Peer-review Comments and Author Responses

Reviewer 1

<u>Abstract</u>

1. *It can be assumed that doctors have an idea of what pain is. Therefore, I would not explain this in an abstract.*

The paragraph has been delated and changed. See below:
"Pain is a significant, multifactorial problem worldwide."

2. *I would use the word analgesic effects. Antinociceptive: describes only part of the pain process, but the included clinical studies focus on the entire "pain control".*

The word has been changed to "analgesic". See below:
"This mini review aimed to provide a summary of the analgesic effect of curcumin in the literature."

3. *Please use the complete name "Cochrane risk-of-bias tool for randomized trials (RoB 2)"*

Has been changed.
"Risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB2) tool."

4. *That is very vague. Here should be facts that you have found. And then your disscusion should then be based on these facts.*
Has been changed.
"All of them reported an effect of curcumin on knee OA pain reduction compared to placebo or similar effect to other pain medicines. Results regarding other pain categories are inconclusive with two studies showing no effect of curcumin. The RoB assessment results in five studies with overall low risk of bias and eight with high risk."

5. *Information regarding the limitations of the mini-review is missing*
"Within the limitations of this mini-review, curcumin has the potential to be an effective agent for treating pain, particularly when used to manage knee OA-related pain."

6. *Based on the results of this study, no such conclusion can be drawn.*

Has been changed.
"Curcumin has the potential to be an effective agent for treating pain, particularly when used to manage knee OA-related pain. However, further studies on the impact of curcumin, particularly in other pain categories are needed."

7. *This should be omitted.*

Has been deleted.
"However, further studies on the impact of curcumin, particularly in other pain categories are needed."

<u>Introduction</u>
8. *The definition of pain is a very complex subject, I would not start my article with it. If you want to take it, please take the current definition: An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.Your definition that pain is caused by tissue damage is probably no longer widely accepted.*

Definition has been changed. "Across all age groups, pain is a significant clinical, social, and financial burden, with 1% to over 60% reported estimates of monthly prevalence (Henschke 2015). Pain is an unpleasant sensory and emotional experience associated with or resembling that is associated with actual or potential tissue damage."

9. *Your readers are mainly medical professionals. For them, this information is part of their general knowledge. Therefore, this information should not be listed here.*

Reviewed and corrected. "Steroidal and nonsteroidal drugs (NSAIDs) are common management strategies for pain. However, most of these drugs are associated with side effects, and the risk of misuse and dependence (Hoffman et al., 2019)."

10. *I would not use "traditional analgesics" for steroidal and nonsteroidal medications when referring to traditional Asian medicine next.*

Has been changed. "Commonly used analgesics"

11. *It remains unclear why you think it became "socially" necessary? And why in "recent years"? I would leave that out.*

Dear Reviewer, then you for your comment. We think it is necessary to mention the social aspect of pain, especially chronic pain. It is social necessity to manage pain of these individuals as there is lack of social recognition of chronic pain, that has major impact on GoL of these patients.
Koesling, D., Bozzaro, C. Chronic pain patients' need for recognition and their current struggle. Med Health Care and Philos 24, 563–572 (2021). https://doi.org/10.1007/s11019-021-10040-5
" Therefore, the development of safe and effective alternatives to commonly used analgesics has become a clinical and social necessity. "

12. *I would not use the word significant here. I would use the word significant only when judging on the result of a static test.*

Dear Reviewer, then you for your comment. In fact, the results of the cited study by Zhao et al. 2021 has been statistically significant, therefore this formulation was used and not changed, see the citation from the original text below:
"For behavioral tests, the PWTs between groups were analyzed using one-way ANOVA, followed by Dunnett's or Bonferroni's post hoc test. For RT-PCR and ELISA results, t-test was used to compare differences between groups. The difference was considered significant when $P < 0.05$."
Zhao, G., Shi, Y., Gong, C., Liu, T., Nan, W., Ma, L., Wu, Z., Da, C., Zhou, K., & Zhang, H. (2021). Curcumin Exerts Antinociceptive Effects in Cancer-Induced Bone

Pain via an Endogenous Opioid Mechanism. Frontiers in Neuroscience, 15, 696861. https://doi.org/10.3389/fnins.2021.696861

13. *If this is the aim of your review, this should be part of your abstract.*

Pain categories have been added to the abstract and specified in the aim of this study. "Randomized controlled trials (RCT) on the effect of oral curcumin on pain control in five different categories (1) arthritis, (2) muscle soreness, (3) abdominal pain, (4) oral pain, and (5) other types of pain were included."
"In this mini-review, we aim to highlight the antinociceptive effects of curcumin on somatic, visceral, and neuropathic pain differed in the following categories: arthritis, muscle soreness, abdominal pain, oral pain, and other types of pain."

Material & Method
14. *I would already include the name of the databases here.*

We have included the name of the data bases.
"A comprehensive literature search was conducted using the following databases: Cochrane Central Register of Controlled Trials and MEDLINE (PubMed)."

15. *Did both perform a full screening of both databases to ensure quality, or was the screening split between two people to reduce work?*

Two authors independently performed the full screening of both databases.

16. *So usually only one investigator decides on the quality of a paper? - Later you specify: "Each article was assessed by two investigators and triple-checked in case of differences."*

This was done by two authors, and if needed the third was asked, to ensure that the assessment of the quality was accurate.
"The first screening process consisted of two independent investigators screening the titles and abstracts according to the pre-specified eligibility criteria. Subsequently, secondary screening and quality assessment of the full text were performed by two investigators. If necessary, a third investigator was consulted to reach the final decision."

17. *Please specify what you mean by: Records removed for other reasons. You can not just remove data.*

Dear Reviewer we have used the Flow Diagram Sample by PRISMA that can be seen at https://estech.shinyapps.io/prisma_flowdiagram/
That includes the reason: "records removed by other reasons" as standard and in accordance with the PRISMA guidelines.

18. *"We aimed to highlight the antinociceptive effects of curcumin on somatic, visceral, and neuropathic pain" -> Why do you choose 5 groups now? If you want to use these groups, you should elaborate on them in your abstract.*

Pain categories have been added to the abstract and specified in the aim of this study.

"Randomized controlled trials (RCT) on the effect of oral curcumin on pain control in five different categories (1) arthritis, (2) muscle soreness, (3) abdominal pain, (4) oral pain, and (5) other types of pain were included."
"In this mini-review, we aim to highlight the antinociceptive effects of curcumin on somatic, visceral, and neuropathic pain differed in the following categories: arthritis, muscle soreness, abdominal pain, oral pain, and other types of pain."

19. *Relative adverbs, please avoid relative adverbs, using numbers is recommended. To ensure the best transparency, please provide at least % and absolute numbers. for example: 5% (15/150)*

20. *Please avoid relative verbs, using numbers is recommended.*

21. *Relative adverbs*

The relative verbs have been changed to total numbers. The phrase have been summarized, and the text rephrased.
"Ten studies describing the effects of curcumin on pain focus on its effect on joint pain and arthritis, with nine studies on knee OA. Five studies evaluated curcumin in comparison with a placebo and found curcumin to be more effective with a significant reduction in pain scores (Lopresti et al. 2021, Madhu et al., 2013, Raj et al., 2020, Thanawala et al., 2021, Panda et al., 2018).The KOSS pain scale, VAS, and WOMAC scores were used. "

22. *To ensure the best transparency, please provide at least % and absolute numbers. for example: 5% (15/150)*

The text has been rewritten and results of more than one study have been summarized thus numbers were omitted.
"Additionally, curcumin showed a good tolerance profile with adverse events that were not statistically different from the placebo, including abdominal pain, bloating, headache, and dyspepsia (Panda et al., 2018, Madhu et al. 2013). ""

23. *I do not think that this conclusion can be reached here. It appears that the conclusions of several studies on this subject have been summarized here in a completely uncritical manner. The trustworthiness of the individual studies was not addressed here at all.*

Conclusion was revised and critical assessment added.
"Of the 10 studies on knee OA and knee joint pain only the study conducted by Raj et al. 2020 was assessed with an overall low risk of bias (Raj et al., 2020). Other nine studies showed overall high risk (5/10) or some concerns (4/10) of bias (Figure 2a). Although many of the analyzed studies (9/20) are related to knee OA pain and show promising results for curcumin there is still a need for high-quality studies with a low risk of bias to gain a general therapeutic recommendation."

24. *Please delete the extra blank space*

Blank space was deleted.)

25. *This is not "concrete proof" ... some evidence*

The sentence was changed.
"These findings provided the first evidence that curcumin may be used to prevent and treat DOMS caused by strenuous exercise.

26. *Seems to be.*

The sentence was changed.
"There seems to be an overall positive effect of curcumin intake on muscle soreness; however, further studies are needed in this field.

27. *You superficially and uncritically summarize the results of many, very different studies. This is not usefull. You should also address the results of your bias risk assessment somehow. I can imagine that studies that do not show a significant result will not be published on this topic.*

Thank you for your comments, we have summarized the results section especially results of curcumin on knee pain in a more concise manner in order to be more specific and clear on what the body of evidence has found on this specific topic.
 Moreover, several studies without significant results have been published and included in this review, for instance, we discussed the null effect of curcumin on synovitis effusion, irritable bowel syndrome, oral lichen planus, periodontal surgery, and diabetic sensorimotor polyneuropathy. This is usually addressed properly with a funnel plot or egger tests in order to look for publication bias, however, since we are to analyzing any data, this was not possible.
Finally, we have also now described the results of RoB analysis from Figure 2a and b in the result section and address the overall risk of bias analysis of the evidence in the discussion section.
"Ten studies describing the effects of curcumin on pain focus on its effect on joint pain and arthritis, with nine studies on knee OA.
Five studies evaluated curcumin in comparison with a placebo and found curcumin to be more effective with a significant reduction in pain scores (Lopresti et al. 2021, Madhu et al., 2013, Raj et al., 2020, Thanawala et al., 2021, Panda et al., 2018). The KOSS pain scale, VAS, and WOMAC scores were used. Additionally, curcumin showed a good tolerance profile with adverse events that were not statistically different from the placebo, including abdominal pain, bloating, headache, and dyspepsia (Panda et al., 2018, Madhu et al. 2013). One trial by Wang et al. 2020 evaluated the effect of curcumin on knee symptoms and effusion synovitis of knee OA when compared to placebo and observed a significant reduction in pain according to VAS, but it did not improve effusion synovitis (Wang et al., 2020).
Four non-inferiority studies compared the effects of curcumin on pain in knee OA with the standard of care, including ibuprofen, diclofenac, and paracetamol (Shep et al. 2019, Kuptniratsaikul et al., 2014, Kuptniratsaikul et al., 2009, Gomes et al., 2021, Singhal et al., 2021).
Two trials compared curcumin against ibuprofen, using the WOMAC pain scale or pain improvement on walking, and taking the stairs using NRS (Kuptniratsaikul et al., 2014, Kuptniratsaikul et al., 2009,). Non-inferiority of curcumin over ibuprofen was observed and no difference between both for pain improvement on walking was found (Kuptniratsaikul et al., 2014, Kuptniratsaikul et al., 2009). Additionally, there was no difference between the adverse events of curcuma and ibuprofen (Kuptniratsaikul et al. (2009), Kuptniratsaikul et al., 2014). Nevertheless, when compared against

diclofenac, fewer side effects were associated with curcumin, with both treatments describing a significant and similar reduction in the VAS pain score levels from baseline in OA of the knee. (Shep et al. (2019)."

"There seems to be an overall positive effect of curcumin intake on muscle soreness; however, the study shows an overall high risk of bias, and further studies are needed in this field."

"Hesami et al. (2021) showed a significant reduction in menstrual pain with curcumin compared with that with the placebo using VAS. This study showed an overall low risk of bias."

"The use of curcumin did not show any therapeutic benefit over the placebo. Nevertheless, the overall risk of bias was high for this study."

"The study by Maulina et al (2013) showed an overall high risk of bias where's the study by Kia et al. (2020) showed an overall low risk."

"Both studies were assessed with a low risk of bias."

Discussion

28. *Please address the limitations of your study in this section. You should also include an assessment of risk of bias in your discussion. Is the evidence you have found good? Please compare with other similar studies*
    https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7812094/

The limitations have been acknowledged and the RoB addressed on the main manuscript.

"This mini review compiles 20 articles on the use of curcumin in different types of pain categorized as follows: arthritis, muscle soreness, abdominal pain, oral pain, and other types of pain. Despite the high risk of bias in the evidence, the results suggest that curcumin may have a potential for use in pain management, especially in pain related to knee OA………However, because of the lack of low-risk bias studies on knee OA in our assessment, more studies with low risk of bias are needed to confirm and support these conclusions."

29. *The bioactivities of curcumin is not topic of this paper and its not part of your results, so ple do not discuss this here*

The section mentioned above has been removed since it is not an objective of our study to evaluate the bioactiviy of curcumin.

30. *There is some evidence for the effect of curcumin.*

The sentece was re-formated to address the level and quality of the evidence, rather than an absolute indication.

31. *Ensure*

The verb was change.

32. *Table 2. Characteristics of the included studies. Please correct the formatting of the table.*

The formatting of the table has been correctad.

Reviewer 2

33. *I suggest to put this phrase at the end of the manuscript, before the other affiliations.*

Has been changed.

34. *This will be given when the manuscript is published.*

Dear Reviewer, this number was a part of the template.

Material & Methods

35. *Did you do a Hand search besides of looking through databases?*

Dear Reviewer, we did not do a hand search for articles, and concentrate on online databases.

36. *Did you use an Excel spreadsheet or a tool as Rayyan?*

We have used a google spreadsheet downloaded after the exclusion of duplicates with Zotero.
"Zotero software (Corporation for Digital Scholarship, USA) and Google Sheets online editor (Google Docs, Google LLC, CA, USA) was used for the screening process."

37. *You only included articles written in English? Since some articles might have been not included and some of you are Spanish or Portuguese speakers.*

Dear reviewer we've included all the articles in the search. Coincidently, all the included full text articles were in English.

Discussion

38. *Agree, since VAS or WOMAC scales may be a bit subjective. Were there any studies that showed positive effects with scans or other more objective measures?*

Dear Rewiever, the most studies use pain scales as primary outcome and other parameters as secondary ones (Qol, blood test, safety parameters etc). As the aim of our study was to analyse only studies with pain scales as primary outcome we did nor concentrate on the secondary parameters as they have only an explanatory character. Also pain is very subjective and do not have to correlate with objective measures.
"Pain assessment is enigmatic. Although clinicians and researchers must rely upon observations to evaluate pain, the personal experience of pain is fundamentally unobservable. "
Wideman TH, Edwards RR, Walton DM, Martel MO, Hudon A, Seminowicz DA. The Multimodal Assessment Model of Pain: A Novel Framework for Further Integrating the Subjective Pain Experience Within Research and Practice. Clin J Pain. 2019 Mar;35(3):212-221. doi: 10.1097/AJP.0000000000000670. PMID: 30444733; PMCID: PMC6382036.

39. *I suggest including the # you put above in this place.*

Has been changed.