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Ayurvedic interventions for osteoarthritis: a systematic review and meta-analysis

Christian S. Kessler · Lea Pinders · Andreas Michalsen · Holger Cramer

Abstract Ayurveda is one of the fastest growing systems within complementary and alternative medicine. However, the evidence for its effectiveness is unsatisfactory. The aim of this work was to review and meta-analyze the effectiveness and safety of different Ayurvedic interventions in patients with osteoarthritis (OA). 138 electronic databases were searched through August 2013. Randomized controlled trials, randomized cross-over studies, cluster-randomized trials, and non-randomized controlled clinical trials were eligible. Adults with pre-diagnosed OA were included as participants. Interventions were included as Ayurvedic if they were explicitly labeled as such. Main outcome measures were pain, physical function, and global improvement. Risk of bias was assessed using the Cochrane risk of bias tool. 19 randomized and 14 non-randomized controlled trials on 12 different drugs and 3 non-pharmaceutical interventions with a total of 2,952 patients were included. For the compound preparation,Rumalaya, large and apparently unbiased effects beyond placebo were found for pain (standardized mean difference [SMD] −3.73; 95 % confidence interval [CI] −4.97, −2.50; $P < 0.01$) and global improvement (risk ratio 12.20; 95 % CI 5.83, 25.54; $P < 0.01$). There is also some evidence that effects of the herbal compound preparation Shunti-Guduchi are comparable to those of glucosamine for pain (SMD 0.08; 95 % CI −0.20, 0.36; $P = 0.56$) and function (SMD 0.15; 95 % CI −0.12, 0.36; $P = 0.41$). Based on single trials, positive effects were found for the compound preparations RA-11, Reosto, and Siriraj Wattana. For *Boswellia serrata*, *Lepidium Sativum*, a *Boswellia serrata* containing multicomponent formulation and the compounds Nirgundi Taila,Panchatikta Ghrita Guggulu, and Rhumayog, and for non-pharmacological interventions like Ayurvedic massage, steam therapy, and enema, no evidence for significant effects against potential methodological bias was found. No severe adverse events were observed in all trials. The drugs Rumalaya and Shunti-Guduchi seem to be safe and effective drugs for treatment of OA-patients, based on these data. However, several limitations relate to clinical research on Ayurveda. Well-planned, well-conducted and well-published trials are warranted to improve the evidence for Ayurvedic interventions.

Keywords Ayurveda · Complementary medicine · Osteoarthritis · Systematic review · Meta-analysis

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Abbreviations

ACR	American College of Rheumatology
CAM	Complementary and alternative medicine
CCT	Controlled clinical trial
CI	Confidence interval
DHARA	Digital helpline for Ayurveda research articles
OA	Osteoarthritis
NSAID	Non-steroidal anti-inflammatory drug
RCT	Randomized controlled trial
RR	Risk ratio

SMD	Standardized mean difference
TCM	Traditional Chinese medicine
TIM	Traditional Indian medicine
TM	Traditional medicine
WHO	World Health Organization
WMS	Whole medical system
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Introduction

Among chronic diseases, osteoarthritis (OA) has an increasing significance and is responsible for a major part of disease burden, work disability and healthcare costs worldwide [1]. The guidelines for treatment of, e.g., OA of the knee from the American College of Rheumatology, the National Institute for Health and Clinical Excellence and the European League Against Rheumatism recommend non-pharmacologic modalities for the management of knee and hip OA, including aerobic, aquatic, and/or resistance exercises as well as weight loss for overweight patients; insoles, taping, manual therapy, walking aids, thermal agents, Tai Chi, self-management programs, and psychosocial interventions. Pharmacologic modalities (conditionally) recommended for the initial management of patients with OA include acetaminophen, oral/topical NSAIDs, tramadol, and intra-articular corticosteroid injections. Intra-articular hyaluronate injections, duloxetine, andopioids are conditionally recommended in patients who had an inadequate response to initial therapy [1–5]. However, pharmacologic modalities, in particular NSAIDs, are associated with a number of side effects like upper gastrointestinal bleeding renal failure [6] and myocardial infarction and stroke, especially in the COX-2 inhibitor category [7, 8].

Due to this and frequent unsatisfying results of conventional medicine treatment, a substantial proportion of patients suffering from OA seek complementary therapies (CAM) such as mind–body medicine, nutritional therapy and supplements, herbal therapies, acupuncture, massage, and traditional or whole medical systems (TM) like Traditional Chinese Medicine (TCM) or the Traditional Indian Medicine (TIM) Ayurveda [9–13].

The Whole medical system (WMS) Ayurveda has been experiencing a resurgence in popularity in its native countries (e.g., India and Sri Lanka) and abroad (e.g., Europe and North America) and has become more accessible and more in demand over the last years [13–16]. In India, Ayurveda is officially recognized by the state and is used as a broad system of medicine. It is recognized by the World Health Organization (WHO) as a medical science [15–19].

Ayurvedic clinical research is slowly finding its way into mainstream medical journals, and the past decade has seen the first of larger clinical trials that point toward future directions [20–23]. In 2011, the launch of the first digital research databases for Ayurveda could be observed [24, 25].

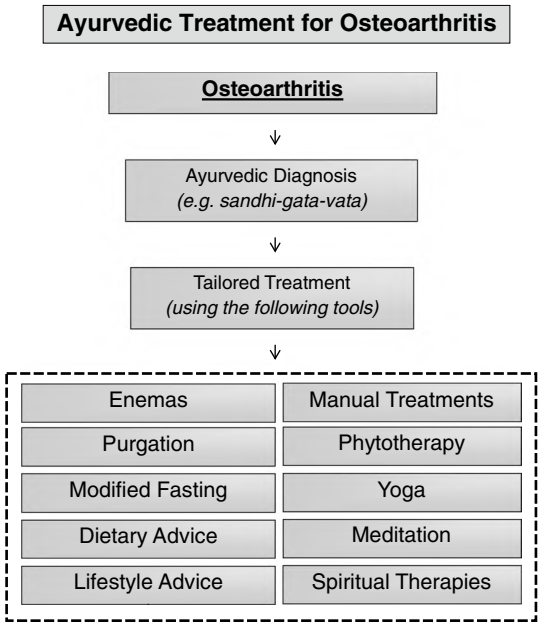


Fig. 1 Ayurvedic treatment for osteoarthritis

Nevertheless, the evaluation of Ayurveda with evidence-based medicine tools is still in its infancy in spite of a limited number of well-designed Ayurveda trials; in particular, a paucity of Ayurveda trials on disease entities with high incidence and prevalence on a global scale (like OA) is evident, and data from reviews and meta-analyses are scarce [26–33].

Ayurveda claims to be effective in treating chronic diseases of the musculoskeletal system, such as OA [34, 35]. Here, main treatment methods are nutritional therapy, mind–body medicine, cleansing processes, manual and physical therapies, and yoga and herbal therapies in individually tailored regimes (Fig. 1) [23, 36].

The aim of this review was to systematically assess and meta-analyze the effectiveness and safety of Ayurvedic interventions in patients with OA, a chronic condition of global relevance.

Methods

Eligibility criteria

Types of studies

Randomized controlled trials (RCTs), randomized crossover studies, cluster-randomized trials, and non-randomized

controlled clinical trials (CCTs) were eligible. No language restrictions were applied.

Types of participants

Studies on adults (at least 18 years) with OA diagnosed according to the classification criteria of the American College of Rheumatology [37, 38] or according to any other criteria were eligible.

Types of interventions

Experimental Interventions were included if they were explicitly labeled as Ayurvedic or TIM interventions in the respective publications. For example, massage therapy and leech therapy are commonly part of a multimodal Ayurvedic treatment approach for OA. However, trials on these therapies were only included into the search and analysis of this work if explicitly and clearly described as Ayurvedic or TIM treatment modalities (e.g., leeches and massage therapies are also part of other TM and CAM systems and are commonly used within different sets of paradigms and indications in comparison with Ayurveda).

While yoga postures and meditation are traditionally used as parts of complex Ayurvedic treatment regimes, yoga is not commonly used as a single intervention for osteoarthritis in Ayurveda [23]. Moreover, today's yoga therapy is mostly not applied in accordance with Ayurvedic principles [39]. Therefore, studies investigating yoga as a single intervention for osteoarthritis were excluded from this review (and were included into a review of yoga for rheumatic diseases) [40].

Control Studies comparing Ayurvedic interventions to usual care or any active control intervention were eligible. Studies comparing different Ayurvedic interventions were also eligible.

Separate meta-analyses were conducted for different experimental and control conditions.

Types of outcome measures

For inclusion, studies had to assess at least 1 important patient-centered outcome according to OMERACT III [38, 41–43], namely improvement in pain, physical function, or global improvement. According to OMERACT III [41, 42], secondary outcomes included generic health-related quality of life, stiffness, imaging, and safety of the intervention.

Search methods

The literature search comprised 138 electronic databases that were searched from their inception through August 30, 2013. The search comprised MEDLINE, PubMed, the Cochrane library, MEDPILOT, CAMbase, CAM-Quest, PsycINFO, clinicaltrials.gov, the Annotated Bibliography of Indian Medicine, DHARA, and 128 further databases [44].

The following search terms for Ayurveda were used: "ayurved*" and "traditional Indian medicine," were combined with conventional and Ayurvedic search terms for OA: "osteoarthritis," "osteoarthrosis," "arthritis," "arthrosis," "sandhi gata vata," and "sandhi vata" (the Sanskrit term "sandhi-gata-vata" is most commonly used for OA by Ayurvedic physicians [45–47]). No limits were used. The search strategy was adapted for each database as necessary. Reference lists of identified original articles or reviews and an analog bibliography of Ayurveda-related dissertations were searched manually. Only trials on humans were included.

Abstracts identified during the literature search were screened by 2 review authors independently. Potentially eligible articles were read in full by 2 review authors to determine whether they met the eligibility criteria. Disagreements were discussed with a third review author until consensus was reached. If necessary, additional information was obtained from the study authors.

Data extraction and management

Two authors independently extracted data on study design, participants, interventions, control, outcomes, and results using an a priori developed data extraction form. Discrepancies were discussed with a third review author until consensus was reached. If necessary, the study authors were contacted for additional information.

Risk of bias in individual studies

Two authors independently assessed risk of bias using the Cochrane risk of bias tool [48, 49] on the following domains: selection bias (random sequence generation, allocation concealment), performance bias (double-blinding), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias, and the risk of bias was rated as (1) low risk of bias, (2) unclear, (3) high risk of bias. Discrepancies were rechecked with a third reviewer and consensus achieved by discussion.

Data analysis

Assessment of overall effect size

If at least 2 studies of a specific comparison and outcome were available, meta-analyses were conducted using

Review Manager 5 software (version 5.1 [50]) using a random effects model.

For continuous outcomes, standardized mean differences (SMD) with 95 % confidence intervals (CI) were calculated as the difference in means between groups divided by the pooled standard deviation. Where no standard deviations were available, they were calculated from standard errors, confidence intervals, or *t* values [48], or attempts were made to obtain the missing data from the trial authors by email.

To evaluate the magnitude of the overall effect size, Cohen's categories were used with (1) SMD = 0.2–0.5: small; (2) SMD = 0.5–0.8: medium and (3) SMD > 0.8: large effect sizes.

For dichotomous outcomes, risk ratios (RR) with 95 % CI were calculated by dividing the risk of event in the experimental group (i.e., the number of participants with the respective outcome divided by the total number of participants) by the risk of event in the control group [48].

Assessment of heterogeneity

In order to analyze statistical heterogeneity between studies, the I^2 statistics was calculated; and categorized as (1) I^2 = 0–24 %: low heterogeneity; (2) I^2 = 25–49 %: moderate heterogeneity; (3) I^2 = 50–74 %: substantial heterogeneity; and (4) I^2 = 75–100 %: considerable heterogeneity [48, 49]. Further, the Chi-square test was used to assess whether differences in results are compatible with chance alone; a P value ≤ 0.10 was regarded to indicate significant heterogeneity [48].

Subgroup and sensitivity analyses

Subgroup analyses were conducted for

1. Diagnosis (patients with OA diagnosed according to the Classification Criteria of the American College of Rheumatology versus patients with OA diagnosed according to any other criteria).
2. Affected joints (OA of the knee versus OA of any other joint).

To test the robustness of significant results, sensitivity analyses were conducted for studies with high versus low risk of selection bias and for studies with high versus low risk of performance bias.

If statistical heterogeneity was present in the respective meta-analysis, subgroup and sensitivity analyses were also used to explore possible reasons for heterogeneity.

Risk of bias across studies

If at least 10 studies were included in a meta-analysis, assessment of risk of publication was originally planned by visual analysis of funnel plots [48, 51]. As <10 studies were included in each meta-analysis, analysis of risk of publication bias was not possible.

Results

Literature search

Overall, 19 RCTs and 14 CCTs on 12 different Ayurvedic formulas and 3 non-pharmaceutical interventions (svedana; snehana; basti) with a total of 2,952 patients with OA were included. Characteristics of these studies and risk of bias are shown in Tables 1 and 2. Authors of 4 trials were contacted by email for missing data; however, none of them replied [52–55].

Details are also shown in the PRISMA flowchart in Fig. 2.

Boswellia serrata

Four RCTs and 1 CCT on *Boswellia serrata* were included. Three RCTs compared *Boswellia serrata* to placebo in patients with OA of the knee [56–58]. Two RCTs used ACR criteria [57, 58]. All 3 RCTs had low risk of selection bias, while only 2 RCTs had low risk of performance bias [57, 58]. All 3 RCTs reported significant group differences favoring *Boswellia serrata* for pain and function; and 2 RCTs found group differences for stiffness [57, 58]. Meta-analyses also revealed significant large effects of the intervention on pain (SMD = −3.20; 95 % CI −5.21; −1.18; $P < 0.01$; Fig. 3) and function (SMD = −2.85; 95 % CI −4.72; −0.98, $P < 0.01$; Fig. 3). Both effects were no longer significant when only trials were included that used ACR diagnostic criteria [57, 58]. The same was true when only trials with adequate blinding were included [57, 58]. No effects were found in meta-analysis for stiffness (SMD = −2.06; 95 % CI −4.38; 0.26; $P = 0.08$; Fig. 3).

One RCT and 1 CCT compared *Boswellia serrata* to other medication [59–61]. In 1 unblinded RCT on OA, knee effects favoring *Boswellia serrata* over a COX-2 inhibitor (valdecoxib) were found for pain and physical function but not for imaging data after 7 months of treatment [61]. The CCT compared the effects of *Boswellia serrata* on global improvement to Ibuprofen in mixed OA but did not report group differences [60].

Table 1 Characteristics of the included studies

Reference Origin	Design	Disease	Patients (total, groups)	Inclusion criteria	Experimental intervention	Control intervention	Duration	Outcome measures	Adverse effects (AE)	Dropouts
Boswellia serrata										
Gupta (1993) India	CCT	OA (knee, ankles and hip)	50 (30 + 20)	50–72 year, chronic osteoarthritis (2–5 year)	Compound—*Boswellia serrata* (2 × 600 mg)	Ibuprofen 3 × 400 mg	12–14 Weeks	Pain, walking, joint movement	8 % Had dyspeptic symptoms in the Boswellia group, 60 % in Ibuprofen group	Not reported
Kimmatkar (2003) India	RCT	OA (knee)	30 (crossover)	> 40 Year, NSAID and physiotherapy, walking distance, joint swelling, difficulty in kneeling down, VAS (0–3)	*Boswellia serrata* extract	Placebo	8 Weeks	Decrease in pain and swelling, improvement of the function	No major AE	Not reported
Sengupta (2008) India	RCT	OA (knee)	75 (25 + 25 + 25)	40–80 Year, diagnosis of OA (classification criteria of the ACR), VAS 40–70 (during most painful knee movement), Lequesne's Functional Index (LFI) < 7 points after 7 days, withdrawal of medication, ability to walk	5-Loxin (*Boswellia serrata* extract) 100 mg or 5-Loxin (*Boswellia serrata* extract) 250 mg	Placebo	90 Days	Pain and physical function (WOMAC index and VAS), hematologic and biochemical evaluations, assessment of synovial fluids (MMP-3)	Minor AE in all 3 groups: placebo = 30, low-dose = 18, high-dose = 27	5 Dropouts (viral infection during course of study)
Sengupta (2010) India	RCT	OA (knee)	60 (20 + 20 + 20)	40–80 Year, OA (unilateral or bilateral) > 3 months (classification criteria of the ACR), VAS 40–70 (during most painful knee movement), Lequesne's Functional Index (LFI) < 7 points after 7 days withdrawal of medication, ability to walk	5-Loxin (*Boswellia serrata* extract) 100 mg or Aflapin 100 mg	Placebo	90 Days	Pain and physical function (WOMAC index and VAS), hematologic and biochemical evaluations, in vitro studies with Aflapin (expression of ICAM-1 and MMP3)	No major AE, acidity in 2 patients (Aflapin, placebo)	3 Dropouts (one from each group) because of unavailability

Table 1 continued

Reference Origin	Design	Disease	Patients (total, groups)	Inclusion criteria	Experimental intervention	Control intervention	Duration	Outcome measures	Adverse effects (AE)	Dropouts
Sontakke (2006) India	RCT	OA (knee)	66 (33 + 33)	40–70 Year, classification criteria of the ACR, clinical findings and X-ray	*Boswellia serrata* extract	Valdecoxib (COX-2-Inhibitor)	6 Months	WOMAC Score (primary outcome) and radiographs	Gastrointestinal, no major AE	1 Dropout
Boswellia serrata, *Withania somnifera*, *Curcuma longa*, *zinc complex*										
Kulkarni (1991) India	RCT	OA	42 (crossover)	Pain, morning stiffness, stiffness and/or swelling joint, disability and/or loss of function, radiological changes	Formulation (*Boswellia serrata*, *Withania somnifera*, *Curcuma longa*, zinc complex)	Placebo	2 × 3 Months	Severity of pain (score), morning stiffness, Ritchie articular index, joint score (American Rheumatism Association), disability score and grip strength (Madhok and Capell)	Nothing serious	None
Lepidium sativum										
Raval (2009) India	CCT	OA	98 (40 + 58)	Pain in joints, inflammation over the joint, stiffness, radiographic changes	Chandrashura (*Lepidium sativum*) 6 mg (2 × 3 mg/d)	Placebo (starch capsules)	30 Days	Joint pain, swelling, stiffness, tenderness, crepitus, difficulty in movement	Not reported	Not reported
Nirgundi Taila										
Das (2002) India	CCT	OA	32 (12 + 12 + 8)	> 40 J, swelling of the joints, stiffness of the joints, loss of function of the joint(s), crepitus and small effusion	I: Nirgundi Taila massage 20 ml daily, II: Nirgundi Taila massage 20 ml + 5 ml intake daily	Diclofenac Sodium 50 mg 3×/d	28 Days	Joint flexion, stiffness, crepitation, tenderness, walking time	Coated tongue, tastelessness loss of appetite	None
Panchatikta Ghrita Guggulu										
Akhtar (2010) India	CCT	OA (knee (94 %), hip, ankle, shoulder)	49 (31 + 18)	30–70, classical signs and symptoms of Sandhigatavata	Guggulu Vati (2 × 2) + (Abhyanga with Bala Taila + Nadi Swedana with Dashamula Kwatha + Panchatikta Ghrita Guggulu)	(Abhyanga with Bala Taila + Nadi Swedana with Dashamula Kwatha + Panchatikta Ghrita Guggulu)	30 Days	Improvement in walking and climbing time, improvement of joint flexion,	Not reported	9 Dropouts = 5 (intervention group) + 4 (control group)

Table 1 continued

Reference Origin	Design	Disease	Patients (total, groups)	Inclusion criteria	Experimental intervention	Control intervention	Duration	Outcome measures	Adverse effects (AE)	Dropouts
Sharma (2003) India	CCT	OA	30 (10 + 10 + 10)	Signs and symptoms of OA as described in modern texts	I: Shamana Chikitsa (Panchatikta Ghrita Guggulu) + Abhyanga and Swedana + Dashmool Taila and Dashmool Kwatha, II: Tikta Ksheer Vasti Chikitsa + Abhyanga and Swedana + Dashmool Taila and Dashmool Kwatha, III: Shamana + Tikta Ksheer Vasti Chikitsa + Abhyanga and Swedana + Dashmool Taila and Dashmool Kwatha	I, II, III (three arms)	30 Days	Feeling of well being, physical and mental fitness and improvement in various joint activities	Not reported	Not reported
RA-11										
Chopra (2004) India	RCT	OA (knee)	90 (45 + 45)	ACR clinical and radiological criteria, VAS > 40 mm	RA-11 (2 × 2) (*Withania somnifera*, *Boswellia serrata*, Zingiber off., *Curcuma longa*)	Placebo	32 Weeks	Pain (VAS), modified WOMAC	Mild averse events	28 (lack of compliance)
Reosto										
Nachinolcar (2007) India	RCT	OA (knee ± other)	100 (50 + 50)	40–70 Year, ACR criteria (clinical and radiological change II-III), clinical symptoms ≥ 2 year	Rumalaya forte (1 TA) + Reosto (2 TA)	Rumalaya forte (1 TA) + Placebo (2 TA)	6 Months	Primary outcome measure: decrease in the total sign and symptom score and clinical evaluation done by assessment of free mobility of the joint(s) without causing joint discomfort or pain, improvement in BMD score, bone specific biochemical parameters	No adverse effects	Not reported

Table 1 continued

Reference Origin	Design	Disease	Patients (total, groups)	Inclusion criteria	Experimental intervention	Control intervention	Duration	Outcome measures	Adverse effects (AE)	Dropouts
Rumalaya										
Agarwal (1971) India	RCT	OA (knee: 115 (70 bilat, 45 unilat), spine: 17, ankle: 2, carpo-metacarpal joint: 1)	135 (92 + 43)		Rumalaya (3 × 1)	Placebo	1–4 Weeks	Complete relief: 84,6 % (94), partial relief: 9 % (10), ineffective: (7)	5 Patients: loose motion after taking the drug	None
Chandanwale (2003) India	RCT	OA (knee)	57 (36 + 21)	ARA I-III, clinical and radiographical diagnosis, < 6 months	Rumalaya forte	Placebo	3 Months	Pain (VAS), joint swelling, joint malfunction, muscle weakness, difficulty in climbing steps	Moderate abdominal discomfort,	None
Khare (2004) India	RCT	OA (knee (71), spine, hands, feet, hip))	100	Clinical and radiological evidence, OA > 2 J	Rumalaya forte (JT-2000), (2 × 2)	Placebo	6 Months	Decrease in total sign and symptom score + clinical evaluation (assessment of free mobility of the joint/s without causing joint discomfort or pain)	No patient withdrew due to complications	None
Mathur (2004) India	CCT	OA (Knee)	100 (50 + 50)	50–65, clinical symptoms ≥ 6 months, moderate—severe pain, morning stiffness > 30 min, radiological evidence, biochemical investigation	JT-2000 (Rumalaya forte) (2 × 2)	Ibuprofen (400 mg) (3 × 1)	6 Months	Decrease in total signs (joint effusion, tenderness, crepitus, range of movements, synovial hypertrophy, muscle wasting, joint deformity) and symptom score(number of joints involved, degree of pain, joint swelling, joint stiffness, activity level	JT-2000: no major side effects, 1× headache, decrease of SGOT and SGPT and creatinine, Ibuprofen: 20 reported side effects	None
Rastogi (2003) India	RCT	OA	50 (25 + 25)	50–65 year, clinical and radiological evidence	Rumalaya forte (2 × 1 TA)	Placebo	6 Months	Relief in pain and other subjective symptoms	No adverse events	Not reported

Table 1 continued

Reference Origin	Design	Disease	Patients (total, groups)	Inclusion criteria	Experimental intervention	Control intervention	Duration	Outcome measures	Adverse effects (AE)	Dropouts
Sandhu (1978) India	CCT	OA (70× knee)	146	Not described	Rumalaya (2 × 1 for 3–7 day, then 1 × 1 for 5–10 weeks)	Placebo	5–10 Weeks	Pain and tenderness, swelling of the joints, stiffness, range of movements, clinical picture	No toxic effect (transient nausea and vomiting in 13 cases)	13 Dropouts (failed to follow-up)
Sen (1980) India	CCT	OA	75 (50 + 25)	Clinical diagnosis, X-ray, laboratory	Rumalaya (2 TA after meals)	Other drugs	9 Months	Relief of pain, stiffness of knees, increased movement, gradual improvement	10 (gastric intolerances in control group)	9 Dropouts (only in control group)
Singh (1997) India	RCT	OA	80 (40 + 40)	36–73 year, clinical and radiological examination	Rumalaya (every 8 h)	Ibuprofen 400 mg (every 8 h)	6 Weeks	Tenderness, stiffness, swelling, range of joint motion, joint pain (1–10)	No side effects	None
Srivastava (2005) India	RCT	OA (knee)	100 (50 + 50)	Clinical and radiological evidence of OA, moderate to severe knee pain, morning stiffness < 30 min, > 2 year	Rumalaya forte (2 × 2)	Placebo	6 Months	Primary endpoint: reduction in sign- and symptom score (involved joints, joint swelling, pain, joint malfunction, secondary muscle weakness, difficulty in climbing steps), blood, radiological and clinical examination	No significant adverse events	None
Taneja (1975) India	CCT	OA (knee)	90 (70 + 20)	Clinical diagnoses (pain, swelling, squatting difficulty, inability to walk long distances, restriction of movement, tenderness, effusion, synovial thickening, limitation of movements, wasting of the quadriceps group of muscles), crepitus, routine blood examination, urine and radiological examination,	Rumalaya (tablets 2 × 1 and cream physiotherapy)	Placebo	≥6 Weeks	Symptoms (pain, swelling, limitation of movements, difficulty in getting up from squatting position, pain on walking long distance), signs (tenderness, swelling (fluid and/or syn. thickening), limitation of movements, wasting)	Side effects negligible	166 Patients not included (intake of a minimum of 6 weeks, without interruption, attended follow-up)

Table 1 continued

Reference Origin	Design	Disease	Patients (total, groups)	Inclusion criteria	Experimental intervention	Control intervention	Duration	Outcome measures	Adverse effects (AE)	Dropouts
Upadhyay India	RCT	OA (knee)	100 (50 + 50)	20–80 Year, clinical and radiological evidence of OA, blood examination, moderate-severe pain, morning stiffness < 30 min, > 2 year OA,	JT-2000 (Rumalaya forte) (2 × 2)	Placebo	6 Months	Primary outcome measure: decrease in total sign and symptom score (number of joints involved, joint swelling, joint pain, joint malfunction, secondary muscle weakness, difficulty in climbing steps)	Not reported	1 Dropout
Rumayog										
Jamdar (2004) India	CCT	OA	45 (23 + 22)	Degenerative osteoarthritis, radiological evidence	Rhumayog tab	Brufen	3 Months	Pain index, joints movement, limitation of movements, pain during night time, hot joint feelings, tender joints, general clinical assessment	Not reported	7 Drop outs (due to non-compliance)
Siriraj Wattana										
Pengkhum (2012) Thailand	RCT	OA (knee)	60 (30 + 30)	> 50 Year, radiographic diagnosis, Kellgren grading scale, pain, VAS ≥ 4 cm	Siriraj Wattana (900 mg/day)	Diclofenac (75 mg/day)	12 Weeks	Oxford-12 (pain, function), VAS, patient global assessment, physician global assessment	2 Adverse events in Wattana, 2 in Diclofenac; mainly gastrointestinal, no serious adverse events	9 Dropouts
Shunti-Guduchi										
Chopra (2011) India	RCT	OA (knee)	245 (7 × 35)	> 40 Year, ACR criteria (clinical and radiological examination), VAS > 4 cm, unsatisfying regular NSAID-consumption	Formulations A–E. A (Zingiber off. + Tinospora cordifolia); B ((Zingiber off. + Tinospora cordifolia + Emblica off.); C (Zingiber off. + Tinospora cordifolia + *Withania somnifera*); D (Zingiber off. + Tinospora cordifolia + Tribulus terrestris); E (Zingiber off. + Tinospora cordifolia + *Withania somnifera* + Tribulus terrestris)	Placebo and Glucosamine	16 Weeks	Pain (VAS), modified WOMAC	Mild adverse events	43 (lack of compliance)

Table 1 continued

Reference Origin	Design	Disease	Patients (total, groups)	Inclusion criteria	Experimental intervention	Control intervention	Duration	Outcome measures	Adverse effects (AE)	Dropouts
Chopra (2011) India	RCT	OA (knee)	92	40–70 Year, ACR criteria (clinical and radiological examination), VAS ≥ 4 cm, regular analgesics/NSAID-consumption	I. Shunti (1500 mg daily dose) + Guduchi (330 mg) + Ashwagandha (900 mg) + Gokshura (324 mg) II. Shunti (2000 mg) + Guduchi (440 mg) + Ashwagandha (1200 mg) + Gokshura (432 mg) III. Shunti (1000 mg) + Guduchi (220 mg) + Shallaki Guggul (2000 mg) IV. Bhallataka Parpati (1125 mg) Shunti (1500 mg) + Guduchi (330 mg) + Amalaki (750 mg)	I, II, III, IV	6 Weeks	Pain (VAS), WOMAC	I: 9 Mild adverse events II: 11 mild adverse events III: 11 mild adverse events IV: 3 adverse events; elevated serum liver enzymes	6 Dropouts
Chopra (2013) India	RCT	OA (knee)	440	40–70 Year, ACR criteria (clinical and radiological examination), VAS ≥ 4 cm, regular analgesics consumption	1. SGCG (Zingiber off., Tinospora cordifolia, Phyllanthus emblica, *Boswellia serrata*) (3 × 2) 2. SGC (Zingiber off., Tinospora cordifolia, Phyllanthus emblica) (3 × 2)	1. Glucosamine (2 g/day) 2. Celecoxib (200 mg/day)	24 Weeks	Pain (VAS), WOMAC, physician global assessment, patient global assessment	SGCG: 29 adverse events; SGC: 33 adverse events; Glucosamine; 34 adverse events; Celecoxib: 34 adverse events Significant higher SGPT elevation in intervention groups	22 Dropouts
Snehana/Swedana										
Joshi (2011)	RCT	OA (knee)	116 (51 + 65)	Signs and symptoms of Sandhigata Vata as described in Ayurvedic texts	I: Nirgundi Patra pinda sweda + Ashwagandhadi Guggulu I: Ashwagandhadi Guggulu	I, II	45 Days	Pain, swelling, pain during movement, crepitus, tenderness, overall improvement, walking time, climbing stair time, knee joint movement, X-ray examination	Not reported	15 Dropouts

Table 1 continued

Reference Origin	Design	Disease	Patients (total, groups)	Inclusion criteria	Experimental intervention	Control intervention	Duration	Outcome measures	Adverse effects (AE)	Dropouts
Pathak (1992) India	CCT	OA	30 (10 + 10 + 10)	Physical examination (diagnosis based on sign, symptoms and positive findings according to Ayurveda (Sandhishula, Sotha) and Modern System of medicine (American Rheum. Association), X-ray	I: Snehana + Swedana, II: A.G. (Ashwagandha Guggulu) Capsule (3 ×/d 2 × 500 mg), III: Snehana + Swedana + A.G. Capsule	I, II, III	90 Days	Pain, stiffness, swelling, walking time, radiological changes, improvement of crepitus, improvement in other associated symptoms	Nothing reported	Not reported
Rajoria (2010) India	CCT	OA (knee)	30 (10 + 10 + 10)	> 40 Year, primary OA (Knee), clinical investigations, hematologic investigations, serological investigations, radiological investigations	I: Laksha guggulu (2 mg/d) II: Snehana (Abhyanga) and Sweda (15 min) and Traction III: Laksha Guggulu + Snehana and Swedana andTraction	I, II, III	28 Days	Joint pain, edema, tenderness, restriction of joint movement, stiffness, local crepitation, walking time	Not reported	None
Vasti										
Prameshwar (2002) India	CCT	OA (knee)	104 (50 + 43 + 11)	Diagnostic criteria of primary OA (knee pain, osteophytes, 40–80 Years/stiffness < 30 min/crepitus)	I: Trial drug (Rasna Panchanga, Eranda Mool, Sunthi, Ras Sindura, Shudhkupilu, Godanti Bhasma); II: Trial drug + Yoga Vasti; III: Yoga Vasti	I, II, III	Not reported	Pain, swelling, tenderness, stiffness, restriction of movement and crepitus	Not reported	29 Dropouts
Shah (2010)	CCT	OA	35	40–70 Year, signs and symptoms of Sandhigatavata as described in Ayurvedic texts	I: sarvang Abhyanga-swedana + Matra Vasti, II: sarvang Abhyanga –swedana + Matra Vasti + indigenous compound drugs (Kupuli churna, Godanti Bhasma, Pippali Churna, Yashtimadhu churna, Shallaki, Guggulu)	I, II	3 Weeks	Pain, swelling, pain during movement, crepitus, tenderness, walking time, climbing stair time, X-ray examination	Not reported	2 Dropouts

Boswellia serrata, *Withania somnifera*, *Curcuma longa*, zinc complex

A crossover RCT compared a multicomponent formulation consisting of *Boswellia serrata*, *Withania somnifera*, *Curcuma longa*, and a zinc complex to placebo in a mixed joints OA group [62]. The RCT was insufficiently reported, and risk of bias was unclear. This study found significant group differences favoring the verum group for pain and physical function but not for stiffness and imaging data.

Lepidium Sativum

A CCT in mixed joints OA compared *Lepidium Sativum* Linn. to placebo [63]. While more patients in the verum group reported global improvement than in the placebo group, no statistical group comparison was performed in this trial. Risk of bias was high.

Nirgundi Taila

Nirgundi Taila massage (massage using Vitex negundo oil) and Nirgundi Taila massage combined with oral intake of Nirgundi Taila were compared to oral diclofenac in a CCT on mixed joints OA [64]. Risk of bias was high. While no group comparison was performed, more patients in the diclofenac group reported global improvement compared to both intervention groups.

Panchatikta Ghrita Guggulu

Two CCTs assessed Panchatikta Ghrita Guggulu (tablets containing medicated butter fats) [65, 66]. Both trials had a high risk of bias. Both trials compared different Ayurvedic formulations without a non-Ayurveda control group. Neither trial performed group comparisons.

RA-11

In an RCT with low risk of bias, the polyherbal RA-11 was compared to placebo in OA of the knee [67]. Significant group differences favoring RA-11 over the placebo were found for pain and function, but not for stiffness.

Reosto

An RCT with mixed risk of bias compared Reosto combined with Rumalaya to a placebo combined with Rumalaya [68]. Both groups had significantly improved pain, function and stiffness after treatment; however, group comparisons were not performed for these variables. Significantly more patients in the Reosto group reported global improvement as compared to the placebo group.

Rumalaya

Seven RCTs [53, 69–71, 73–75] and 4 CCTs [76–79] compared Rumalaya to placebo or other drugs. No trial used ACR diagnostic criteria; 5 trials included patients with OA of the knee [70, 74–76, 79], and the other trials included patients with OA of mixed joints.

In 5 RCTs and 2 CCTs, Rumalaya was compared to placebo. Risk of bias was generally high in individual trials; only 3 RCTs reported adequate randomization [71, 74, 75]; and no trial reported adequate allocation concealment. Two RCTs were adequately blinded [69, 70]. Three trials assessed pain and function [53, 70, 75]; however, only 1 trial reported group comparisons [74]. In this RCT, significant group differences favoring the verum group over placebo were found for pain and function. Meta-analysis revealed a significant group difference favoring Rumalaya over placebo for pain (SMD $= -3.73$; 95 % CI -4.97; -2.50; $P < 0.01$; Fig. 4). Effects were comparable for studies with OA knee and those with mixed OA groups (Fig. 4). Effects did not change when only trials with low risk of bias regarding random sequence generation or blinding were included. Five trials assessed global improvement [53, 69, 71, 77, 79]. While all trials reported higher numbers of patients with global improvement in the verum groups compared to placebo, none of them computed statistical group comparisons. In meta-analysis, more patients in Rumalaya reported global improvement than in placebo groups (RR 12.20; 95 % CI 5.83; 25.54; $P < 0.01$; Fig. 4), both for studies with OA of the knee and those with mixed OA groups (Fig. 4). Effects did not change when only trials with low risk of bias regarding random sequence generation or blinding were included.

One RCT [73] and 1 CCT [76] compared Rumalaya to ibuprofen. Both trials had high risk of bias. In both trials, both interventions provoked comparable rates of global improvement. Another high risk of bias CCT compared Rumalaya to other drugs that were not further defined [78]. While more patients in the Rumalaya group reported global improvement as compared to the control group, no statistical group comparisons were performed.

Rhumayog

A high risk of bias CCT compared Rhumayog tablets to Brufen [72]. Significant group differences favoring Rhumayog were found for pain and function.

Siriraj Wattana

A RCT compared Siriraj Wattana to diclofenac [80]. The RCT had low risk of bias regarding random sequence generation but unclear risk of bias regarding allocation

concealment and blinding. No significant differences between groups were found for pain, function, and global improvement.

Shunti-Guduchi

Three RCTs on Shunti-Guduchi (Zingiber officinale and Tinospora cordifolia) in patients with OA knee were included; 3 RCTs had low overall risk of bias; and 2 used ACR criteria [81–83].

A RCT [81] compared 4 different Ayurvedic formulations with a common base of Zingiber officinale and Tinospora cordifolia without a non-Ayurveda control, while another RCT compared 5 such combinations with placebo and glucosamine [83]. The latter RCT reported significant group differences favoring 1 of the Shunti-Guduchi formulas over placebo for overall improvement but not for pain or function. The other formulas had no effect beyond placebo. All formulas were comparable to glucosamine. The third RCT compared Shunti-Guduchi to glucosamine and celecoxib and reported comparable effects of the 3 interventions on pain and function [82]. Meta-analysis confirmed equivalent effects of Shunti-Guduchi and glucosamine on pain (SMD 0.08; 95 % CI −0.20, 0.36; ; $P = 0.56$; Fig. 5) and function (SMD = 0.15; 95 % CI −0.12; 0.36; $P = 0.41$; Fig. 5). Effects did not change when only RCTs were included that used ACR criteria [82].

Snehana/Svedana

A RCT compared the effect of svedana (herbal stamp massage) combined with Ashvagandhadi Guggulu (herbal compound tablets containing *Withania somnifera* and Commiphora mukul as the main herbal ingredients) to Ashvagandhadi Guggulu alone on OA knee [84]. The RCT had high risk of bias. Both groups reported improvements in pain, function, and stiffness. More patients in the combined group reported global improvement compared to the Ashvagandhadi Guggulu alone group. No group comparison was reported for any variable.

Two CCTs investigated snehana (massage) and svedana (Ayurvedic steam therapy) [85, 86]. Due to the non-randomized study design, risk of bias was high in both trials. One trial compared oral Laksha Guggulu (herbal compound tablets containing Ficus religiosa and Commiphora mukul as main ingredients) with (a) snehana and svedana traction and (b) Laksha Guggulu combined with snehana and svedana traction in OA knee [85]. The combination was superior to the isolated interventions for reducing pain and disability while there were no differences between Laksha Guggulu alone and snehana/svedana traction alone. Another trial compared snehana and svedana with (a) Ashvagandhadi Guggulu and (b) snehana and svedana combined with Ashvagandhadi Guggulu [85]. Significant improvements for pain and function as well as a significantly reduced function were observed in all 3 groups; no group differences were computed. More patients in the combined group reported global improvement as compared to the other 2 groups; again, no group comparisons were performed.

Basti/Vasti

A high risk of bias CCT assessed the effect of samshodhana drug therapy alone and combined with basti (enema) to basti alone (prameshva). All 3 groups demonstrated improvement with regard to pain, stiffness, and global improvement. However, no group comparisons were performed [87].

Another high risk of bias CCT compared the effect of svedana combined with basti to svedana combined with basti and a multicomponent drug. Both groups reported improvements in pain, function, stiffness, and imaging parameters. More patients in the combined group reported global improvement compared to the Ashvagandhadi Guggulu alone group. No group comparison was reported for any variable [88].

Discussion

In this systematic review of 33 controlled trials, some evidence of effectiveness for several Ayurvedic interventions in OA was revealed. For Rumalaya, large and apparently unbiased effects beyond placebo were found for pain and global improvement. Based on single RCTs, effects beyond placebo are also conceivable for RA-11 and possibly Reosto.

Equivalence or superiority beyond other drugs was inconclusive for Rumalaya. On the other hand, evidence for equivalent effects of Shunti-Guduchi compared to glucosamine on pain and function was found. While being less clear, equivalence is also likely for Shunti-Guduchi compared to celecoxib and perhaps for Siriraj Wattana compared to diclofenac.

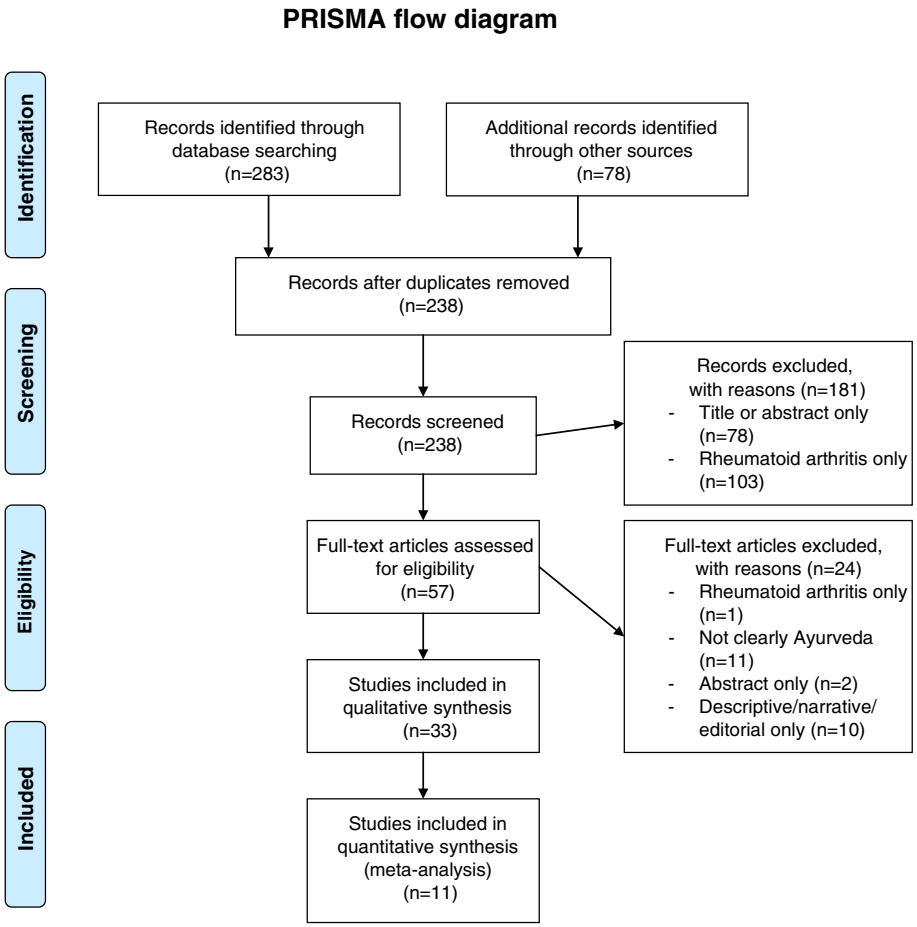
None of the Ayurvedic formulas were reported to be associated with severe adverse events.

For *Boswellia serrata* as single drug, a multicomponent formulation consisting of *Boswellia serrata* and other drugs, *Lepidium Sativum*, Nirgundi Taila, Panchatikta Ghrita Guggulu, and Rhumayog, no evidence for effects was found that was robust against potential methodological bias. The same was true for non-pharmacological interventions such as Ayurvedic massage, steam therapy, and enema.

Table 2 Risk of bias assessment of the included studies using the Cochrane risk of bias tool

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias
Boswellia serrata						
Gupta (1993)	No	No	No	Unclear	Unclear	Unclear
Kimmatkar (2003)	Yes	Yes	Unclear	Yes	Yes	Unclear
Sengupta (2008)	Yes	Yes	Yes	Yes	Yes	Yes
Sengupta (2010)	Yes	Unclear	Yes	Yes	Yes	Yes
Sontakke (2006)	Yes	Unclear	No	Unclear	Yes	Unclear
Boswellia serrata, *Withania somnifera*, *Curcuma longa*, *zinc complex*						
Kulkarni (1991)	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Lepidium sativum						
Raval (2009)	No	No	No	Unclear	Unclear	Unclear
Nirgundi Taila						
Das (2002)	No	No	No	Yes	Unclear	Unclear
Panchatikta Ghrita Guggulu						
Akhtar (2010)	Unclear/No	No	No	Yes	Unclear	Unclear
Sharma (2003)	No	No	No	Unclear	Unclear	Unclear
RA-11						
Chopra (2004)	Yes	Yes	Yes	Yes	Yes	Unclear
Reosto						
Nachinolcar (2007)	Yes	Unclear	Unclear	Unclear	Yes	Unclear
Rumalaya						
Agrawal (1971)	No	Unclear	Yes	Unclear	Unclear	No
Chandanwale (2003)	No	Unclear	Yes	Yes	Yes	Unclear
Khare (2004)	Yes	Unclear	Unclear	Yes	Unclear	Unclear
Mathur (2004)	No	No	No	Yes	Yes	No
Rastogi (2003)	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Sandhu (1978)	No	No	No	Unclear	Unclear	No
Sen (1980)	No	No	No	Unclear	Unclear	Unclear
Singh (1997)	Unclear	No	No	Unclear	Yes	Unclear
Srivastava (2005)	Yes	Unclear	Unclear	Yes	Yes	Unclear
Taneja (1975)	No	No	No	No	Unclear	No
Upadhyay	Yes	Unclear	Unclear	Yes	Yes	Unclear
Rumayog						
Jamdar (2004)	Unclear	No	No	Unclear	Yes	Unclear
Siriraj Wattana						
Pengkhum (2012)	Yes	Unclear	Unclear	Yes	Yes	Yes
Shunti-Guduchi						
Chopra (2011)	Yes	Yes	Yes	Yes	Yes	Yes
Chopra (2011)	Yes	Yes	Yes	Yes	Yes	Yes
Chopra (2013)	Yes	Unclear	Yes	Yes	Yes	Yes
Swedana						
Joshi (2010)	Unclear	Unclear	Unclear	Yes	Yes	Yes
Pathak (1992)	No	No	No	Unclear	Unclear	Unclear
Rajoria (2010)	Unclear	No	No	Yes	Unclear	Unclear
Vasti						
Prameshwar (2002)	No	No	No	No	Unclear	Unclear
Shah (2010)	No	No	Unclear	Yes	Yes	Yes

Fig. 2 PRISMA flow diagram



Strengths and weaknesses

This is the first meta-analysis available on Ayurvedic interventions for OA. Subgroup analyses were conducted to assess the effects of different Ayurvedic interventions, and in patients with different affected joints. No language restrictions were imposed.

The primary limitation of this review is the low methodological quality of most of the RCTs. While several high quality RCTs were located for Rumalaya and Shunti-Guduchi, only a single RCT with low risk of bias was included on RA-11. For the other interventions, the high risk of bias of the analyzed studies limits the interpretation of their results. Several studies compared different Ayurvedic formulations without an adequate non-Ayurvedic control group.

A further limitation is the small sample size of the studies. A meta-epidemiological study of 13 meta-analyses on RCTs that compared therapeutic interventions with placebo or non-intervention control in patients with osteoarthritis found that small study effects can distort results of meta-analyses on OA [89]. Specifically, large trials with sample sizes of more than 100 patients in each arm had lower estimated treatment estimates than smaller trials. Since in the present review, only 1 study met this definition of a large trial [20], and small study effects could not be ruled out.

However, in spite of the positive data for Rumalaya, notably all isolated trials on this drug were found in journals that are not MEDLINE-indexed and thus could not be located in major international databases like PubMed. Of course, this poses an obvious cutback for the interpretation of these data.

Another limitation relates to the fact that in the case of the Shunti-Guduchi trials, Ayurvedic remedies were compared to control interventions including glucosamine preparations, while a controversy remains about the use and effectiveness of glucosamine in OA guidelines [90, 91].

It also remains questionable whether the trial documentation (e.g., of adverse events) is being done adequately and according to international good research practice in South Asian countries, particularly as there was not a single reported case of serious adverse event in 33 trials.

Yet probably, the most important limitation of this and most other present reviews and clinical trials on Ayurvedic

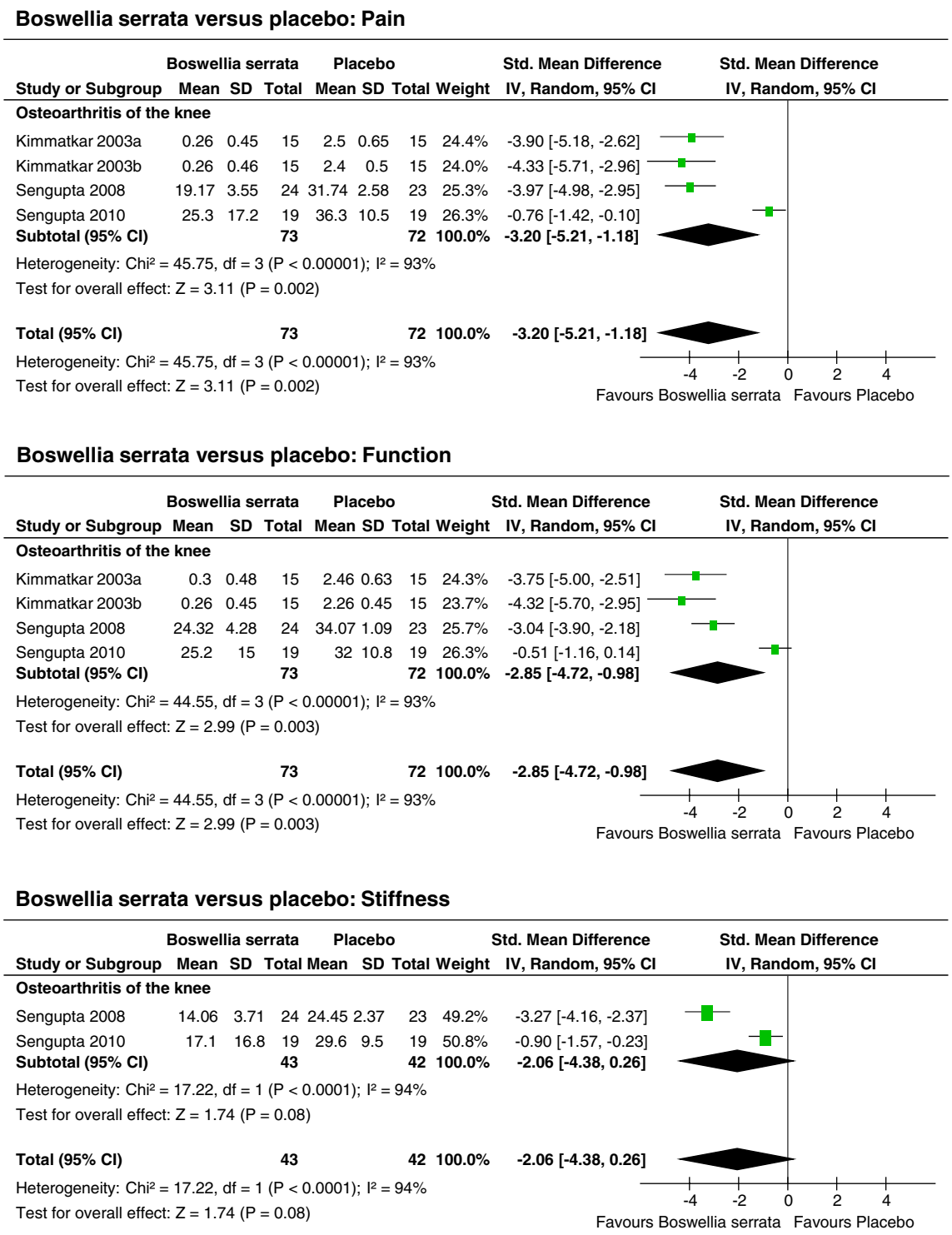


Fig. 3 Effect sizes of Boswellia serrate versus placebo

therapies is the fact that to date, hardly any study has investigated multimodal individualized treatment as generally proposed by traditional Ayurvedic principles and as practiced in routine Ayurvedic care up-to-date [23].

Implications for further research and clinical practice

Reviews of research studies done on Ayurveda so far show that the majority of them are experimental and explorative,

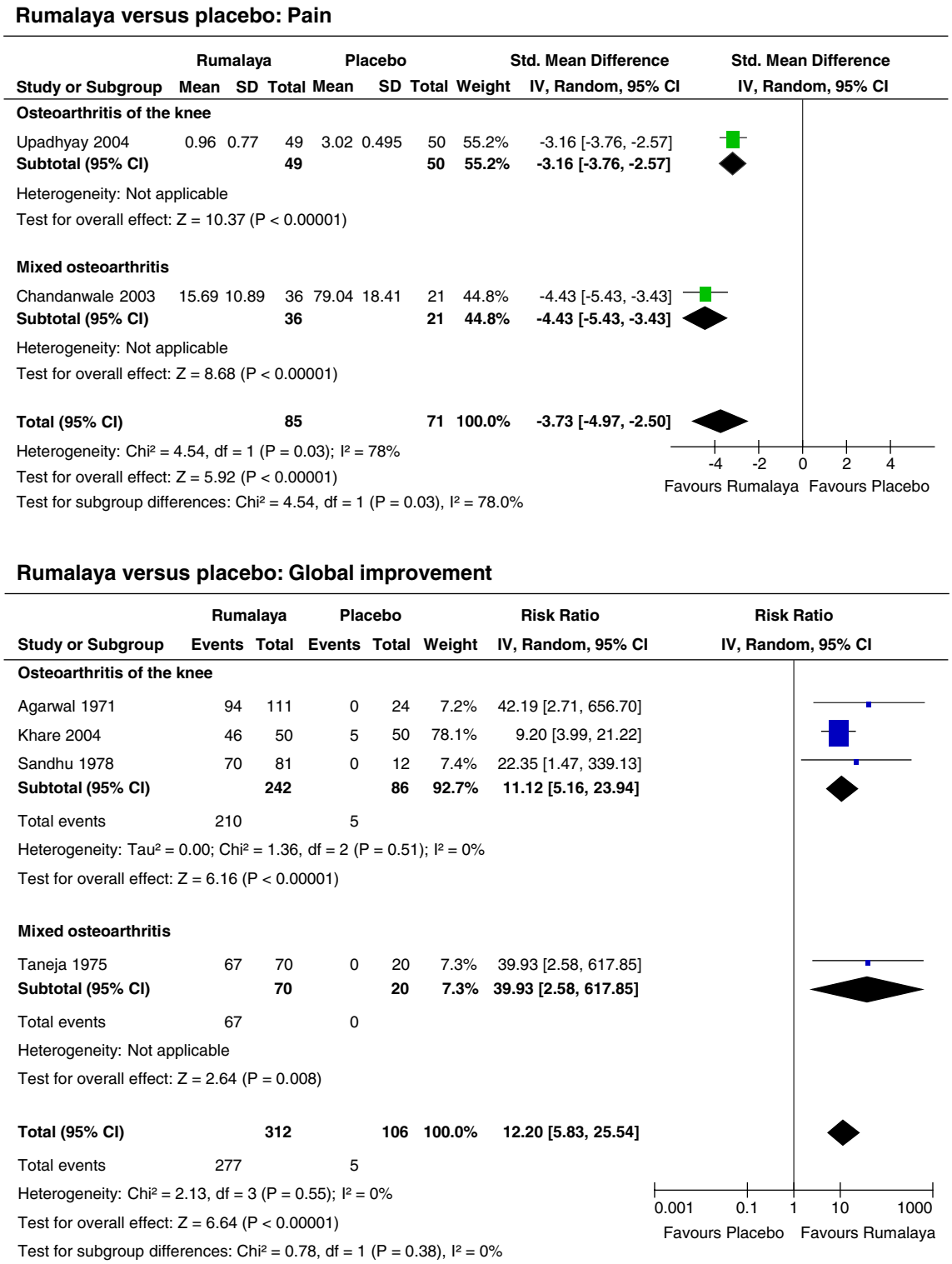


Fig. 4 Effect sizes of Rumalaya versus placebo

focusing on single herbs, compound formulations or single therapies. A minority of existing Ayurveda research is clinical and is focused either exclusively on drug therapy or on non-pharmacological interventions such as Yoga. Moreover, many of these trials have severe methodological limitations [29, 92].

During recent years, a change of this trend could be observed in a couple of RCTs demonstrating that a

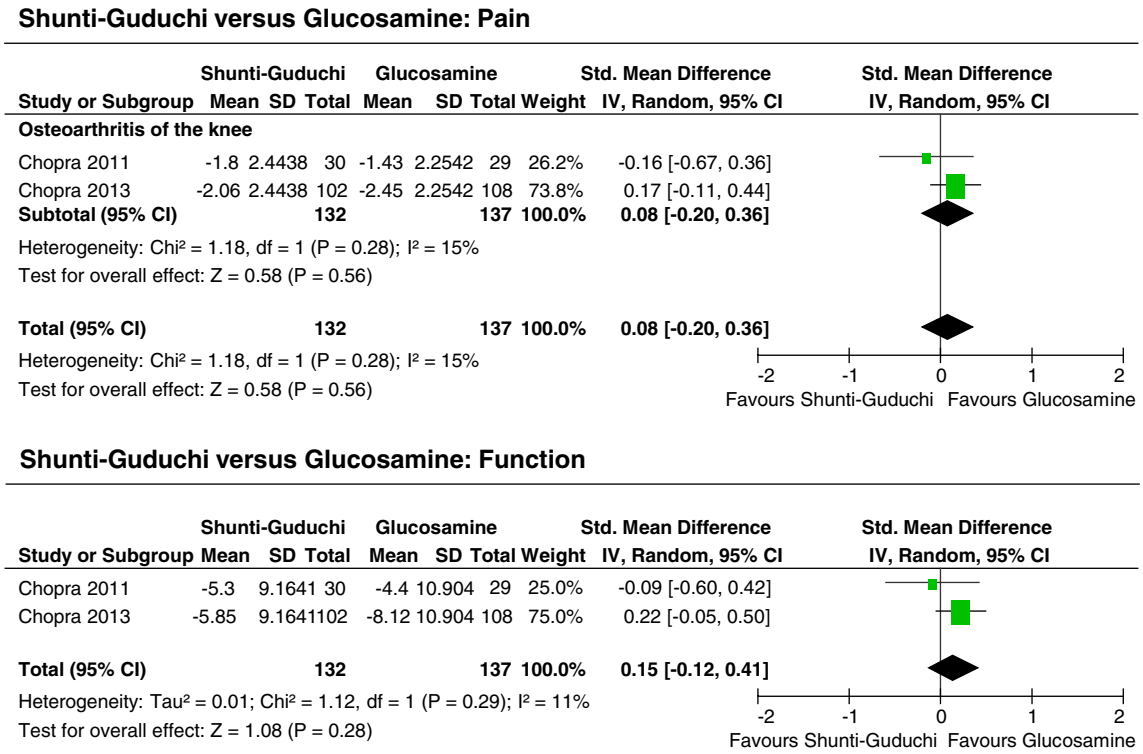


Fig. 5 Effect sizes of Shunti-Guduchi versus Glucosamine

tailored Ayurvedic treatment approach can be incorporated in RCT designs and that blinding can also be done successfully [21, 22].

However, so far Ayurveda has rarely been studied as a WMS and in the manner in which it is actually being practiced today [23].

Clinical trials on TM and WMS have to consider additional obstacles in research related to aspects their specific and non-conventional nomenclature, approaches and paradigms, etc. Future trials could try to incorporate both the conventional and the TM/WMS approaches into their trial designs.

In order to improve the quality of evidence, future RCTs in this field should ensure rigorous methodology and reporting, adequate sample size, adequate randomization, allocation concealment, intention-to-treat analysis, and blinding of at least outcome assessors [93].

Based on these data, only Rumalaya can be seen as a safe and effective Ayurvedic herbal drug for patients with OA knee and OA of other joints. Shunti-Guduchi can also be considered to some extend; however, the evidence of its effectiveness is limited to OA knee and the comparison to glucosamine adds further tentativeness to the results. Since the evidence of effectiveness for RA-11 is derived from only a single trial, it cannot be considered as routine intervention so far. Other Ayurvedic interventions cannot currently be recommended to patients with OA based on the findings of this review and meta-analyses.

As several Ayurvedic herbal formulation have been shown to be possibly polluted with heavy metals such as lead, mercury, and arsenic in both Western countries and in South Asia [94–98], it seems to be of utmost importance to establish an effective and transparent quality control for manufacturers and distributors of Ayurvedic drugs on a global scale.

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