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REVIEW

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

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Correspondence: Laura L Laslett Menzies Institute for Medical Research, University of Tasmania, Private Bag 23, Hobart, Tasmania 7000, Australia Tel +61 3 6226 7736 Fax +61 3 6226 7704 Email laura.laslett@utas.edu.au **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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© 2015 Lastett et al. This work is published by Dove Medical Press Limited, and Licensed under Greative Commons Attribution — Non Commercial (unported, v3.0) License. The full terms of the License are available at http://creativecommons.org/license/by-nd/3.0/. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. Permissions byeond the scope of the License are administered by Dove Medical Press Limited, Information on how to request permission may be found at http://www.dovepress.com/permissions.php 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 moderate⁹ 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

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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 plantderived 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.

Study, duration	5	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	198		Hand	Arnica gel (Arnica montana,	lbuprofen	Topical	Pain VAS, hand	I	
3 weeks		51 M:147 F		50 g/100 g gel)	gel 5%		function (hand algofunctional index)		
Kulkarni et al ⁸¹ 12 weeks	42	48 10 M:32 F	Knee, hip	Articulin-F (<i>Withania somnifera,</i> 900 mg; Boswellia serrata, 200 mg; <i>Curcuma longa,</i> 100 mg; zinc, 50 mg)	Placebo	Oral	NRS pain	Dermatitis, abdominal pain, nausea	Case-crossover trial
Aquamin F									
Frestedt et al ⁴⁷	22	62 7 M. F E	Knee	Aquamin F (seaweed)	Placebo	Oral	WOMAC	Increased pain	Trial was 12 weeks, but only
4 WEEKS									4 weeks pain uata included
Frestedt et al ⁵⁵ 12 weeks ASU	39	58 17 M:19 F	Knee	Aquamin F (seaweed)	Placebo	Oral	WOMAC	Musculoskeletal complaints	
Povello at a ¹⁴⁰	364	67	Knee	ASI1 300 mg	Chondroitin	Oral		Allargic reactions	
r arcina cuai 2 montho	-			Sin 000 (000)		0 B	l'actionale finericael		
		1 66711 70			l.200 mg		index. VAS pain		
000000000000000000000000000000000000000	671	67			Discho	C		- Claumatome	
Lequesne et al	3		2			QA	functional index	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	I	Dose-finding study
Maheu et al ⁷⁹	164	64	Knee, hip	ASU, 300 mg	Placebo	Oral	VAS pain, Lequesne's	I	
6 months		46 M:I I8 F)			functional index		
Blotman et al ⁸⁰	163	64	Knee, hip	ASU, 300 mg	Placebo	Oral	VAS pain, Lequesne's	I	
3 months		55 M:108 F					functional index		
Ayurved Siriraj Wattana recipe	attana	recipe							
Pengkhum et al ³⁰	60	63	Knee	Ayurved Siriraj Wattana recipe,	Diclofenac,	Oral	VAS pain (0–100),	Edema, diarrhea	Open label
12 weeks		8 M:52 F		900 mg (see Notes for ingredients)	75 mg		Oxford knee scores		-
Boswellia serrata									
Sengupta et al ³⁸	38	52	Knee	Boswellia serrata extract (5-Loxin®;	Placebo	Oral	WOMAC,	Acidity	
12 weeks		12 M:26 F		Aflapin®)			Lequesne's functional index, VAS pain		
Sengupta et al ⁵⁴	75	53	Knee	5-Loxin [®] (Boswellia serrata extract,	Placebo	Oral	WOMAC, VAS,	I	Only total n of adverse
90 dave		20 M·ED F		100 mg and 250 mg)			Lequesne's index		events reported

Study, duration	_	Mean age (years)	OA site	Formulation (daily dose)	Comparator	Route	Pain and function outcomes	Adverse events#	Comments
Sontakke et al ^{s9} 6 months	66	Not stated	Knee	Boswellia serrata, I g	Valdecoxib, 10 mg	Oral	WOMAC	Gl symptoms, inadequate pain	Open label; dropouts reported, not adverse
Usha and Naidu ⁶⁰ 6 weeks	40	55 13 M:F 27	Клее	EazMov Plus: Picrorhiza kurroa (270 mg); Boswellia serrata (200 mg); Cyperus rotundus (100 mg); Tinospora cordifolia (100 mg); Gycyrrhiza glabra	lbuprofen, 1,200 mg	Oral	Likert pain, VAS pain, Lequesne's index	control GI symptoms	events Total n of patients with adverse events not reported
Chopra et al ⁶⁶ 32 weeks	06	57 23 M:67 F	Knee	(60 mg); Zingiber officinale (50 mg); Tradhyspermum ammi (100 mg) RA-11: Withania somnifera; Boswellia serrata; Zingiber officinale; Curcuma honar (amounts not estrad), four	Placebo	Oral	VAS pain, WOMAC	Skin rash	
Kimmatkar et al ⁶⁸ 8 weeks	30	59 12 M:18 F	Knee	capsules daily Boswellia serrata extract (333 mg)	Placebo	Oral		GI symptoms	Case-crossover trial
Capsaicin Kosuwon et al ⁴¹ 4 wooks	00	61 61 0 M-99 F	Knee	Capsaicin, 0.0125%	Placebo	Topical	Pain VAS, WOMAC	Application site	Case-crossover
McCleane ⁷⁸ 5 weeks	80	48 39 M:41 F	Knee, hip, shoulder, hand	Capsaicin, 0.025%	Placebo	Topical	Pain VAS	0	No info on adverse events
Altman et al ⁸³ 12 weeks	113	62 41 M:72 F	Knee, ankle, elbow, wrist,	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 45 60 Knee 4 weeks Currunia (Curruna domestica)	1 tomer 45	ntosa, Uncaria 60 45 M:0 F	1 guianensis) Knee	Cat's claw (Uncaria tomentosa, Uncaria guianensis), 100 mg	Placebo	Oral	Likert pain scale (pain at rest)	Headache	
Madhu et al ²⁴ Kuptniratsaikul et al ⁴⁵ 6 weeks	42 107	estudy 120 56 37 M:83 F 61 21 M:86 F	Knee Knee	Curcuma domestica extract, 1000 g (NR-INF-02) Curcuma domestica extract, 2 g	Placebo, glucosamine Ibuprofen, 800 mg	Oral Oral	VAS pain WOMAC pain subscales	Body pain, cough, dyspepsia -	
Castor oll Medhi et al ⁴³ 4 weeks	001	55 37 M·68 F	Knee	Castor oil, 2.7 mL	Diclofenac	Oral	VAS pain	Ι	No info on SD

Rash		Not stated		I			I			Fracture			I			ratch site reaction		Abdominal distension, mild diarrhea
VAS pain. KOOS	pain and stiffness	Pain VAS		WOMAC			WOMAC,	Lequesne's functional	Index	VAS pain score,	WOMAC		Total WOMAC	score		rain VAS (waiking on flat surface); WOMAC score (Likert scale)		VAS pain
Topical	- -	Topical		Oral			Oral			Oral			Oral			ratch		Oral
Placebo		Placebo		Naproxen, 500 mg			Diclofenac, 75 mg			Placebo			Naproxen,	I ,000 mg		rlacebo		Glucosamine sulfate 1,500 mg
4lointz. 3.5 mg. Comfrev extract	Symphytum officiale (200 mg/g); tannic acid (100 mg/g); aloe vera (300 mg/g); eucalyptus oil (40 mg/g); frankincense oil (1.0 mg/g)	Kytta-Salbe F (comfrey root liquid,	Symphytum officinale, 35%) 6 cm	Derris scandens		Duhuo Jisheng Wan (Radix Angelicae Pubescentis, Loranthus parasiticus)	Duhuo Jisheng Wan (DJW) ^a 3 g			E-OA-07 (shyonak [Oroxylum	indicum], ashwagandha [Withania somnifera], shunthi [Zingiber officinde], guggul [Commiphora wighti], chopchini [Smilox chind], rasana [Pluchea lanceolata], shallaki [Boswellia serrata]); amounts not stated		Flavocoxid, 1,000 mg (Scutellaria	baicalensis; Acacia catechu)		rivzus; აეს (see notes tor ingredients)		GBT, 400 mL: drynaris rhizoma, 18–20 g: eucommia bark, 20–30 g; cibot rhizome (<i>Rhizoma</i> <i>Cibotii</i>) 25–30 g; psoralea fruit, 10–15 g; tubeimu tuber (<i>Bolbostemma paniculatum</i>) 15–20 g; orientvine (<i>Caulis Sinomenii</i>) 20–30 g; spatholobus stem (Spatholobus suberectus), 20–30 g; epimedium herb, 10–15 g
Knee		Knee		Knee		ubescentis, Lorai	Knee			Knee			Knee		li Jietong Gao	Nnee		Knee
64.8			67 M:153 F	60	18 M:89 F	dix Angelicae P	200 62	41 M:159 F		55	3 M:13 F			13 M:90 F	ong Gao, Shangsr	57 13 M:136 F		63 52 M:38 F
133		220		1 ³⁵ 125		Van (Ra	200			16			103	F	Zhitong			6
Comfrey Laslett et al ²⁵	12 weeks	Grube et al ^{s8}	3 weeks Derris scandens	Kuptniratsaikul et al ³⁵	4 weeks	Duhuo Jisheng V	Teekachunhatean	et al ⁶²	4 weeks E-OA-07	Kulkarni et al ³⁴	12 weeks	Flavocoxid	Levy et al ⁴⁶	4 weeks		v ang I week	GBT	Tao et al ⁴² 8 weeks

(Continued)

Study, duration	c	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 (0–1 00)	1	
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	1	Adverse events not reported
Zakeri et al ³⁷ 6 weeks Yip and Tam ⁵³ 4 weeks	204 59	47 40 M:164 F 74 11 M:42 F	Knee Knee	Ginger (Zintoma: Zingiber officinale) 250 mg Massage + 1% ginger essential oil, 0.5% orange essential oil	Placebo Massage + no essential oils;	Oral Topical, massage	VAS pain (standing, walking), WOMAC WOMAC	1 1	
Wigler et al ⁶⁷ 12 weeks Altman and Marcussen ⁷¹	29 261	62 6 M:23 F 65 98 M:163 F	Knee Knee	Ginger extract (Zingiber officinale, Zintona EC) 1,000 mg Ginger extract EV.EXT 77 (Zingiber officinale, Alpinia galanga) 255 mg	Placebo Placebo	Oral Oral	VAS pain on movement VAS pain on standing (0–100), WOMAC	– Gl events	Case-crossover trial
6 weeks Harpagophytum procumbens Chantre et al ⁷⁷ 122 61 16 weeks 45 M:7 Individualized herbal treatment	rocumb 122 rbal tre	oens 61 45 M:77 F atment	Knee, hip	Devil's claw, Harpadol, 2,610 mg (Harpagophytum procumbens)	Diacerein, 100 mg	Oral	VAS pain, Lequesne's functional index	I	
Hamblin et al ⁵¹ 20 67 Kne Hamblin et al ⁵¹ 20 67 Kne I o weeks 6 M:14 F Individualized traditional Chinese medicine Lechner et al ³² 102 59 Hip	20 ditional 102	67 6 M:I4 F I Chinese med 59	Knee licine Hip or knee	Individualized herbal treatment + multivitamins Individualized traditional Chinese	Placebo + multivitamins Nonspecific	Oral Oral, as	WOMAC WOMAC, SF-36	Not reported	Adverse events not reported
20 weeks Olive oil Bohlooli et al ²⁹ 4 weeks Passion fruit peel	71	29 M:63 F 40–80 0 M:71 F	Knee	medicine prescription Virgin olive oil	herbal treatment 0.5% piroxicam (amount not stated)	tea Topical	WOMAC	I	
Farid et a ¹³⁹ 33 90 days Phellodendron amurense	33 urense	53 8 M:25 F	Knee	Passion fruit peel extract (Passiflora edulis), 150 mg	Placebo	Oral	WOMAC	1	
Oben et al ⁴⁴ 8 weeks	8	I	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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				Case-crossover trial	Case-crossover trial			Open label	Dose-finding study		Case-crossover trial; some patients with RA and AS (Continued)
Fishy belching, increased pain, infection, falls, muscle pains		1	1	I	Micturition, waterbrash, diarrhea, cancer	1	I	Feverish sensation in limbs, stomach burning	1 1	Localized skin rash	Localized skin rash
WOMAC	VAS, WOMAC	WOMAC	WOMAC, Pain VAS	WOMAC	Likert pain	Likert pain score for symptom improvement (0–4)	WOMAC, SF-36	Arthralgia and joint dysfunction indexes	Pain VAS, Lequesne's functional index VAS pain, Lequesne index	VAS pain, WOMAC	VAS pain
Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Topical	Topical
Placebo	Placebo	Placebo	Glucosamine sulfate, 1,500 mg	Placebo	Placebo	Placebo	Placebo or celecoxib, 200 mg daily	Sulindac, 0.4 g	Diclofenac, 100 mg Placebo	Placebo (Urtica galeopsifolia)	Placebo
Phytalgic (fish oils, <i>Urtica dioica</i> , zinc, vitamin E)	Pycnogenol (French maritime bine Pinus maritima), 150 mg	Pycnogenol (French maritime pine, <i>Pinus maritima</i>), 150 mg	Reparagen (Uncaria guianensis, 300 mg; Lepidium meyenii, 1,500 mg), 1,800 mg	Rosehip (Rosa canina), 5 g	Hyben Vita (Rosa canina fruits), 5 g	Standardized rosehip powder (Roso canina), 5 mg	UP446 (extracts of Scutellaria baicalensis and Acacia catechu), 250 mg or 500 mg	Shu Feng Huo Luo Pian, I.2 g	SK1306X (600 mg): Clematis Radix; Trichosanthes root; Prunella spike SK1306X (600 mg, 1,200 mg, 1,800 mg): Clematis mandshurica; Trichosanthes kirilowii; Prunella vulgaris	Stinging nettle (Urtica dioica)	Stinging nettle (Urtica dioica)
Knee or hip	Knee	Knee	Knee	Knee or hip	Various	Knee or hip	Knee or hip	Not stated	Knee Knee	Knee	Base of thumb
57 26 M:55 F	54 32 M:68 F	48 3 M:35 F	53 24 M:71 F	65 40 M:54 F	67 41 M:71 F	65 35 M:65 F	57.6 22 M:38 F	63 13 M:37 F	63 18 M:231 F 59 9 M:84 F	66 24 M:18 F	60 4 M:23 F
Ξ	001	37	95	94	112	100 alensis	60 Luo Pian	50	249 72 (1 Irrico di	42	27
Phytalgic Jacquet et al ⁴⁶ 4 weeks	Cisár et al ⁵² I5 weeks	Farid et al ²² 90 days Reparagen	Mehta et al ⁵⁶ 8 weeks Rosehip	Winther et al ⁶¹ 3 months	Rein et al ⁶⁴ 3 months	Warholm et a ^{lss} 4 months Scutellaria baicalensis	Sampalis and 60 Brownell ²⁸ 12 weeks Shu Feng Huo Luo Pian	Wu and Zhou ⁷⁰ 4 weeks SKI306X	Jung et al ⁶⁵ 249 63 4 weeks 181 Jung et al ⁷⁴ 72 59 4 weeks 9 M	Randall et al ⁵⁰ I6 weeks	Randall et al ⁷⁶ I week

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Table I (Continued)	(p								
Study, duration	c	Mean age (years) Sex (M:F)	OA site	Formulation (daily dose)	Comparator	Route	Pain and function outcomes	Adverse events [#]	Comments
Tipi tea (Petiveria alliacea)	alliacea								
Ferraz et al ⁸² I week	20	62 2 M: 20 F	Knee, hip	Tipi tea (Petiveria alliacea), 9 g in 600 mL water	Placebo tea (Imperata exaltata [sane1)	Oral, as tea	Pain subscales (pain at rest, pain on morion, pain at night)	Not reported	Case-crossover trial; AE not reported
Willow bark (Salix daphnoides)	daphnc	vides)					(a. 0		
Biegert et al ⁶³ 42 days	127 62 53	62 53 M:74 F	Knee or hip	Willow bark (Salix daphnoides), 240 mg	Diclofenac 100 mg or placebo	Oral	WOMAC	1	
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	I	
Notes: "Duhuo Jisheng Wan (DJW): 7.75% each of Radix Angelicæ Pubescentis (Duhuo), Rad (Sangjisheng), Radix Rehmanniae Preparata (Shudihuang), Rhizoma Chuanxiong (Chuanxiong), C (Gancao) and Poria (Fuling), as well as 2.5% of Herba Asari (Xixin). FNZG, hypaconitine and en Panicudati, Olibanum, myrrah, camphora, Borneolum Syntheticum). SJG, 17 different herbs, inc Cortex Acanthopanacis, Rhizoma Curcuma Longoe, Flos Canthami, Folium Artemisiae, argvi, Rhizom more frequent in participants receiving plant-based therapy. Adverse events of active comp Boesenbergia pondurato, Tinospora cordifolia, Terminalia chebula, Cladogynos orientalis, Ferula as univitatum, and Cryptolepis buchanani. Individual amounts not stated. ³⁰ 'Boswellia serrata: also st Phytalgic (Jacquet). ⁴⁸ Abbreviations: n. unber of study participants; M. male; F, female; OA, osteoarthritis; AE, NRS, numeric rating scale; ASU, avocado/soybean unsaponifiables; Gl, gastrointestinal; SD, Gubitong Recipe: BMI, body mass index; RA, rheumatoid arthritis; AS, ankylosing spondylitis	Wan (D manniae I ling), as w yrrah, car thizoma C thizoma C thorants re ipants re ipants re ipants of st buchan ale; ASU, body mas	JW): 7.75% each Preparata (Shudihu eell as 2.5% of Her mphora, Borneolun urcuma Longae, Fl ceiving plant-base t cordifolia, Termit omi. Individual am omi. Individual am udy participants; avocado/soybeat s index; RA, rheu	of Radix Angelecae P uang), Rhizoma Chuc ba Asari (Xixin). FN. n Syntheticum). SJG, los Carthami, Folium J ed therapy. Adverse adia chebula, Cladog iounts not stated; ³⁰¹ nounts not stated; ³⁰¹ no unsaponifiables; G imatoid arthritis; AS	Notes: Duhuo Jisheng Wan (DJW): 7.75% each of Radix Angelicae Pubescentis (Duhuo), Radix Gentiance Moranomi (Rougu) and Radix Ledebourielloe (Fangleng), 5% each of Radix Parentiae (Nuxi), Radix Angelicae Shrensis (Dangshen), Radix Gyorrhizze (Gancao) and Ponia (Fulnionar), Radix Angenicae Albo (Baishao), Radix Cadonopsis (Dangshen), Radix Kehmannice Preparata (Shudhuang), Rhizama Churanoing), Cartex Cimamomi (Rougu) and Kadix Ledebourielloe (Fangleng), 5% each of Radix Parentiae Altor (Xinoni), Fulti Chunanoin, Radix Angelicae Albo (Baishao), Radix Cadonopsis (Danamomi, Radix Angelicae Alboria), Radix Angelicae Albora (Kinoni) Syntheticam), Sila, Pitatinae Tunanoin, Radix Angelicae Albora (Rhizama Churanoin, Radix Angelicae Albora san, Rhizama Churanoing Radix Angelicae Albora (Rhizama Churanoin), Radix Angelicae Albora (Rhizama Churano Lingue), Farina Dana Syntheticum, Nadix Angelicae Nuescents, Garta Kadix Conting Rhizama Churano Lingue), Farnina Landon (Rhizama Aircandus, Rhai Angelicae Angelicae Albora (Rhizama Churanoin), Radix Angelicae Albora (Rhizama Rhizama Educitae), Radix Angelicae Albora (Rhizama Rhizama Educitar), Rhizama Educitae, Rhizama Rhizama Educitae, Rhizama Educitae, Rhizama Educitae, Radix Angelicae Albora (Rhizama Rhizama Educi	llee (Qinjiao), Cortex Eucomi qui) and Radix Ledebouriellae smatis, Radix Aconiti, Flos Cany matis, Radix Aconiti, Radix Ai Pinellice, Semen Sinapis, Sem Adverse events are nor lisi arni (E-OA-07); ³⁴ ¥Ginger (Z arni (E-OA-07); ³⁴ ¥Ginger (Z arni (FOA-07); ³⁴ ¥Ginger (Z arni (FOA-07); ³⁴ Yong (Cortis VA; arni (FOA-07); ³⁴ Yong (Cortis VA; DOS, Knee injury and Oste	miae (Duzhon (Fangfeng), 5' ophylli), Corte ngelicae Dahu en Vaccariae, tead if similar candens, Ana tead if similar fingiber officin S, visual analc soarthritis O.	(g), Radix Achyranthis Bident % each of Radix Paeoniae Alb x Cinnamomi, Radix Angelica ricae, Cortex Cinnamomi, ca Radix Aconiti Kusnezoffi, and Batterns were observed in mirta cocculus, Drypetes roxi ale): also see EazMov Plus, de): also see EazMov Plus, ale): also see EazMov Plus, ale): also see EazMov Plus, alcome Score; FNZG, Fufa utcome Score; FNZG, Fufa	attee (Niuxt), Radix Angelica a (Baishao), Radix Codonoj e Dahuricae, Herba Asari, Ri mphora, Borneolum Synthe Herba Menthae. "Adverse therba Menthae." Adverse both groups. Ayuuved Sir urghii, Ginapas. Ayuuved Sir urghii, Ginapas. "Adverse urghii, Ginapas." Adverse Decod. 27, ³⁴ and RA-11, 0 e E-OA-07, ³⁴ and RA-11, 0 ng Nanxing Zhitong Gao: ng Nanxing Zhitong Gao:	uo), Radix Gentianae Macrophyllae (Qinjiao), Cortex Eucommiae (Durhong), Radix Achyranthis Bidentatae (Niuxi), Radix Angelicae Sinensis (Dangshen), Radix Gyorrhizae iciong), Cartex Cinnamomi (Rougui) and Radix Ledebouriellae (Fangfeng), S% each of Radix Paceonice Alba (Baishao), Radix Codonopsis (Dangshen), Radix Gyorrhizae re and eugenol (Rhizoma Arisaematis, Radix Aconiti, Flas Caryophylli), Cortex Cinnamomi, Radix Angelicae Dahuricae, Herba Asari, Rhizoma Chuanxiong, Radix Cynanchi erbs, including Rhizoma Arisaematis, Radix Aconiti, Radix Angelicae Dahuricae, Ierba Asari, Rhizoma Chuanxiong, Radix Cynanchi erbs, including Rhizoma Arisaematis, Radix Angelicae Dahuricae, Cortex Cinnamomi, camphora, Borneolum Syntheticum, Radix Angelicae Pubescentis, Rhizoma Atracylodis, Rhizoma Pinelitae, Semen Sinapis, Semen Vaccariae, Radix Aconiti Kusnezoffi, and Herba Menthae. "Adverse events that are events are not listed if similar patterns were observed in both groups. Ayurved Siriaj Wattana recipe: Piper nigrum, evila cosforeida, Saussurea lappa, Cyperus roundus, Derris scandens, Anomirta cocculus, Drypetes rowburghii, Cimamomum siamense, Aegle marmelos, Conioselluum a: also see Kulkarni ⁸¹ and Kulkarni (E-OA-O7); ³⁴ «Ginger (Zingiber officinde): also see EazMov Plus, ⁶⁶ E-OA-O7) ³⁴ and RA-11, Chopra: ⁶⁶ Singing nettle, see also ritis, S.D., standard deviation; KOOS, Knee injury and Osteoarthritis Outcome Score; FNZG, Fufang Nanxing Zhitong Gao; SJG, Shangshi Jietong Gao; GBT, ondpiltis.

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-cross-over 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,

$$\sqrt{(\mathrm{SE}_{\mathrm{Baseline}}^{2} + \mathrm{SE}_{\mathrm{Follow-up}}^{2} - 2 \times r \times \mathrm{SE}_{\mathrm{Baseline}} \times \mathrm{SE}_{\mathrm{Follow-up}})} \quad (1)$$

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	Allocation concealment	Blinding: participants	Blinding: outcome	Incomplete outcome	Selective reporting	Other
		generation			assessment	data		
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 al⁴	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 al49	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	Aguamin F	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Hamblin et al ⁵¹	Individualized herbal	Risk unclear	Low risk	Risk unclear	Risk unclear	Low risk	Low risk	Low risk
	treatment							
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-II	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)
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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, antiinflammatory 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 ($\rho=-0.01$; 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 (TurmacinTM, *Curcuma longa*);²⁴ pine bark extract (Pycnogenol[®]);⁵² SKI306X (extract of *Clematis mandshurica, Trichosanthes kirilowii,* and *Prunella vulgaris*);⁷⁴ E-OA-O7 (LancononeTM, 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 (Rosa 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 which⁷¹ 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

treatment⁵¹ 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 (P=90.1%, P<0.001 [Figure 3]; P=85.9% [Figure 4]) There was no association between the risk of bias and ES for either

Study Yea	ar n		Botanical treatment	Pain medications ceased	Risk of bias score		SMD (95% CI)	% weight
General botanii Madhu 2013 ²⁴ Kulkarni 2011 ³⁴ Cisár 2008 ⁵² Rein 2008 ⁵² Rein 2004 ⁵⁴ Jung 2001 ⁷³ Schmid 2001 ⁷³ Randall 2000 ⁷⁶ Subtotal (<i>f</i> =82.	6 1 5 1 4 7 5	0 42 5 84 2 42 00 105 12 90 8 28 8 14 4 7	NR-INF-02 E-OA-07 AIF Pycnogenol Rosehip SKI306X 600 mg Willow bark Stinging nettle	No Yes No No Yes Yes No	0 5 3 1 0 3 0 2		2.08 (1.45, 2.72) 2.63 (1.20, 4.07) 0.33 (-0.22, 0.87) 1.06 (0.64, 1.48) 0.31 (-0.06, 0.69) 1.35 (0.72, 1.98) 0.47 (0.02, 0.92) 0.36 (-0.17, 0.90) 0.36 (-0.48, 1.40)	3.89 2.60 4.01 4.17 4.22 3.89 4.14 4.02 30.95
Comfrey Laslett 2012 ²⁵ Grübe 2007 ⁵⁸ Subtotal (<i>P</i> =98.	2	33 84 20 21 2=0.000)	4Jointz (comfrey, tannic acid) Comfrey	No Yes	0 5		0.42 (0.07, 0.76) 2.98 (2.60, 3.37) 1.70 (-0.82, 4.22)	4.25 4.21 8.46
Boswellia serra Vishal 2011 ³⁶ Sengupta 2010 ³ Sengupta 2003 ⁵ Chopra 2004 ⁶⁶ Kimmatkar 2003 Kulkarni 1991 ⁸¹ Subtotal (<i>f</i> =85.	5 3 3 3 4 4 9 5 8 3 4 9 5 8 3 4 9 5 8 3 4 9 5 8 3 4 9 5 8 3 8 9 8 8 3 8 9 8 8 8 8 8 8 8 8 8 8 8 8 8	8 84 8 84 7 90 0 224 0 56 4 91	Aflapin 5-Loxin Aflapin 5-Loxin 100 g RA–11 <i>Boswellia serrata</i> Articulin F	Yes Yes Yes Yes Yes Yes	1 0 0 0 1 2 3		1.86 (1.25, 2.48) 1.23 (0.53, 1.93) 2.33 (1.50, 3.17) 2.24 (1.50, 2.97) 0.41 (-0.00, 0.83) 1.00 (0.24, 1.76) 0.53 (0.10, 0.97) 1.33 (0.74, 1.92)	3.92 3.79 3.57 3.73 4.17 3.69 4.15 27.03
Capsaicin Kosuwon 2010 ⁴¹ McLeane 2000 ⁷⁶ Altman 1994 ⁸³ Schnitzer 1994 ⁸⁴ Subtotal (<i>f</i> =0.0	8 1 5	0 35 13 84 9 21	Capsaicin Capsaicin Capsaicin Capsaicin	No No Yes No	4 2 6 6		0.38 (-0.04, 0.79) 0.41 (-0.04, 0.85) 0.47 (0.10, 0.84) 0.80 (0.26, 1.33) 0.48 (0.27, 0.70)	4.17 4.15 4.22 4.03 16.58
Avocado/soybe Lequesne 2002 ⁶ Appelboom 200 Maheu 1998 ⁷⁰ Blotman 1997 ⁸⁰ Subtotal (<i>P</i> =97. Overall (<i>P</i> =93.4	⁹ 1 1 ⁷⁵ 1 1 9%, F	63 365 73 90 62 183 63 91 2=0.000)	es ASU 300 mg ASU 300 mg ASU 300 mg ASU 300 mg	No No Yes No	1 — 4 1 3		-0.09 (-0.40, 0.22) 1.25 (0.92, 1.57) 2.97 (2.52, 3.42) 0.26 (-0.05, 0.56) 1.09 (-0.08, 2.25) 1.08 (0.72, 1.44)	4.29 4.27 4.14 4.28 16.98 100.00
					-0.5	0 0.5 1 1.5 2 2.5 3 3.5 4		

Favors comparator Favors botanical therapy

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, antiinflammatory factor; ASU, avocado/soybean unsaponifiables.

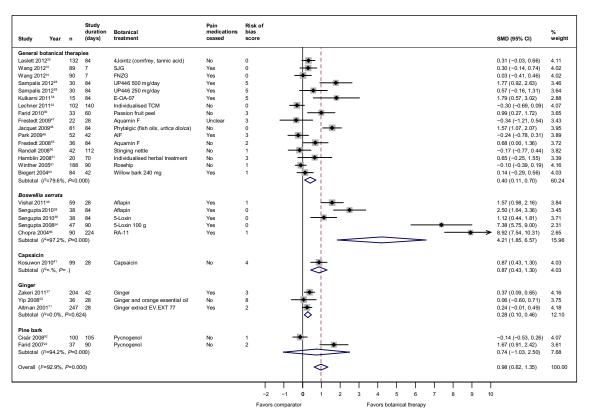


Figure 2 Efficacy of plant-derived therapies compared to placebo on pain WOMAC and KOOS pain scores. Note: Weights are from random effects analysis.

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 mg⁷⁷ (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 days⁶³ 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; $P \le 0.001$). 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 SK1306X (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 patients⁴⁴ (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 treatment⁵¹ 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 e	efficacy findings of plant-l	based therapy compared to	placebo, by therapy class
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Class of plant-based therapy	VAS/NRS	WOMAC/	WOMAC/
	pain score	KOOS pain	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 ($l^2=92.7\%$; P<0.001). Botanical therapies that demonstrate efficacy when compared to an active comparator are olive oil²⁹ and UP446²⁸ (both low and high doses). Du huo ji sheng wan⁶² and willow bark⁶³ 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 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 trial⁷¹ 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

Study	Year	n	Study duration (days)	Botanical treatment	Active comparator	Pain medications ceased	Risk of bias score		SMD (95% CI)	% weight				
Madhu 201324		60	42	NR-INF-02 (curcumin)	Glucosamine sulfate 1,500 mg	No	0		1.01 (0.48, 1.55)	8.46				
Pengkhum 2012 ³⁰		60	84	Ayurved Siriraj Wattana recipe	Diclofenac 75 mg	No	5	++	0.36 (-0.15, 0.87)	8.63				
Zahmatkash 2011	33	92	42	Ginger, mastic, sesame oil	Salicylate 6 g	No	4		0.17 (-0.24, 0.58)	9.22				
Pavelka 201040		361	183	ASU 300 mg	Chondroitin sulfate 1,200 mg	No	1	-	-0.17 (-0.38, 0.03)	10.14				
Tao 200942		90	56	Gubitong recipe 400 mg	Glucosamine sulfate 1,500 mg	No	7		0.21 (-0.20, 0.63)	9.19				
Widrig 200757		198	21	Arnica gel (50 g/100 g gel)	Ibuprofen gel 5%	No	1		0.11 (-0.17, 0.39)	9.86				
Mehta 200756		95	56	Reparagen 1,800 mg	Glucosamine sulfate 1,500 mg	No	1		-0.21 (-0.61, 0.19)	9.25				
Jung 200465		249	28	SKI 306X	Diclofenac 100 mg	Yes	5		-0.08 (-0.33, 0.17)	9.99				
Wu 2002 ⁷⁰		50	28	Shu Feng Huo Luo Pian	Sulindac 0.4 g	Unclear	8		0.09 (-0.48, 0.66)	8.29				
Chantre 200077		122	112	Harpadol 2,610 mg	Diacerein, 100 mg	No	0		2.09 (1.65, 2.54)	9.03				
Usha 2006 ⁶⁰		40	42	Eazmov Plus (Boswellia serrata)	Ibuprofen 1,200 mg	Yes	5		0.05 (-0.57, 0.67)	7.95				
Overall (P=90.1%	, <i>P</i> =0.00	00)						\diamond	0.32 (-0.04, 0.67)	100.00				
								-1 0 1 2	3					
							Favors botanical therapy							

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 plantbased 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 al⁶⁹ 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

Study Ye	ar n	Study duration (days)	Botanical treatment	Active comparator	Pain medications ceased	Risk of bias score		SMD (95% CI)	% weight
Niempoog 2012 ²⁶	100	42	Plygersic (Plai and ginger gel)	Diclofenac gel 1%	Yes	3	+	0.11 (-0.28, 0.50)	10.52
Sampalis 2012 ²⁸	30	90	UP446 500 mg/day	Celecoxib 200 mg	Yes	5	-	0.55 (-0.18, 1.28)	7.73
Sampalis 2012 ²⁸	30	90	UP446 250 mg/day	Celecoxib 200 mg/day	Yes	5		0.71 (-0.03, 1.45)	7.66
Bohlooli 2012 ²⁹	71	28	Virgin olive oil	Piroxicam 0.5%	Yes	2	+-	0.20 (-0.27, 0.66)	9.92
Kuptniratsaikul 201145	125	28	Derris scandens	Naproxen 500 mg	Yes	4 -	•	-0.25 (-0.60, 0.10)	10.83
Pavelka 201040	361	183	ASU 300 mg	Chondroitin sulfate 1,200 mg	No	1	•	-0.21 (-0.42, -0.00)	11.76
Mehta 200756	95	56	Reparagen 1,800 mg	Glucosamine sulfate 1,500 mg	No	1	•	0.33 (-0.07, 0.74)	10.42
Sontakke 200759	66	183	<i>Boswellia serrata</i> 1 g	Valdecoxib 10 mg	Unclear	7	+	0.03 (-0.45, 0.52)	9.78
Teekachunhatean 2004	² 200	28	Duhuo Jisheng Wan 3 g	Diclofenac 75 mg	Yes	3 🛨		-1.11 (-1.41, -0.81)	11.22
Biegert 200463	86	42	Willow bark 240 mg	Diclofenac 100 mg	Yes	1 -	-	-0.73 (-1.17, -0.29)	10.16
Overall (I ² =85.9%, P=0.	000)						\diamond	-0.08 (-0.42, 0.25)	100.00
						-2	0 1 2	2	

Favors botanical therapy

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.

,	n	Botanical treatment		RR (95% CI)	Events, treatment	Events, control	weight (M-H)
Sampalis 2012 ²⁸ Sampalis 2012 ²⁸	60 30 30	NR-INF-02 100 mg UP446 250 mg UP446 500 mg		1.00 (0.15, 6.64) 1.17 (0.51, 2.66) 1.00 (0.42, 2.40)	2/30 7/15 6/15	2/30 6/15 6/15	0.50 1.49 1.49
Vang 2012 ³¹ Vang 2012 ³¹	90 89	FNZG SJG		4.57 (0.25, 82.26) 4.65 (0.26, 83.62)	4/60 4/59	0/30 0/30	0.16 0.16
Kulkarni 2011 ³⁴	16	E-OA-07		0.33 (0.04, 2.56)	1/8	3/8	0.74
echner 201132	102	Individualised TCM		1.15 (0.74, 1.81)	24/52	20/50	5.05
acquet 2009 ⁴⁸ Oben 2009 ⁴⁴	81 40	Phytalgic (fish oils, Urtica dioica) Phellodendron and citrus extracts		0.91 (0.51, 1.63) 1.00 (0.07, 14.90)	14/41 1/20	15/40 1/20	3.76 0.25
Oben 200944	40	Phellodendron and citrus extracts	• • • • • • • • • • • • • • • • •	2.00 (0.20, 20.33)	2/20	1/20	0.25
	57 90	AIF Gubitong regine		1.03 (0.50, 2.09) 0.67 (0.12, 3.80)	11/31 2/45	9/26 3/45	2.42
ung 200174	47	Gubitong recipe SKI306X 600 mg		1.04 (0.35, 3.13)	5/23	5/24	1.21
Piscoya 2001 ⁷²	45 84	Cat's claw	_	1.38 (0.53, 3.60) 17.00 (1.01, 285.40)	11/30 8/42	4/15 0/42	1.32 0.12
arid 2010 ³⁰	84 33	Articulin_F Passion fruit peel extract		17.00 (1.01, 285.40) (excluded)	8/42 0/17	0/42 0/16	0.12
/I-H subtotal (/2=0.0%, / D+L subtotal	P=0.85	3)	\$	1.20 (0.94, 1.54) 1.10 (0.86, 1.41)	102/508	75/426	19.67
Aquamin F Frestedt 200947	22	Aquemia E	li li	0.72 (0.41 .1.20)	5/8	12/14	2 16
Frestedt 2009 ⁵⁵	48	Aquamin F Aquamin F		0.73 (0.41, 1.30) 0.79 (0.47, 1.33)	5/6 12/25	12/14	3.61
/I-H subtotal (/2=0.0%, / D+L subtotal	P=0.84	2)	8	0.77 (0.52, 1.14) 0.76 (0.52, 1.12)	17/33	26/37	5.77
Avocado–soybean uns .equesne 2002 ⁶⁰	aponi 163	fiables ASU 300 mg		0.92 (0.67, 1.26)	39/85	39/78	10.07
Appelboom 2001 ⁷⁵	173	ASU 300 mg ASU 300 mg		1.26 (0.79, 2.00)	28/85	23/88	5.60
Maheu 1998 ⁷⁹	162	ASU 300 mg	_ _	1.07 (0.64, 1.79)	23/84	20/78	5.14
Blotman 1997 ⁸⁰ //-H subtotal (/ ² =0.0%, /	163 P=0.72	ASU 300 mg		0.93 (0.40, 2.18) 1.04 (0.82, 1.30)	9/80 99/334	10/83 92/327	2.43 23.24
0+L subtotal	-0.72		ک	1.02 (0.81, 1.28)	33/334	321321	25.24
	59	Aflapin		0.97 (0.06, 14.74)	1/30	1/29	0.25
Sengupta 2010 ³⁸ Sengupta 2010 ³⁸	38 38	Aflapin 5-Loxin		1.00 (0.07, 14.85) 0.33 (0.01, 7.70)	1/19 0/19	1/19 1/19	0.25
Chopra 200466	90	RA-11	·	1.05 (0.69, 1.58)	23/45	22/45	5.45
Kimmatkar 2003 ⁶⁸ A-H subtotal (I ² =0.0%, I	30	Boswellia serrata extract (333 mg)	\rightarrow	7.00 (0.39, 124.83) 1.11 (0.74, 1.67)	3/15 28/128	0/15 25/127	0.12 6.44
0+L subtotal		(2)	*	1.06 (0.71, 1.58)	20/120	25/127	0.44
Capsaicin Kosuwon 201041	99	Capsaicin 0.0125%		3.75 (1.78, 7.91)	43/65	6/34	1.95
Altman 1994 ⁸³ M-H subtotal (/ ² =59.3%)	113	Capsaicin 0.025%	! ····	12.77 (3.18, 51.28)	26/57	2/56 8/90	0.50 2.45
M-H subtotal (P=59.3%, D+L subtotal	P=0.1	17)		5.59 (2.92, 10.69) 6.03 (1.81, 20.12)	69/122	8/90	2.45
Comfrey aslett 2012 ²⁵	129	4Jointz	+	1.17 (0.91, 1.50)	48/67	38/62	9.78
Grübe 200758	220	Comfrey	·	0.47 (0.20, 1.10)	7/110	15/110	3.72
M-H subtotal (P=79.5%, D+L subtotal	P=0.0	127)	\rightarrow	0.98 (0.76, 1.26) 0.80 (0.30, 2.11)	55/177	53/172	13.49
Ginger Zakeri 2011 ³⁷	204	Ginger		0.70 (0.23, 2.13)	5/103	7/101	1.75
rip 200853	36	Ginger and orange essential oil	· · · · · · · · · · · · · · · · · · ·	0.30 (0.01, 6.91)	0/19	1/17	0.39
Vigler 200367 Altman 200171	29 247	Ginger extract (Zintona EC) 1,000 mg Ginger extract EV.EXT 77		1.07 (0.07, 15.54) 1.54 (1.19, 1.99)	1/14 76/124	1/15 49/123	0.24 12.19
A-H subtotal (I ² =0.0%, I D+L subtotal		(6)		1.40 (1.19, 1.80) 1.46 (1.14, 1.87)	82/260	58/256	14.57
Pine bark							
Cisár 200852 Farid 200722	100 37	Pycnogenol Pycnogenol	• • •	0.33 (0.04, 3.10) (excluded)	1/50 0/19	3/50 0/18	0.74 0.00
	.)	i yonogeriti		(excluded) 0.33 (0.04, 3.10) 0.33 (0.04, 3.10)	1/69	3/68	0.00
Rosehip			!				
Winther 2005 ⁶¹ Rein 2004 ⁶⁴	188 112	Rosehip (Rosa canina) 5 g Hyben vita (Rosa canina fruits)		1.50 (0.64, 3.50) 2.20 (0.82, 5.92)	12/94 11/56	8/94 5/56	1.98 1.24
Varholm 2003 ⁸⁵	100	Rosehip		1.00 (0.26, 3.78)	4/50	4/50	0.99
/I-H subtotal (/2=0.0%, / D+L subtotal	P=0.63	(8)		1.59 (0.89, 2.82) 1.58 (0.89, 2.83)	27/200	17/200	4.21
Stinging nettle Randall 2008 ⁵⁰	42	Stinging nettle		2.00 (0.20, 20.41)	2/21	1/21	0.25
Randall 200076	54	Stinging nettle		5.00 (0.25, 99.51)	2/27	0/27	0.12
/I-H subtotal (/2=0.0%, / D+L subtotal	P=0.63	12)		3.00 (0.49, 18.23) 2.82 (0.45, 17.68)	4/48	1/48	0.37
Willow bark Biegert 2004 ⁶³	84	Willow bark 240 mg		0.91 (0.57, 1.43)	19/43	20/41	5.07
Schmid 200173	78	Willow bark	—	1.00 (0.59, 1.70)	16/39	16/39	3.96
M-H subtotal (/2=0.0%, / D+L subtotal	P=0.78	13)	*	0.95 (0.67, 1.34) 0.94 (0.67, 1.34)	35/82	36/80	9.03
M-H overall (P=28.0%, I	P=0.05	i0)		1.23 (1.11, 1.37)	519/1,961	394/1,831	100.00
0+L overall			P	1.13 (0.98, 1.30)			

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, antiinflammatory 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

Madhu 2013 ²⁴ 60 NR-INF-02 100 mg Glucosamine sulfate 1,500 mg 0.40 (0.08, 1.90) 2/30 Bohlooli 2012 ²⁸ 71 Virgin olive oil Piroxicam 0.5% 0.34 (0.01, 8, 14) 0/35 Drozdov 2012 ²⁷ 43 Ginger Diciofenac 100 mg 0.21 (0.03, 1.65) 1/21 Niempoog 2012 ²⁸ 100 Plygersic Diciofenac (1%) 0.67 (0.12, 3.71) 2/30 Sampalis 2012 ²⁸ 30 UP446 250 mg Celecoxib 200 mg 0.67 (0.12, 3.71) 2/30 Sampalis 2012 ²⁸ 30 UP446 500 mg Celecoxib 200 mg 0.86 (0.38, 1.95) 6/15 Suppalis 2012 ²⁸ 30 UP446 500 mg Celecoxib 200 mg 0.75 (0.49, 1.15) 22/63 Kuptniratsalkul 2019 ¹¹⁵ 125 Derris scandens Naproxen 500 mg 0.75 (0.44, 1.25) 16/45 Levy 2009 ⁴¹ 100 Castor oil 2.7 mL Diciofenac sodium 150 mg 0.91 (0.61, 1.35) 24/52 Methi 2007 ⁴⁶ 95 Reparagen 1,800 mg Glucosamine sulfate 1,500 mg 0.33 (0.07, 1.53) 2/33 Vidrig 2007 ³⁷		% weight
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Kuphiratsaikul 2011 ³⁵ 125 Derris scandens Naproxen 500 mg 0.75 (0.49, 1.15) 22/63 Pavelka 2010 ¹⁶⁰ 361 ASU 300 mg Chondroitin sulfate 1,200 mg 0.67 (0.50, 0.89) 50/183 Kuptniratsaikul 2009 ¹⁶⁴ 100 Curcumin 2 g Ibuprofen 800 mg 0.75 (0.49, 1.15) 22/63 Medhi 2009 ¹⁶⁴ 100 Curcumin 2 g Ibuprofen 800 mg 0.75 (0.46, 1.25) 16/48 Levy 2009 ⁴⁶ 103 Flavocoxid 1,000 mg Naproxen 1,000 mg 0.91 (0.61, 1.35) 22/52 Medhi 2007 ¹⁶⁵ 95 Reparagen 1,800 mg Glucosamine sulfate 1,500 mg 0.73 (0.17, 3.11) 3/48 Sontakke 2007 ¹⁶⁶ 66 Boswellia serrata 1 g Valdecoxib 10 mg 0.33 (0.07, 1.53) 2/33 Widrig 2007 ¹⁵⁷ 204 Amica gel (50 g/100 g gel) Ibuprofen gel 5% 1.65 (0.72, 3.76) 14/105 Biegert 2004 ⁴⁶ 266 Villow bark 240 mg Diclofenac 100 mg 0.63 (0.43, 0.33) 19/43 Jung 2004 ⁴⁷⁶ 200 Duhuo Jisheng Wan Diclofenac 75 mg 1.00 (0.64, 1.56) 28/100 Vu 2002 ¹⁷⁰ 50 TCM Sulindac 0.4 g	7/15	2.06
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Zahmatkash 2011 ³³ 92 Ginger, mastic, sesame oil Salicylate 6 g (excluded) 0/46	1/20	0.35
	26/60	7.77
Overall (F=3.3%, P=0.417) 0.75 (0.65, 0.85) 255/1.1	0/46	0.00
	337/1,163	100.00

Favors botanical Favors comparator

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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