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[Intervention Protocol]

Boswellia for osteoarthritis

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of boswellia extracts (BEs), or formulations containing BEs for osteoarthritis.

BACKGROUND

Description of the condition

Osteoarthritis (OA) is a common, chronic disorder of the joints that imparts a substantial and ever-increasing health burden, especially in the elderly population (Cross 2014; Glyn-Jones 2015). OA affects 7% of the global population and is responsible for 2% of total global years lived with disability (GBD 2020). OA prevalence is higher in women, and increases with advancing age and increasing body mass index (BMI (Palazzo 2016)). Due to the increasing prevalence of obesity and an ageing global population, the prevalence of OA has been steadily increasing over the past few decades (GBD 2020). OA is a leading cause of chronic pain and long-term disability in adults; its major symptoms include joint pain, stiffness, and joint functional loss (Martel-Pelletier 2016). OA most commonly affects the joints in the knees, hips, hand, foot, ankle, back, and neck (Kapoor 2015). The pathogenesis of OA is complex, and involves a dynamic process mediated by mechanical, inflammatory, and metabolic factors (Katz 2021; Mobasheri 2016).

The current treatment guidelines for OA list few management options, which include non-pharmacological and pharmacological options. Non-pharmacological treatments are the core treatment option for the management of OA, and include weight loss, self-management and education programmes, and physical exercise. Pharmacological treatments include oral nonsteroidal anti-inflammatory drugs (NSAIDs) in those without contraindications, topical NSAIDs, and glucocorticoid injections (Bannuru 2019; Fransen 2015; Katz 2021; Messier 2013; Rini 2015). NSAIDs are often the first-line pharmacologic treatment for OA; however, they are often contraindicated in people with OA, who often have comorbidities (Honvo 2019; Mason 2004; Rannou 2016).

Description of the intervention

Frankincense (also known as olibanum) is a fragrant resinous extract from moderate-sized deciduous trees of the genus *Boswellia* (Tucker 1986; Weeks 2005). Four *Boswellia species* in the Burseraceae family produce frankincense, including *Boswellia sacra* (synonym *B. carterii*), *B. frereana*, *B. serrata*, and *B. papyrifera* (The Plant List 2013). Boswellia extract (BE) is produced from frankincense using extraction, fraction, purification, and identification techniques. Boswellic acids are the main active components of BE; they contain acetyl-keto-beta-boswellic acid (AKBA) as the key pharmacologically active ingredient (Abubakar 2020; Cameron 2014).

Pharmacokinetic studies have found that boswellic acids exhibit poor bioavailability when taken orally (Abdel-Tawab 2011; Skarke 2012). However, they are lipophilic (or fat-loving) in nature, hence, ingestion of the boswellia extract with high-fat meals have shown an increased plasma concentration of boswellic acids and AKBA (Sterk 2004). Combining BE with other herbal extracts and phospholipid-based delivery systems has also shown an increase in its bioavailability (Husch 2013;Yu 2020).

Formulations containing boswellia extracts have exhibited medicinal properties, and have been used in the management of OA, rheumatoid arthritis, Crohn's disease, and collagenous colitis (Ernst 2008; Hughes 2007). Dozens of *Boswelliaserrata* preparations are commercially available, and sold as food supplements (Ernst 2008). They are generally taken orally for OA, and are available as capsules or tablets (Ernst 2008; Yu 2020). Several studies have found BEs to have a favourable and acceptable safety profile (Cameron 2014; Ernst 2008; Krishnaraju 2010; Yu 2020). No significant levels of toxicity have been noted; minor adverse effects of boswellia include diarrhoea, abdominal pain, and nausea (Ernst 2008; Yu 2020).

How the intervention might work

Inflammatory mechanisms and oxidative stress have been known to play an important role in the pathogenesis of OA, leading to loss of articular cartilage, synovitis (inflammation of the joint-lining), and osteophyte (bone spurs) formation (Ansari 2020; Kapoor 2015; Lepetsos 2016; Loeser 2012; Robinson 2016). The main pharmacologically active ingredients of BEs, such as α and β boswellic acids, AKBA, and other pentacyclic triterpenic acids, have been shown to inhibit pro-inflammatory processes, by their effects on 5-lipooxygenase and cyclo-oxygenase on the complement system (Ammon 2006; Ammon 2010). Treatment with BEs has been associated with the reduction of oxidative stress (Mbiantcha 2018; Zhang 2016), and reduction of inflammatory symptoms, through the combined inhibition of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) pathways (Li 2016; Ren 2015).

Preclinical and clinical evidence suggests that the active compounds of BEs (α- and β-BA, AKBA) exhibit anti-inflammatory and antioxidant properties that may be relevant in the treatment of OA (Efferth 2020; Iram 2017). Previous randomised controlled trials (RCTs) have shown that boswellia extracts significantly improve pain and physical function scores in people with knee OA when compared with a placebo (Kimmatkar 2003; Sengupta 2008). Another trial compared the analgesic activity of BEs to placebo in healthy adults, and found that BEs significantly increased the pain threshold and pain tolerance force compared to placebo (Prabhavathi 2014).

A recent review has also shown the beneficial effects of boswellia on metabolic syndrome (MetS (Mahdian 2020)). There is increasing evidence on the role of MetS in the development of OA symptoms and structural abnormalities, and any effect of BE on MetS could be relevant for the management of OA (Zhuo 2012), including reduction of insulin resistance (Ammon 2019; Gomaa 2019), mitigation of hyperglycaemia (Azadmehr 2014), and alleviation of hyperlipidaemia (Mahdian 2020). Hence, BEs may present a promising option for the treatment of OA (Gupta 2011; Kimmatkar 2003; Kulkarni 2020; Shah 2010).

Why it is important to do this review

NSAIDs are the first-line pharmacologic treatment option for OA; however, their safety profile and contraindications limit their long-term use in people with OA, who often have comorbidities (Katz 2021). Intra-articular glucocorticoid injections are another pharmacologic treatment option for OA, however, they provide pain relief only for a few weeks, and their effect on cartilage is debatable (Katz 2021). The lack of effective treatment options for the management of OA highlights the need for alternative treatments. Complementary and alternative medicines (CAMs) have good acceptability among the general population, and studies have found that more than half of the people with OA reported using herbal medicines during the course of their disease (Lapane 2012; Unsal 2010). Furthermore, there is widespread over-the-counter (OTC) use of phytopharmaceuticals based on BEs (Abdel-Tawab 2011).

Three systematic reviews of RCTs evaluated the efficacy and safety of boswellia for the treatment of OA (Cameron 2014; Liu 2018; Yu 2020). Cameron 2014 evaluated oral medicinal plant products for the treatment of OA, and included five studies that compared three different boswellia extracts with placebo and valdecoxib. Liu 2018 assessed the efficacy of various dietary supplements for the treatment of OA, and found that boswellia extracts reduced pain (standardised mean difference (SMD) -1.61, 95% confidence interval (CI) -2.10 to -1.13), and improved physical function (SMD -1.15, 95% CI -1.63 to -0.68) more than other supplements at three months. Yu 2020 also found that *Boswelliaserrata* and its extracts may relieve pain (mean difference (MD) -8.33, 95% CI -11.19 to -5.46) better than placebo and ibuprofen.

However, these systematic reviews did not include primary studies that explored different types of extracts (non-bio-enhanced extracts, bio-enhanced extracts, etc.), or different combinations of BEs. New evidence from recent clinical trials has also become available since the publication of these systematic reviews. Therefore, it is important to do a new synthesis of existing evidence, including different combinations of BEs, to inform consumers and stakeholders about the efficacy and safety of boswellia for the management of OA.

OBJECTIVES

To assess the benefits and harms of boswellia extracts (BEs), or formulations containing BEs for osteoarthritis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCT). We will include studies reported as full text, those published as abstract only, and unpublished data. There will be no language restriction.

We will exclude observational, cross-over, cluster, and non-randomised trials.

Types of participants

We will include adults (18 years and older), of any sex, diagnosed with osteoarthritis (OA), at any site (e.g. knee, hip, or hand), according to the criteria proposed by the American College of Rheumatology (ACR), or other similar criteria defined in the studies (Altman 1986).

We will include studies that only have a subset of eligible participants if the outcomes are reported for eligible participants separately, or most (at least 75%) of the study population consists of eligible participants.

Types of interventions

The interventions of interest are boswellia extracts (BE) obtained from trees of the genus boswellia (*Boswellia sacra*, *B. carterii*, *B. frereana*, *B. serrata*, and *B. papyrifera*) and any formulations containing these BEs (The Plant List 2013). We will include trials with formulations containing BE and any bioavailability enhancing combination of BE (e.g. BE combined with piperine, soy lecithin formulation of BEs, or BEs enriched in acetyl-keto-beta-boswellic acid (AKBA) and the non-volatile oil portion of *B. serrata* gum resin (Abdel-Tawab 2021)).

The planned comparisons are:

1. BE versus placebo
2. BE versus standard care, no treatment, or waiting-list control
3. BE versus nonsteroidal anti-inflammatory drugs (NSAIDs)

We will include studies that compare BE in combinations with other pharmacological interventions (e.g. NSAIDs, curcumin, etc.) only if the same active interventions (except BE) are present in the comparator group (e.g. both the treatment and control group received NSAIDs, curcumin, etc.).

We will exclude trials with multiherbal formulations containing BE.

Types of outcome measures

Major outcomes:

1. Pain
2. Physical function
3. Health-related quality of life
4. Participant-reported global assessment of success, as measured by a participant-reported global impression of clinical change (much or very much improved), or similar measure (e.g. proportion achieving 30% reduction in pain)
5. Withdrawals due to adverse events
6. Serious adverse events
7. Adverse events

For studies reporting more than one measure of pain, we will use the following hierarchy, and extract the measure that ranks first in the list (Juni 2006):

1. Pain overall
2. Pain on walking
3. WOMAC (Western Ontario and McMaster Universities Arthritis Index) pain subscale
4. KOOS (Knee injury and Osteoarthritis Outcome Score) pain subscale
5. Pain on activities other than walking
6. WOMAC global scale
7. Lequesne osteoarthritis index global score
8. Other algofunctional scales
9. Participant's global assessment
10. Physician's global assessment

Similarly, for studies providing more than one physical function scale, we will use the following hierarchy, and extract the measure that ranks first in the list (Juni 2006):

1. Global disability score
2. Walking disability
3. WOMAC disability subscore
4. KOOS composite disability subscores
5. Other composite disability subscores
6. Disability other than walking
7. WOMAC global scale

8. KOOS global scale
9. Lequesne osteoarthritis index global score
10. Other algofunctional scales

For studies reporting more than one quality of life scale, we will use the following hierarchy, and extract the measure that ranks first in the list (Juni 2006):

1. Short-Form Health Survey (SF-36; mental health component)
2. EQ-5D (EuroQol 5-dimension questionnaire)
3. EuroQoL 15D
4. Sickness Impact Profile (SIP)
5. Nottingham Health Profile (NHP)
6. Assessment of Quality of Life instrument (AQoL)
7. Other validated quality of life scores

Minor outcomes:

1. The Osteoarthritis Research Society International (OARSI) recommended a set of physical performance measures for knee and hip osteoarthritis. For studies reporting more than one measure, we will use the following hierarchy, and extract the measure that ranks first in the list.
   a. sit-to-stand (30-second chair stand test, the maximum number of chair stand repetitions possible in a 30-second period)
   b. walking short distances (4*10 m) fast-paced walk test; a fast-paced walking test that is timed over 4 x 10 m (33 ft) for a total 40 m (132 ft)
   c. stair negotiation (the time (in seconds) it takes to ascend and descend a flight of stairs (Dobson 2013))
2. Change in OA-associated biochemical marker interleukin 6 (IL-6 (Kraus 2017; Zhu 2021))
3. Change in OA-associated biochemical marker tumor necrosis factor-α (TNF-α (Kraus 2017; Zhu 2021))
4. Change in OA-associated biochemical marker high-sensitivity C-reactive protein (hs-CRP (Kraus 2017; Zhu 2021))
5. Change in OA-associated biochemical marker Matrix metalloproteinase-3 (MMP-3 (Kraus 2017; Zhu 2021))
6. Participant adherence (numbers of pills of the investigations drugs given to the participants, counted at the beginning of the trial and at the end of the trial, the proportion of pills taken is surrogate for participant adherence)

We will not exclude studies based on the outcomes listed above.

We will consider the following time points for the extraction of outcomes: short-term (≤ 3 months), medium-term (4 to 6 months), and long-term (> 6 months).

Search methods for identification of studies

We will develop a search strategy using previous search strategies to identify studies of BE and BE formulations for the treatment of OA. Search terms for interventions will include: *Boswellia,Boswellia serrata*, *Boswelliacarteri*, *Boswelliafrereana, Boswellia* ru xiang (乳香, the Chinese name for *Boswellia serrata*), boswellic acid, Frankincense, Shallaki, Salai, aflapin, 5-loxin, and other formulations, such as Acujoint, Lanconone. Search terms for participants will include Osteoarthritis, Osteoarthritides, Osteoarthrosis, Osteoarthroses, Degenerative Arthritis, Arthritides.

Electronic searches

We will search the following sources from their inception to the present:

1. Cochrane Central Register of Controlled Trials (CENTRAL) OVID
2. MEDLINE OVID
3. Embase OVID
4. China Network Knowledge Infrastructure (CNKI; www.cnki.net/)
5. Chinese Scientific Journals Database (VIP; www.cqvip.com/)
6. Wan Fang data (www.wanfangdata.com.cn/index.html)
7. SinoMed (www.sinomed.ac.cn/)

We will also conduct a search of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en/), using terms, such as boswellia and boswellic acid. We will search all databases from their inception to the present, and we will impose no restriction on the language of publication while searching the database. For detailed search strategies, see Appendix 1.

Searching other resources

We will include both published and unpublished trials, with the latter including, e.g. abstracts, conference proceedings, and posters with available data.

We will include abstract booklets from the last two years' conference proceedings; and will search abstracts and poster sessions from the web, using the online sources of major international associations involved in OA research: European League Against Rheumatism (EULAR), Osteoarthritis Research Society International (OARSI), American Academy of Orthopaedic Surgeons (AAOS), and ACR, using relevant keywords, such as boswellic acid and boswellia.

Data collection and analysis

Selection of studies

Two review authors (ZW and AS) will independently screen titles and abstracts for inclusion of all the potentially relevant studies identified as a result of the search, and code them as 'retrieve' (eligible, or potentially eligible, or unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publication, and two review authors (ZW and AS) will independently screen the full text to identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion, or if required, we will consult a third review author (BA).

We will identify and exclude duplicates, and collate multiple reports of the same study under a single reference ID so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete the characteristics of excluded studies table and a PRISMA flow diagram (Page 2020).

Data extraction and management

1. Two review authors (ZW and AS) will independently perform data extraction, using a data collection form piloted on at least

one included study. We will extract the following data from each eligible study:

a. method: study design, study duration, study locations, study setting, and funding of the trial
b. characteristics of the population: N (sample size), mean age, sex, and body mass index (BMI)
c. intervention details: intervention and comparator dosage, frequency, route of administration, duration, and co-medications
d. outcome measurements: mean change values of the relevant outcome, and the number of adverse event reports, and medication change
e. notes: funding for trial, and notable declarations of interest of trial authors

Two review authors (ZW and AS) will independently extract outcome data from included studies. We will extract the number of events and number of participants per treatment group for dichotomous outcomes, and means and standard deviations and number of participants per treatment group for continuous outcomes. In the characteristics of included studies table, we will note if outcome data were not reported in a usable way, and when data were transformed or estimated from a graph. We will resolve disagreements by consensus or by involving a third review author (BA).

We will use Plot Digitizer software to extract data, in duplicate, from graphs or figures (Plot Digitizer 2021).

We will extract data according to the following rules.

1. If multiple time points are reported, we will extract the outcome data closest to the three-month time point for the short-term, closest to six months for intermediate-term, and collect all other available time points as long-term follow-up.
2. We will extract intention-to-treat (ITT) analysis data, if available. In the absence of ITT data, we will extract 'per protocol' or 'as treated' data.
3. We will extract change scores if both change and endpoint values are reported.

Main planned comparisons

The primary comparison will be BE versus placebo.

The other main comparisons will be:

1. BE versus standard care, no treatment, or waiting-list control
2. BE versus NSAIDs

Assessment of risk of bias in included studies

Two review authors (ZW and AS) will independently evaluate the risk of bias of the selected studies using Cochrane's RoB 1 (Higgins 2017). We will resolve any disagreements by discussion with our senior review author (BA).

We will assess the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias

We will assess each potential source of bias as high, low, or unclear risk, and provide a quote from the study report together with a justification for our judgement in the risk of bias table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for self-reported outcomes and assessor-reported outcomes, and will judge them separately. In addition, we will consider the impact of missing data by key outcomes.

When information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the risk of bias table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

We will present the figures generated by RoB 1 to provide summary assessments of the risk of bias.

Measures of treatment effect

We will analyse continuous data as mean differences (MD) or standardised mean differences (SMD), depending on whether the same scale is used to measure an outcome, and 95% confidence intervals (CIs). We will enter data presented as a scale with a consistent direction of effect across studies. When different scales are used to measure the same conceptual outcome (e.g. disability), we will calculate SMDs, with corresponding 95% CIs. We will back-translate the SMDs to the typical scale (e.g. 0 to 100 mm for VAS pain, and 0 to 100 for WOMAC pain) by multiplying the SMD by an average among-person standard deviation (SD), taken from the control group at baseline from the most representative trial (Higgins 2021).

In the Effects of interventions section of the results, and the What happens column of the summary of findings tables, we will report the absolute per cent change, and the relative per cent change from baseline.

We will analyse dichotomous safety data as risk ratios (RRs), or Peto odds ratios (ORs) when an outcome is a rare event (approximately less than 10%), and use 95% CIs. We will calculate the absolute per cent change from the difference in the risks between the intervention and control group using GRADEpro GDT, and express this as a percentage (GRADEpro GDT). We will calculate the relative per cent change as the RR - 1, and express this as a percentage.

Unit of analysis issues

The unit of analysis will be the individual participant for all trials. When multiple trial arms are reported in a single trial, we will include only the relevant arms. If two sets of comparisons (e.g. drug X versus placebo, and drug Y versus placebo) from a single trial are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data, when possible (e.g. when a study is identified as an abstract only, or

when data are not available for all participants). When this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results, with a sensitivity analysis. Any assumptions and imputations used to handle missing data will be clearly described, and the effect of imputation explored with sensitivity analyses.

For dichotomous outcomes (e.g. number of withdrawals due to adverse events), we will calculate the withdrawal rate using the number of participants randomised to the group as the denominator.

For continuous outcomes (e.g. mean change in pain score), we will calculate the MD or SMD based on the number of participants analysed at that time point. If the number of participants analysed is not presented for each time point, we will use the number of participants randomised to each group at baseline.

When possible, we will calculate missing standard deviations from other statistics, such as standard errors, confidence intervals, or P values, according to the methods recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). If standard deviations cannot be calculated, they will be imputed (e.g. from other studies in the meta-analysis).

Assessment of heterogeneity

We will assess the clinical and methodological diversity of participants, interventions, outcomes, and study characteristics (e.g. study design, outcome measurement tools, etc.) from the included studies to determine whether a meta-analysis is appropriate, by observing these data in the characteristics of included studies tables. We will assess statistical heterogeneity by visual inspection of the forest plot to assess the direction and magnitude of effects, and the degree of overlap between CIs.

We will use the I^2 statistic to quantify inconsistency among the trials in each analysis. We will also consider the P value from the Chi^2 test. If we identify substantial heterogeneity, we will report it, and explore possible causes by prespecified subgroup analysis. When there are few studies, we will use caution in applying the thresholds below to interpret statistical heterogeneity.

We will use this approximate guide for the interpretation of an I^2 value (Deeks 2021)

1. I^2 value 0% to 40%: might not be important
2. I^2 value 30% to 60%: may represent moderate heterogeneity
3. I^2 value 50% to 90%: may represent substantial heterogeneity
4. I^2 value 75% to 100%: considerable heterogeneity

We will keep in mind that the importance of the I^2 value depends on the (i) magnitude and direction of effects, and (ii) strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a confidence interval for I^2). Uncertainty in the value of I^2 is substantial when fewer studies are included in the meta-analysis (Deeks 2021).

We will interpret the Chi^2 test with $P \leq 0.10$ as evidence of statistical heterogeneity.

If we identify substantial heterogeneity, we will report it and investigate possible causes, by following the recommendations in section 10.10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021).

Assessment of reporting biases

We will create and examine a funnel plot to explore possible small study biases, if we have at least 10 studies in a meta-analysis. In interpreting funnel plots, we will examine the possible reasons for funnel plot asymmetry, as outlined in Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions,* and relate this to the results of the review. If we are able to pool more than 10 trials, we will undertake formal statistical tests to investigate funnel plot asymmetry, and will follow the recommendations in section 13.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2021).

To assess outcome reporting bias, we will check trial protocols against published reports. For studies published after 1 July 2005, we will screen ClinicalTrials.gov and WHO ICTRP trial registers for the a priori trial protocol. We will evaluate whether selective reporting of outcomes is present.

Data synthesis

We will perform meta-analyses if the treatments, participants, underlying clinical question, and timing of assessments are similar enough for pooling to make sense. We will use the random-effects model for the meta-analysis, and the fixed-effect model for the sensitivity analyses. In the primary analysis, we will include all studies, regardless of the risk of bias. If the included studies do not allow pooling of data, we will present the results in a narrative format.

Subgroup analysis and investigation of heterogeneity

If there are sufficient data, we will conduct subgroup analyses to assess if pain and physical function differ for different subgroups, listed as follows:

1. Different BE formulation types: non-bio-enhanced extracts or bio-enhanced extracts compared to placebo. The bio-enhanced formulations of BE may have increased bioavailability, and thus, may show better protective effects (Sengupta 2011).

We will use the formal test for subgroup intersection in Review Manager 2020, and interpret the results as advised in section 10.11.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021). We will compare the magnitude of the effect between subgroups by assessing the overlap between CIs of the summary effect estimates, where non-overlapping CIs indicate statistical significance.

Sensitivity analysis

We plan to carry out the following sensitivity analyses for the main comparison (BE versus placebo) to investigate the robustness of the treatment effect on pain and physical function:

1. Impact of including studies with high or unclear risk of selection, detection, and attrition biases
2. Impact of including studies with imputed data

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table for the following major outcomes:

1. Pain
2. Physical function
3. Health-related quality of life
4. Participant-reported global assessment of success
5. Withdrawals due to adverse events
6. Serious adverse events
7. Adverse events

The comparison in the first summary of findings table will be BE versus placebo. The comparisons for other summary of findings tables will be BE versus standard care, no treatment, or waiting-list control; and BE versus NSAIDs.

We will follow the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapters 14 and 15 to interpret results, and will distinguish between a lack of evidence of effect and a lack of effect (Schünemann 2021; Schünemann 2021a). We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice; our implications for research will suggest priorities for future research, and outline the remaining uncertainties in the area.

Two authors (ZW and AS) will independently assess the certainty of the evidence, with disagreements resolved by discussion with the senior review author (BA). We will use the five GRADE considerations (study limitations (overall risk of bias), consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence, based on the studies that contribute data to the analyses for each prespecified outcome. We will report the certainty of evidence as high, moderate, low, or very low. We will justify, document, and incorporate our judgements into the reporting of results for each outcome.

We will use GRADEpro software to prepare and display the summary of findings tables (GRADEpro GDT). We will justify all decisions to downgrade the certainty of evidence for each outcome using footnotes, and we will make comments to aid the reader's understanding of the review when necessary.

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APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Osteoarthritis] explode all trees
#2 (osteoarthr*):ti,ab,kw
#3 (*arthrosis):ti,ab,kw
#4 (arthritis, degenerative):ti,ab,kw
#5 #1 OR #2 OR #3 OR #4

#6 MeSH descriptor: [*Boswellia*] explode all trees

#7 (*Boswellia*):ti,ab,kw

#8 (serrata):ti,ab,kw

#9 (aflapin):ti,ab,kw

#10 #6 OR #7 OR #8 OR #9

#11 #5 AND #10

MEDLINE Ovid SP

1	exp osteoarthritis/
2	osteoarthr$.tw.
3	(degenerative adj2 arthritis).tw.
4	arthrosis.tw.
5	or/1-4
6	exp *Boswellia*/
7	*Boswellia*.tw.
8	serrata.tw.
9	aflapin.tw.
10	or/6-9
11	5 and 10

Embase

1	exp osteoarthritis/
2	osteoarthr$.tw.
3	(degenerative adj2 arthritis).tw.
4	arthrosis.tw.
5	or/1-4
6	exp *Boswellia*/ or exp *Boswellia* serrata/ or exp *Boswellia* serrata extract/
7	*Boswellia*.tw.
8	serrata.tw.
9	aflapin.tw.
10	or/6-9
11	5 and 10

Chinese databases search strategies:

China Network Knowledge Infrastructure (CNKI)
(SU = 乳香+薰陆+马尾香+乳头香+乳香酸) and (SU = 关节炎+骨关节炎+骨性关节炎+退化性关节炎+退行性关节炎+关节病+髋关节骨关节炎+髋关节病+膝关节炎+膝关节病+痹症+骨痹+膝痹+痹病)

(Continued)

Chinese Scientific Journals Database (VIP)
任意字段=乳香+薰陆+马尾香+乳头香+乳香酸 AND 任意字段=关节炎+骨关节炎+骨性关节炎+退化性关节炎+退行性关节炎+关节病+髋关节骨关节炎+髋关节病+膝关节炎+膝关节病+痹症+骨痹+膝痹+痹病

Wan Fang data
主题: (乳香+薰陆+马尾香+乳头香+乳香酸) * 主题: (关节炎+骨关节炎+骨性关节炎+退化性关节炎+退行性关节炎+关节病+'髋关节骨关节炎'+'髋关节病'+'膝关节炎'+'膝关节病'+'痹症'+'骨痹'+'膝痹'+'痹病')

SinoMed
("乳香"[常用字段:智能] OR "薰陆"[常用字段:智能] OR "马尾香"[常用字段:智能] OR "乳头香"[常用字段:智能] OR "乳香酸"[常用字段:智能]) AND("关节炎"[常用字段:智能] OR "骨关节炎"[常用字段:智能] OR "骨性关节炎"[常用字段:智能] OR "退化性关节炎"[常用字段:智能] OR "退行性关节炎"[常用字段:智能] OR "关节病"[常用字段:智能] OR "髋关节骨关节炎"[常用字段:智能] OR "髋关节病"[常用字段:智能] OR "膝关节炎"[常用字段:智能] OR "膝关节病"[常用字段:智能] OR "痹症"[常用字段:智能] OR "骨痹"[常用字段:智能] OR "膝痹"[常用字段:智能] OR "痹病"[常用字段:智能])

Clinical trials registers search strategies:

WHO ICTRP (Standard search)
Osteoarthr* AND *Boswellia** OR Osteoarthr* AND boswellic* OR coxarthrosis AND *Boswellia** OR coxarthrosis AND boswellic*OR gonarthrosis AND *Boswellia** OR gonarthrosis AND boswellic* OR arthrosis AND *Boswellia** OR arthrosis AND boswellic* OR arthritis, degenerative AND *Boswellia** OR arthritis, degenerative AND boswellic*

ClinicalTrials.gov (Advanced search)
(osteoarthritis OR osteoarthr* OR arthrosis OR arthritis, degenerative OR gonarthrosis OR coxarthrosis) [DISEASE] AND (*Boswellia** OR boswellic*) [TREATMENT]

CONTRIBUTIONS OF AUTHORS

ZW: drafting of protocol, designing the search strategies for Chinese databases (CNKI, VIP, Wan Fang data, and SinoMed), manuscript writing, approval of the final manuscript

AS: drafting of protocol, manuscript writing, approval of the final manuscript

GJ: drafting of protocol, manuscript writing, approval of the final manuscript

DA: drafting of protocol, manuscript writing, approval of the final manuscript

LL: drafting of protocol, manuscript writing, approval of the final manuscript

SH: drafting of protocol, approval of the final manuscript

PBG: drafting of protocol, approval of the final manuscript

CD: drafting of protocol, manuscript writing, approval of the final manuscript

BA: conceiving the project, drafting of protocol, manuscript writing, approval of the final manuscript, corresponding author

DECLARATIONS OF INTEREST

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