Peer-Review comments and authors responses

Reviewer 1
Comments:
DISCUSSION*: This systematic review evaluates the relationship between green tea and cancer. Some changes could be applied to enhance the efficacy of treatments and explain the impact of interventions in more detail. Interventions could be best assessed if proper subgroup stratification can be applied.*
The limitations, although mentioned, could be discussed thoroughly and may benefit from mentioning the heterogeneity of the study designs used, the doses used for green tea, and the impact of the difference between cancer types studied here.
I find the study promising and an interesting concept to be able to apply extensively.

Response: Thank you for this comment. We fully endorse this valuable suggestion and have expanded our analysis by adding a detailed subgroup discussion in the Results section. We present findings stratified by cancer type, dosage of green tea, and relevant biomarkers where applicable, thus allowing a more complete view of each cancer type's response to green tea. In the Limitations section, we have added a comprehensive discussion of the heterogeneity among the included studies. The text expansion thus helps to show the challenges and constraints of drawing unified conclusions across diverse study designs.

Reviewer 2
Comment:
Dear authors,
Thank you for the chance to review this manuscript. After assessing the manuscript contents and evaluating how the study question was introduced and discussed in the manuscript, I have a few suggestions that might make it stronger and increase its chances for acceptance:

1. ***METHODS****:*
    - *There is significant heterogeneity in the studies shown in this manuscript. When evaluating and comparing cancer outcomes, it is of limited value to combine diseases with such different prognoses (e.g., ovarian and prostate cancer) with limited staging and treatment data. To improve this manuscript, I suggest that the authors review each study separately and clearly describe the disease data in each study, including staging and treatment data when available.*

Response: We wish to thank the reviewer for this insightful review. We have added study-specific descriptions for each regarding disease type, disease stage, and treatment details, if possible. We now show this additional information in the Results section to enable a detailed comparison of outcomes.

- *Still within the description of each study's findings, the authors must remember that treatment might be the most crucial element of patients' outcomes instead of the green tea components. This is why staging, and treatment information is so relevant. Furthermore, not all biomarkers are clinically relevant. The role of the biomarkers in patient management should be mentioned when describing the study. If there is no clinical use for the biomarker, the authors should avoid drawing any conclusions from the finding.*

Response*:* We agree that many of the biomarkers included in this systematic review have no or limited current clinical implications apart from PSA. We mentioned in the discussion, "Other surrogate biomarkers such as insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), proliferating cell nuclear antigen (PCNA), and Clusterin—are currently used in various cancer research settings and of limited clinical applicability".

However, we decided to include them for many reasons. These can be summarized as the following:
Some of these biomarkers, such as VEGF (Vascular et al. Factor) and IGF-1 (Insulin-like Growth Factor 1), have been extensively studied in cancer patients and could be considered the production of certain medications used in cancer treatment, such as anti-angiogenic medications. We decided to include them as they may have a potential role in future clinical applications. Since the current trend in cancer treatment is toward using biological agents and avoiding toxic conventional therapy, some of these biomarkers may help understand the biological pathways, which can be important for manufacturing new treatments. Findings related to biomarkers may encourage further research and open doors for more discoveries related to mechanisms of action and potential role in future clinical monitoring.
Please note that most of the conclusions are related to green tea's effect on those clinical biomarkers, not on the clinical outcome of cancer.

- *From a methodology standpoint, the investigation of BMI as an effect modifier is unclear. The way this review is described, it looks as if green tea is the exposure/intervention in the studies, and the outcomes are either biomarkers or time-to-event outcomes, such as survival. In addition, it is described that BMI is associated with the exposure and the outcome, highlighting a more confounding effect instead of effect modification. In the example listed by the authors, gender could act as an effect modifier, but that is also unclear. I suggest the authors reassess and redesign this part of their analysis plan. Although we should not expect to have confounders in RCTs, we must always account for the possibility of systematic errors that might influence any study findings.*

Response: We would like to thank the reviewer for the feedback regarding the role of BMI in the results of this systematic review. We appreciate the opportunity to clarify our methodology. We agree that green tea is the intervention in this study, and certain biomarkers and specific clinical events are the outcomes.

Regarding the classification of BMI as an effect modifier versus a confounding factor, we would like to stress that our selection of BMI in this systematic review is an effect modifier. In similar studies, we agree that BMI can act as a confounder and effect modifier. However, we are investigating if BMI modifies the effect of green tea on specific cancer outcomes. In the Methods section, we stated our reason for selecting BMI as an effect modifier. The heading of measurement of effect modification: "Cancer patients with a higher BMI may require higher doses of green tea to achieve a similar therapeutic effect as patients with a lower BMI. This effect modification could be due to adipose tissue distribution or metabolic rate". In addition, in the second paragraph of the discussion, it was mentioned that "the potential effect modification of BMI is because fat accumulation in people with high BMI may alter the pharmacokinetics profile of drugs and nutritional supplements, especially their absorption, distribution and elimination (Smit, 2018). Additionally, obesity with high BMI is associated with a chronic

inflammatory state characterized by higher levels of pro-inflammatory cytokines and chemokines expression (Rodríguez-Hernández, 2013). These inflammatory mediators that are associated with obesity could alter the inflammatory effect and anti-cancer properties of green tea".

Ideally, the effect of green tea on different cancer outcomes should be analyzed across various ranges of BMI. Unfortunately, as mentioned in the result section under the heading, BMI is an effect modifier. We noted that "the BMI is similar between the intervention group (green tea) and the placebo group across all the four RCTs in this systematic review. Evaluating the effect modification by BMI within those individual studies becomes challenging because there is not enough variation in BMI within the groups to observe any potential interaction effect. Unfortunately, the unavailability of the data from these studies makes it difficult to perform subgroup or meta-regression analysis".

Reviewer 3
Comment:

Hello dear authors, I'm pleased to inform you that I was able to evaluate and review your work. First, I want to congratulate you on your efforts for demonstrating the importance of green tea consumption on cancer outcomes. I think this review serves as a good example of how simple interventions could amount to great and important findings.
During my review, I found that the review has a clear structure and robustness, however its weakness lies in several grammar errors that I found. Please revisit the manuscript and try to correct the one that I found and any other's I might've missed. Also, there seems to be no limitations section on the conclusions, which should be added based on what limited your review. You also did not mention the possibility of publication bias or even if you did a funnel plot with the studies included.

Response: Thank you for noting this. We have done a grammar and typographical review throughout the manuscript, correcting all the errors reviewed. This revision would most definitely ensure clarity and enhance readability in our work.
The Limitations section in the conclusion has been expanded to include a discussion of study design variability, small sample size, and publication bias. We also comment on the absence of a funnel plot due to a limited number of studies but recognize that the potential for publication bias in this review could not be excluded.

Reviewer 4
Comment:
I do believe it's a good review overall and has a good background, my only advice would be to try to unify more of your manuscript and make it easier for the reader, I do like the conclusions you made clear the limitations with a good explanation.
I uploaded your document with some comments.
Overall, it is a good manuscript Congratulations!

Response: We appreciate the constructive comment of the reviewer. We changed the structure to improve readability, especially in the Introduction and Conclusion
sections. Such changes improve the flow of ideas within the manuscript, making it easier for readers to understand. We have carefully read and responded to each in-text comment. We provided a specific response for every comment here and made corresponding edits in the manuscript to ensure that each one of the suggestions was considered.

We believe these revisions have significantly strengthened our manuscript. Thank you for considering our resubmission. We look forward to your feedback and hope our revised manuscript will be deemed suitable for publication in your esteemed journal.