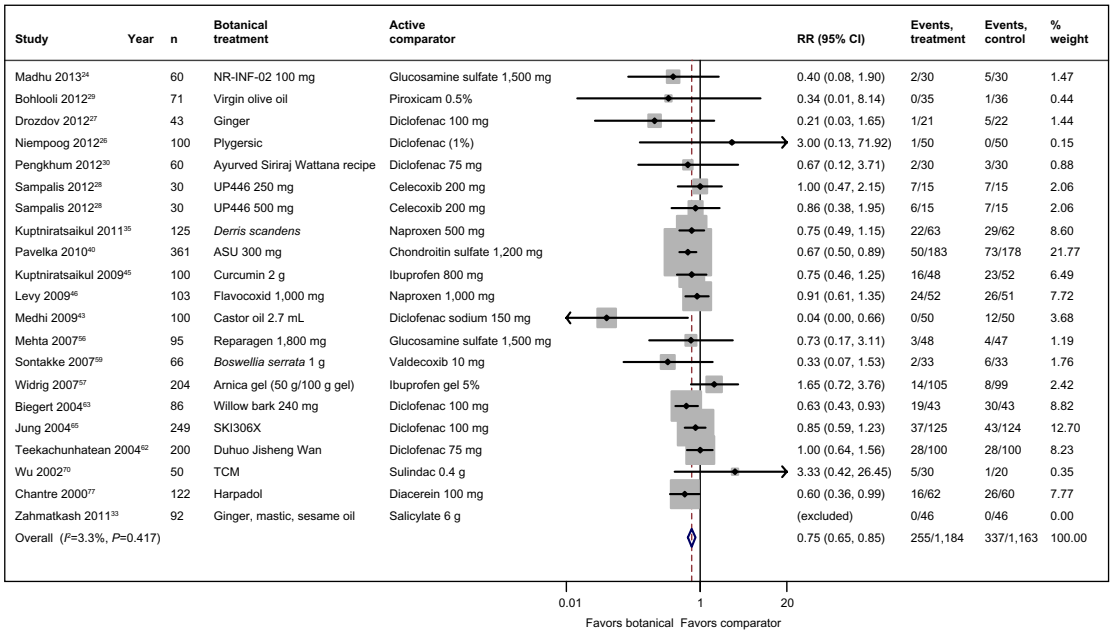

Figure 6 Safety of botanical therapy compared to active comparator: incidence of one or more adverse events.
Abbreviations: n, number of study participants; RR, relative risk; CI, confidence interval; ASU, avocado/soybean unsaponifiables; TCM, traditional Chinese medicine.

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 studied. 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 osteoarthritic 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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