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Curcuma longa (turmeric) or its active ingredients for osteoarthritis (Protocol)

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[Intervention Protocol]

Curcuma longa (turmeric) or its active ingredients for osteoarthritis

Ivan Shirinsky[1], Valery Shirinsky[1], Katerina Filatova[1], Zeyu Yu[2], Yuan Chi[3], Jacqueline Y Thompson[4], Chris Bleakley[5]

[1]Laboratory of Clinical Immunopharmacology, Federal State Budgetary Scientific Institution Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation. [2]Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China. [3]Yealth Network, Beijing Yealth Technology Co., Ltd, Beijing, China. [4]Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK. [5]School of Sport, Ulster University, Newtownabbey, UK

Contact address: Ivan Shirinsky, ivan.shirinsky@gmail.com.

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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 *Curcuma longa* extracts or curcuminoids for osteoarthritis.

BACKGROUND

Description of the condition

Osteoarthritis (OA) is a common disease of the joint (Lawrence 2008), and presents a major public health challenge. OA prevalence has risen during the last decade (Murray 2012), and it is now one of the leading causes of global disability (Cross 2014; Moradi-Lakeh 2017). The social cost of osteoarthritis is estimated to be between 0.25% and 0.50% of a country's gross domestic product (GDP) (Puig-Junoy 2015). With increasing rates of obesity in an aging population, the prevalence of arthritis, including OA, will reach 25% of the adult population by 2030 (Hootman 2006).

The aetiology of OA is multifactorial, and its pathophysiology is a complex interplay of genetic and environmental factors. Older age, obesity and joint trauma are common predictors of worse outcomes in OA (Hunter 2019). Recently, OA has been framed as an evolutionary 'mismatched' disease, mediated by modern-day lifestyle factors such as low physical activity and modern diets — both of which lead to obesity. These factors accelerate the degradation of cartilage and synovial inflammation or contribute to dysbiosis, increased gut leakage and low-grade systemic inflammation, which in turn leads to local damage of the joint tissues (Berenbaum 2018).

The main clinical manifestations of OA are pain and functional limitations in the affected joints. The knee and hip joints are the most commonly affected and present important primary symptomatic OA locations for evaluations (Doherty 2019).

Following recent clinical guidelines (Bannuru 2019; Kolasinski 2020), non-pharmacological modalities have been recommended as core treatments for OA, particularly exercise, weight loss and self-management programmes. Due to the small to moderate effects of these interventions, they are often used in conjunction with recommended pharmacological treatment, such as systemic non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular glucocorticoids (Bannuru 2019; Kolasinski 2020).

Description of the intervention

Curcumin is the main component of turmeric (*Curcuma longa,* synonyms: *Amomum curcuma*; *C brog*; *C domestica*; *C longa var. vanaharidra; C ochrorhiza*; *C soloensis*; *C tinctoria*; *Kua domestica*; *Stissera curcuma* (www.theplantlist.org/)). It belongs to the ginger family *Zingiberaceae* (Yang 2019). The spice derived from rhizome of *C longa* had been extensively used in Oriental Medicine for centuries before it was introduced to the Western world (Hatcher 2008). *C longa* and its constituents have been used in many formulations as dietary supplements and for many indications, including arthritis, eye diseases, skin cancer, infectious diseases, wounds, and gastrointestinal ailments (Gupta 2013). The main active constituents of the rhizome of *C longa* and other *Curcuma spp*. are curcumin, demethoxycurcumin and bisdemethoxycurcumin. These compounds belong to the group of diarylheptanoids and are collectively called curcuminoids (Lestari 2014). In addition, the polysaccharide fraction of the *C longa* extract has biological activity (Chandrasekaran 2013), and has an analgesic effect in healthy adults (Raj 2020).

Curcumin can be administered as turmeric, concentrates of turmeric, substantially pure (95%) curcuminoids or curcumin alone. In the literature, these distinct entities are sometimes described collectively as 'curcumin', leading to confusion. There are also many formulations of turmeric or its active ingredients, with various techniques used to increase the bio-availability of curcuminoids, e.g. the addition of lipids, adsorption and dispersion on matrices and particle size reduction (Stohs 2020).

Tolerability and safety of turmeric/curcumin for various indications have been extensively examined across 26 double-blind, randomised, placebo-controlled trials (Soleimani 2018). No significant levels of toxicity were identified. Adverse events identified were flatulence, hypertension, tachycardia, redness of the tongue, itching, nausea, diarrhoea, changes in liver enzymes and biochemical parameters in the blood, and stomachache. The studies reported acceptable safety levels for oral curcumin even at high doses (up to a dose of 6 g/day). However, no study assessed the use of bioavailable formulations, and the longest trial duration was six months (Soleimani 2018).

How the intervention might work

Curcuminoids have an extensive range of molecular targets (Zhou 2011), many of which are relevant in OA, e.g. nuclear factor kappa B (NF-κB), various pro-inflammatory cytokines and cyclooxygenase-2 (COX-2). NF-κB regulates the synthesis of many pro-inflammatory mediators and participates in various OA-associated events, including chondrocyte catabolism, chondrocyte survival, and synovial inflammation (Choi 2019). Cytokines play a role in the synovial inflammation associated with OA, and many cytokines (including TNF-α, IL-1, IL-6) have pro-algesic effects in osteoarthritic joints (Miller 2014). COX-2 is also a well-established target in OA pain management (Laine 2008), with the use of COX-2 inhibitors supported by international guidelines (Bannuru 2019).

The biological activity of curcumin/curcuminoids has been contested as possibly due to their belonging to pan-assay interference compounds (PAINS). PAINS are compounds that are able to show false activity in multiple types of assays by interfering with the assay readout, rather than through specific compound/target interactions (Nelson 2017). However, others argue that current detection methods used to assess curcumin target engagement may not be adequate (Heger 2017).

Although curcuminoids are poorly absorbed within the intestine (Anand 2007), they may restore gut microbiota, enhancing the growth of beneficial bacteria and suppressing the growth of pathogenic bacteria (Di Meo 2019). This is particularly relevant to the management of OA as this disorder has been linked with gut dysbiosis (loss or gain of bacteria that either promote health or disease). In OA, the presence of some bacterial families in the gut is associated with more pain and joint destruction (Berthelot 2019).

Curcuma and its components are manufactured in various forms, including tablets, capsules, liquid-filled capsules, softgels, drops, liquid, and soft chews (Dietary Supplement Label Database 2021).

Why it is important to do this review

NSAIDs are the most commonly-used pharmacological treatment for OA, but their clinical effects are offset by side effects and safety issues (Cooper 2019; Wongrakpanich 2018). Current guidelines recommend the use of NSAIDs for the shortest length of time possible (Kolasinski 2020).

This gap in pharmacological management highlights the importance of evaluating alternative pharmacological treatments of OA. Herbal medicines, including curcumin, are widely used in the management of arthritic symptoms (Rashrash 2017), but their safety and efficacy remain unclear (Cameron 2014). A recent meta-analysis suggested that curcumin had large and clinically important effects on pain and physical function. The standardised mean difference (SMD) for pain was −1.19 (95% confidence interval (CI) −1.93 to −0.45), and the SMD for physical function was −1.13 (95% CI −1.8 to −0.46) (Liu 2018). A previous 2014 Cochrane Review on herbal therapies in OA included one study that compared *C domestica* with ibuprofen. The study showed that *C domestica* has comparable efficacy to ibuprofen in the treatment of osteoarthritic pain and pain-related functional impairment. However, this evidence was at a high risk of bias due to incomplete outcome data, selective reporting and the diagnosis of OA not being established at baseline (Cameron 2014). Recent publications warrant the updating of this review, as it has the potential to inform OA treatment guidelines and recommendations.

This review will be conducted according to the guidelines recommended by the Cochrane Musculoskeletal Group Editorial Board (Ghogomu 2014).

OBJECTIVES

To assess the benefits and harms of *Curcuma longa* extracts or curcuminoids for osteoarthritis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include studies described as randomised controlled trials (RCTs), irrespective of whether they report their exact method of randomisation or not, trials using quasi-randomised methods of participant allocation, and cross-over trials. We will include full-text reports, abstracts and unpublished data of eligible studies. There will be no language restriction.

Types of participants

We will include participants with osteoarthritis in any joint. Studies will be eligible that classify knee, hip or hand OA according to the American College of Rheumatology (ACR) criteria (Altman 1986; Altman 1990; Altman 1991), the European League Against Rheumatism (EULAR) criteria (Zhang 2009; Zhang 2010), or similar criteria, as reported in the trials.

We will include studies that only have a subset of eligible participants if they report outcomes for eligible participants separately, or at least 75% of the study population consists of relevant participants.

Types of interventions

We will include studies that evaluate orally-administered *C longa* extracts or curcuminoids in comparison with a placebo, no treatment, or another control. We will only consider oral formulations of curcumin, as this review is an update of a subsection of the previous Cochrane Review *Oral herbal therapies for treating osteoarthritis* (Cameron 2014). Studies of curcuminoids with or without bioavailability adjuvants, but not limited to piperine, will be eligible for inclusion. We will not include studies of formulations containing curcumin/curcuminoid combinations with other active compounds, such as *Boswellia serrata*.

Specific comparisons to be considered include:

1. *C longa* extracts or curcuminoids versus placebo;
2. *C longa* extracts or curcuminoids versus standard care/no intervention/waiting-list control;
3. *C longa* extracts or curcuminoids versus NSAID analgesics;
4. *C longa* extracts or curcuminoids versus non-NSAID analgesics;
5. *C longa* extracts or curcuminoids versus supplements (nutraceuticals);
6. *C longa* extracts or curcuminoids versus any other active comparator.

We will include the following co-interventions, provided they are not part of the randomised treatment and are included equally in both arms.

1. Rescue analgesia, including but not limited to paracetamol (acetaminophen).
2. Regular use of NSAIDs, COX-2 inhibitors, or paracetamol at stable doses for at least 14 days before enrolment and throughout the study; this is based on the minimal timeframe required for NSAIDs and COX-2 inhibitors to induce clinically important effects (da Costa 2017).

Types of outcome measures

The choice of outcomes to be considered is based on the recommendations for outcomes in OA trials (Altman 1996; Bellamy 1997). We have chosen either core or highly-recommended 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

If the studies report several measures for pain, we will use the hierarchy suggested by Juni 2006 and extract the measure that ranks highest in the following list.

1. Pain overall
2. Pain on walking
3. WOMAC (Western Ontario and McMaster Universities Arthritis Index) pain subscale
4. Pain on activities other than walking
5. WOMAC global scale
6. Lequesne osteoarthritis index global score
7. Other algo-functional scale
8. Participant's global assessment
9. Physician's global assessment

If studies provide more than one physical function scale, we will extract data using the following hierarchy.

1. Global disability score
2. Walking disability
3. WOMAC disability sub-score
4. Composite disability scores other than WOMAC
5. Disability other than walking
6. WOMAC global scale
7. Lequesne osteoarthritis index global score
8. Other algo-functional scale

In the case that a study reports more than one quality of life scale, we will extract data according to the following hierarchy.

1. Short-Form Health Survey (SF-36) (mental health component);
2. EQ-5D (EuroQol 5-dimensions 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

We will not assess any minor outcomes.

Timing of outcome assessment

We will categorise the duration of follow-up as short term (three months or less), medium term (four to six months), and long term (over six months). The primary time point for this study will be short-term follow-up. The outcomes will be assessed from two weeks to four years after commencing treatment. This is based on evidence that the effect of NSAIDS, the main active comparator, occurs within a few weeks of starting treatment (da Costa 2017). If there are multiple time points, we will extract endpoint data at the short-term follow-up (nearest to but not exceeding three months following treatment), intermediate follow-up (nearest to but not exceeding six months following treatment), and long-term follow-up (the latest time point after six months of treatment).

We will not use outcomes as a criterion for including or excluding studies.

Search methods for identification of studies

Electronic searches

We will search the following sources from their inception to the present, with no restriction on the language of publication:

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

We will also conduct a search of ClinicalTrials.gov (www.clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/).

For detailed search strategies, see Appendix 1.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for trial information. To seek information about unpublished or incomplete studies, we will contact relevant individuals/organisations. We will search for errata or retractions of included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed), and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two English-language and two Chinese-language review authors will independently screen de-duplicated records of a set number of the titles and abstracts of all potentially eligible studies in English language and Chinese-language databases. They will code studies retrieved from the search as 'include' (eligible or potentially eligible/unclear) or 'exclude'. Two review authors will retrieve and independently screen full-text reports using the study eligibility criteria for inclusion. We will record reasons for excluding ineligible studies and will resolve disagreements through discussion or, if required, by an arbitrator. We will identify and exclude duplicates and collate multiple reports of the same study 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 allow for adequate completion of the PRISMA flow diagram (Moher 2009), and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which we will pilot on at least one study in the review. We will translate studies reported in non-English language journals before assessment. Two review authors will independently extract study characteristics from included studies. Another review author will spot-check study characteristics for accuracy against the trial report. We will extract the following study characteristics.

1. Methods: study design, the total duration of the study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of the study.
2. Participants: N, mean age, age range, sex, disease duration, the severity of the condition, classification criteria, important baseline data (types of joints affected, presence of synovitis), inclusion criteria, and exclusion criteria.
3. Interventions: intervention and comparison (dosage, frequency, route, duration), concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Characteristics of the design of the trial as outlined below in the Assessment of risk of bias in included studies section.
6. Notes: funding for the trial, and important declarations of interest of trial authors.

Two review authors 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. For continuous outcomes, we will extract the means, standard deviations, and number of participants per treatment group. We will note in the 'Characteristics of included studies' table if studies did not report outcome data in a usable way, if we transformed the data, or if we estimated data from a graph. We will resolve disagreements by consensus or by involving a third person (CB). One review author will transfer data into the Review Manager file (Review Manager 2020). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports.

We will use Plot Digitizer software to extract data from graphs or figures, in duplicate (Plot Digitizer 2015).

For outcomes measured using more than one tool, we will base our choice of measure on the prespecified hierarchy for outcomes described in the Types of outcome measures section. If studies report both final values and change from baseline values for the same outcome, we will extract the final values. If studies report both unadjusted and adjusted values for the same outcome, we will extract the adjusted values. Where studies analyse data both on the intention-to-treat (ITT) population and another sample (e.g. per-protocol, as-treated), we will extract the ITT values for both efficacy and safety outcomes.

Main planned comparisons

Our primary comparison will be *C longa* extracts or curcuminoids versus placebo. Our other main comparisons will be as follows.

- *C longa* extracts or curcuminoids versus standard care/no intervention/waiting-list control
- *C longa* extracts or curcuminoids versus NSAID analgesics
- *C longa* extracts or curcuminoids versus non-NSAID analgesics

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias for each study according to the Cochrane risk of bias tool, version 2 (RoB 2) (Sterne 2019). We will resolve any disagreements by discussion or by involving another author. We will assess the risk of bias in individually randomised trials (including cross-over trials) according to the following domains.

1. Bias arising from the randomisation process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result

The possibility of identifying cluster-randomised trials is small. However, if we find cluster-randomised trials, we will also assess their risk of bias with RoB 2. RoB 2 includes an additional domain for cluster-randomised trials: (1b) bias arising from identification or recruitment of individual participants within clusters (Sterne 2019).

We will grade each potential source of bias as high, some concerns, or low risk, and provide a quote from the study report together with a justification for our judgement in the risk of bias table. Where information on the risk of bias relates to unpublished data or correspondence with a trialist, we will note this 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 different key outcomes, and will judge self-reported outcomes and assessor-reported outcomes separately. In addition, we will consider the impact of missing data by key outcomes.

Our effect of interest is assignment to the intervention at baseline (the ITT effect). 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 the risk of bias tool to provide summary assessments of the risk of bias.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse the continuous outcomes (pain, function, and quality of life) as mean difference (MD) with 95% confidence intervals (CIs) if the studies use the same scale to measure an outcome. For outcomes where the studies use different scales, we will calculate the standardised mean difference (SMD) instead, with corresponding 95% CIs. We will back-translate SMDs to a typical scale (e.g. 0 to 100 mm for visual analogue scale (VAS) pain, 0 to 100 for normalised WOMAC function), by multiplying the SMD by an average among-person standard deviation (e.g. the standard deviation of the control group at baseline from the most representative trial) (Schünemann 2019a). We will enter data presented as a scale with a consistent direction of effect across studies.

We will calculate the absolute change by dividing the mean difference by the scale of the measure and express this as a percentage. We will calculate the relative difference as the absolute benefit (mean difference) divided by the baseline mean of the control group, and express this as a percentage.

For pain and function, we will calculate the number needed to treat for an additional beneficial outcome (NNTB) using the Wells calculator (available at the CMSG Editorial office, musculoskeletal.cochrane.org/). We will use the minimal clinical important difference (MCID) in the calculation of NNTB. We will assume an MCID of 1.5 points on a 10-point scale for pain; and 10 points on a 100-point scale for function or disability.

In the 'Effects of interventions' results section and the 'What happens' column of the summary of findings table, we will provide the absolute per cent change, the relative per cent change from baseline, and the NNTB (we will only provide the NNTB when the outcome shows a clinically significant difference).

We will analyse safety data as risk ratios (RRs) or Peto odds ratios when an outcome is a rare event (approximately less than 10%), and present them with their 95% CIs. We will calculate the number needed to treat for an additional harmful outcome (NNTH) from the control group event rate and the relative risk using the Visual Rx

NNT calculator (Cates 2008). For dichotomous outcomes, 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. We will calculate the relative per cent change as the RR - 1 and express this as a percentage.

In the 'Effects of interventions' results section and the 'What happens' column of the summary of findings table, we will provide the absolute per cent change, the relative per cent change from baseline, and the NNTH (we will only provide the NNTH when the outcome shows a clinically significant difference).

Unit of analysis issues

Where a single trial reports multiple trial arms, we will include only the relevant arms. If we combine two comparisons (e.g. drug A versus placebo and drug B versus placebo) in the same meta-analysis, we will halve the control group to avoid double-counting. If we find any cross-over trials, we will only analyse the first trial period to avoid any cross-over effect of the intervention (Higgins 2019).

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics, or to obtain missing numerical outcome data for abstracts or unpublished data for study participants. When this is not possible, and missing data might introduce bias, we will explore the impact of including such studies in the overall assessment of results by performing a sensitivity analysis. We will clearly describe any assumptions and imputations to handle missing data, and we will explore the effect of imputation by conducting 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 a trial does not present the number of participants analysed for each time point, we will use the number of randomised participants in each group at baseline.

Where possible, we will compute missing standard deviations from other statistics such as standard errors, CIs or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions, section 6.5.2.3* (Higgins 2019). If we cannot calculate standard deviations, we will impute them (e.g. from other studies in the meta-analysis).

Assessment of heterogeneity

We will assess clinical and methodological diversity in terms of participants, interventions, outcomes and study characteristics for the included studies. We will achieve this by consideration of the information in the data extraction tables. We will assess statistical heterogeneity by visual inspection of the forest plot to look for obvious differences in results between the studies, and by using the I^2 and Chi^2 statistics.

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2019), the interpretation of an I^2 value of 0% to 40% might 'not be important'; 30% to 60% may represent 'moderate' heterogeneity; 50% to 90% may represent 'substantial' heterogeneity, and 75% to 100% represents 'considerable' heterogeneity. As noted in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2019), we will keep in mind that the importance of I^2 depends on (i) the magnitude and direction of effects, and (ii) the strength of evidence for heterogeneity.

When interpreting the Chi^2 test, we will consider a P value ≤ 0.10 to indicate evidence of statistical heterogeneity.

If we identify substantial heterogeneity, we will report it and investigate possible causes by following the recommendations in section 10.11 of the *Cochrane Handbook* (Deeks 2019).

Assessment of reporting biases

We will create and examine a funnel plot to explore possible publication bias. In interpreting funnel plots, we will examine the different possible reasons for funnel plot asymmetry as outlined in section 13.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2019), and relate this to the results of the review. If up to 10 trials are available, 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 2019).

To assess the impact of outcome reporting bias, we will check trial protocols against published reports. For studies published after 1 July 2005, we will screen the WHO ICTRP (www.who.int/ictrp/en/) for the a priori trial protocol. We will evaluate whether selective reporting of outcomes is present.

Data synthesis

We will undertake meta-analyses only where this would be meaningful, i.e. if the treatments, participants, underlying clinical question, and timing of assessments are similar enough for pooling to make sense. We will use random-effect models for the meta-analysis and perform a sensitivity analysis with fixed-effects models. We will perform the primary analysis of self-reported outcomes for this review on all trials, independent of the apparent risk of bias.

If a meta-analysis is not possible, we will provide a structured report of intervention effects without synthesis.

Subgroup analysis and investigation of heterogeneity

If there are sufficient data, we will carry out the following subgroup analyses using the outcomes of pain and function.

- Anatomical location of OA (knee, hip, hand, combination of these locations). We will analyse these subgroups due to possible differences in the pathogenesis of OA in different joint locations.
- Duration of follow-up (short term (3 months or less), medium term (four to six months), and long term (over six months)).

We will use the formal test for subgroup interactions in Review Manager (Review Manager 2020), and interpret subgroup analyses with caution as advised in section 10.11.2 of the *Cochrane Handbook* (Deeks 2019). We will compare the magnitude of the effects between the subgroups by assessing the overlap between

CIs of summary estimates. Non-overlap of the CIs indicates statistical significance.

Sensitivity analysis

We plan to carry out the following sensitivity analysis to investigate the robustness of the treatment effect on pain and function outcomes.

- Only including studies with an overall low risk of bias

We will restrict sensitivity analyses to the following comparisons, for pain and function at the primary time point (three months, or the nearest time point for which data are available):

- *C longa* extracts or curcuminoids versus placebo;
- *C longa* extracts or curcuminoids versus NSAID analgesics; and
- *C longa* extracts or curcuminoids versus non-NSAID analgesics.

Interpreting results and reaching conclusions

We will follow the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions*, chapter 15 (Schünemann 2019b), for interpreting results, and distinguish a lack of evidence of effect from a lack of effect. We will base our conclusions only on findings from the quantitative synthesis or structured report 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 what the remaining uncertainties are in the area.

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table using the following primary 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 outcomes one to four we will use short-term (three months or less) follow-up time points, for outcomes five to seven we will use the longest follow-up time points.

The comparison in the first summary of findings table will be *C longa* extracts or curcuminoids versus placebo. Other comparators planned for other summary of findings tables will be standard care/no intervention/waiting-list control, NSAID analgesics, and non-NSAID analgesics. Two authors will independently assess the certainty of the evidence. The tables will contain key information regarding the certainty of the evidence, the magnitude of the effects of the interventions, and the sum of the available data for the main outcomes (Schünemann 2019a). We will assess the certainty of the evidence using the GRADE criteria. We will use GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the evidence contributing data to the analyses for the prespecified outcomes. We will report the certainty of evidence as high, moderate, low, or very low (Atkins 2004). The overall RoB 2 judgements for the specified outcomes will inform GRADE assessments. We will make a decision to downgrade GRADE assessment using the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019a). We will downgrade by one level if a domain is rated 'some concerns' and potential limitations are likely to lower confidence in the estimate of effect. We will downgrade by one level if the domain is rated 'high risk of bias' and there is a crucial limitation for one criterion, or some limitations for multiple criteria, which are sufficient to lower confidence in the estimate of effect. We will downgrade by two levels if the domain is rated 'high risk of bias' and there is a crucial limitation for one or more criteria that is sufficient to substantially lower confidence in the estimate of effect (Schünemann 2019a).

We will use methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019a). We will use GRADEpro software to prepare the summary of findings tables (GRADEpro GDT). We will justify all decisions to downgrade the certainty of the evidence for each outcome using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

We are unlikely to provide a summary of findings table for every possible comparison identified, but will address the most relevant comparisons to inform current management.

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The methods section is based on the standard Cochrane Musculoskeletal Group Protocol Template. Peer reviewer Dr Benny Antony Senior Research Fellow, Menzies Institute for Medical Research, University of Tasmania and Ms Maureen Smith, Cochrane Consumer, are acknowledged.

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APPENDICES

Appendix 1. Search strategies

MEDLINE (PubMed format)
#1 ((osteoarthritis[mh]) OR (osteoarthr* [tiab] OR (arthrosis [tiab]) OR arthritis, degenerative [tiab])) AND ((curcum*[mh]) OR (turmeric[mh] OR curcum* [tiab] OR turmeric [tiab] OR zedoary [tiab] OR diferuloylmethane [tiab]))

MEDLINE (Ovid SP)
1. osteoarthritis.sh,tw.

(Continued)

2. (osteoarthr* or arthrosis or arthritis).tw.

3. "*arthrosis".tw.

4. 1 or 2 or 3

5. Curcuma.sh.

6. (curcum* or turmeric or zedoary or diferuloylmethane).tw.

7. 5 or 6

8. 4 and 7

EMBASE

1. exp osteoarthritis/

2. osteoarthr*.ti,ab.

3. arthrosis.ti,ab.

4. arthritis, degenerative.ti,ab.

5. or/1-4

6. exp curcum*/

7. exp turmeric/

8. curcum*.ti,ab.

9. turmeric.ti,ab.

10. zedoary.ti,ab.

11. diferuloylmethane.ti,ab.

12. or/6-11

13. and/5,12

Cochrane Central Register of Controlled Trials

#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: [Curcuma] explode all trees
#7	MeSH descriptor: [Diarylheptanoids] explode all trees
#8	(curcum*):ti,ab,kw
#9	(turmeric):ti,ab,kw
#10	(zedoary):ti,ab,kw
#11	(diferuloylmethane):ti,ab,kw

(Continued)

#10	#6 OR #7 OR #8 OR #9
#11	#5 AND #10

WHO ICTRP (Standard search)

Osteoarthr* AND Curcum* OR

Osteoarthr* AND Turmeric OR

coxarthrosis AND Curcum* OR

coxarthrosis AND Turmeric OR

gonarthrosis AND Curcum* OR

gonarthrosis AND Turmeric OR

arthrosis AND Curcum* OR

arthrosis AND Turmeric OR

arthritis, degenerative AND Curcum* OR

arthritis, degenerative AND Turmeric

ClinicalTrials.gov (Advanced search)

(osteoarthritis OR osteoarthr* OR arthrosis OR arthritis, degenerative OR gonarthrosis OR coxarthrosis) [DISEASE] AND (Curcum* OR Turmeric) [TREATMENT]

China Network Knowledge Infrastructure (CNKI)

(SU = 姜黄+姜黄素+郁金+莪术+莒蒲) 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)

Chinese Scientific Journals Database (VIP)

任意字段=姜黄+姜黄素+郁金+莪术+莒蒲 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: (姜黄+姜黄素+郁金+莪术+莒蒲) * 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

("姜黄"[常用字段:智能] OR "姜黄素"[常用字段:智能] OR "郁金"[常用字段:智能] OR "莪术"[常用字段:智能] OR "莒蒲"[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])

CONTRIBUTIONS OF AUTHORS

IS: Drafting of protocol, manuscript writing, approval of final manuscript, corresponding author

VS: Drafting of protocol, manuscript writing, approval of final manuscript.

KF: Drafting of protocol, manuscript writing, approval of final manuscript

YC: Drafting of protocol, manuscript writing, approval of final manuscript

ZY: Manuscript writing, approval of final manuscript

JYT: Drafting of protocol, manuscript writing, approval of final manuscript

CB: Drafting of protocol, manuscript writing, approval of final manuscript

DECLARATIONS OF INTEREST

IS: No conflict of interest declared

VS: No conflict of interest declared

KF: No conflict of interest declared

ZY: No conflict of interest declared

YC: No conflict of interest declared

JYT: No conflict of interest declared

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NOTES

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