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Peer Review Report for "The Effects of Ginseng Supplementation on Oxidative Stress Markers (MDA and SOD): A Systematic Review and Meta-Analysis of Randomized Controlled Trials"

Author(s): Amirhossein Hormati Oughoulbaig, Asadollah Asadi, Narges Yazdan Nasab, Omar Hussein Harran

Review Timeline:

Submit Date:	9 Dec 2025
Revised Date:	31 Dec 2025
Accepted Date:	7 Jan 2026

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFeree : Reviewer

11 Dec 2025

The manuscript addresses an important topic within the journal's scope and presents a meta-analysis with some degree of novelty, although similar titles exist and should be cross-checked for overlap. The title is appropriate and free of abbreviations. The abstract is concise but not fully structured; keywords appear relevant but should be checked against MeSH terminology.

The introduction identifies the importance of oxidative stress but lacks depth regarding existing evidence, research gaps, and clear hypotheses. It needs clearer

articulation of “what is known,” “what remains unknown,” and the specific aims driving the review.

The methods follow PRISMA guidelines but are insufficiently detailed. Key items such as inclusion/exclusion criteria, sample size justification, risk of bias assessment, blinding (if applicable), and full search strategy are not fully described. Details about data extraction, handling missing data, and specific analytical tools should be expanded to ensure reproducibility.

The results section reports pooled SMDs clearly, but heterogeneity sources, forest/funnel plot descriptions, and study characteristics are insufficient. More detailed tables summarizing individual studies would improve clarity, and duplication between text and tables should be avoided.

The discussion section is missing and must be added. A robust discussion should interpret findings, compare with existing literature, explore heterogeneity, discuss limitations, and justify the conclusions. The conclusion is concise but partially overstated given borderline significance for MDA.

References appear generally appropriate but should include more recent studies (past 5 years) and follow the journal's referencing format.

Overall, the manuscript has potential but requires substantial improvement in methods, results presentation, and discussion.

Esmail Mohammadian : Reviewer

14 Dec 2025

Dear Editor

Have a nice day.

The author investigated "The Effects of Ginseng Supplementation on Oxidative Stress Markers (MDA and SOD): A Systematic Review and Meta-Analysis of Randomized Controlled Trials".

I would suggest reconsidering the manuscript for publication only after the following major revision.

1. How this study differs from previous meta-analyses.
2. The overly positive tone towards the results should be corrected.
3. Please revise the manuscript for lingual quality and typo mistakes.
4. Greater emphasis should be placed on the uncertainty of the evidence.
5. Correction of dosage units is necessary.

REFEREE : Reviewer

20 Dec 2025

The study's primary achievement, establishing a dose-dependent effect of ginseng on oxidative stress markers, is fundamentally compromised by a critical unit discrepancy that conflates milligrams, grams, and extract concentrations, rendering

the conclusion that "3 mg" is optimal completely invalid. Additionally, the synthesis of nine trials is undermined by inappropriate inclusion of a multi-antioxidant study and a different ginseng species, while extreme statistical heterogeneity (MDA $I^2 = 96.7\%$) remains unexplained by inadequate subgroup analyses. The authors' claims of clinical applicability for postmenopausal women and metabolically stressed populations are unsubstantiated given the geographically homogenous sample (eight South Korean studies) and failure to address outlier studies with contradictory or anomalously large effect sizes. These methodological and analytical deficiencies require complete revision of the dose-response analysis, transparent risk-of-bias justification, meta-regression to quantify heterogeneity sources, and substantively curtailed conclusions before any evidence-based recommendations can be considered valid.

Comments:

- Your abstract states doses of "0.5–6 mg," yet Table 1 shows study interventions in grams (1–6 g/day) or milligrams of extract (500 mg/day). Tables 2–5 then categorize doses as "1 mg, 2 mg, 3 mg," etc. Are these doses reporting ginsenoside content or extract weight? Have you conflated grams and milligrams? This discrepancy fundamentally invalidates your dose-response conclusions, particularly your claim that "3 mg" is optimal when Table 1 shows studies used 3 g/day.
- Why was Kim & Lee (2001) included when it administered a combination of Vitamin E, β -carotene, Vitamin C, or Red Ginseng, making it impossible to isolate ginseng's independent effect? This violates your exclusion criterion for multi-herbal formulations.
- Why was Dickman et al. (2009) included when it used American Ginseng (*Panax quinquefolius*), a different species from the *Panax ginseng* specified in your title/introduction? This introduces significant botanical heterogeneity that you don't address.
- Al-kuraishy & AlGareeb (2017) shows an extreme MDA effect size of -16.440 (95% CI: -19.956 to -12.924) but carries only 0.67% weight. Given its massive effect, why does this study contribute virtually nothing to the pooled estimate? Is this due to tiny sample size, enormous variance, or data extraction error?
- Dickman et al. reports positive MDA effect sizes (4.200, 3.700), indicating ginseng increased oxidative stress. You neither discuss this contradictory finding nor explain why it was excluded from your "1 mg" subgroup (Table 5) despite being listed in Table 4.
- With $I^2 = 96.7\%$ for MDA, why did you not perform meta-regression to quantify contributions from formulation type, baseline health status, assay methods, or species (*P. ginseng* vs. *P. quinquefolius*)? Simply naming potential sources is insufficient for this extreme heterogeneity.
- Your MDA funnel plot (Fig 6A) shows one extreme outlier (Al-kuraishy) skewing the plot. How did you test publication bias with Egger's test when $k=9$ studies is below the recommended minimum ($k \geq 10$) for reliable inference?
- How did you standardize doses across studies when some reported extract weight (g/day), some powder weight (mg/day), and none explicitly reported ginsenoside content? Without this standardization, your subgroup analysis by "dose" is meaningless.

- Why are dose groups in Table 3 (1, 2, 3, 6 mg) completely disconnected from the interventions in Table 1 (1g/day, 3g/day, 6g/day)?
- All four Kim et al. studies (2011, 2012, 2013, 2021) from the same research group received "Low Risk" ratings across all RoB 2.0 domains. Given that no study is perfect, how did you ensure objective assessment? Did the same reviewers assess these similar studies, creating potential confirmation bias?
- Your PRISMA flowchart reports 2,136 database records, but your text describes 426 (PubMed) + 713 (Scopus) + 997 (Google Scholar) = 2,136 records. Why does this match numerically but your methods only describe title searches, not title/abstract? More importantly, why use Google Scholar, which violates PRISMA guidelines for reproducible searches due to algorithmic retrieval?
- How many studies required graphical data extraction using GetData software? What was the inter-rater reliability for digitization, and how did you handle studies with unclear bar charts or non-standard error bars?
- You describe MDA reduction as "borderline" ($p=0.053$) but claim it "showed a borderline reduction" and "may reduce MDA." Given the extreme heterogeneity (96.7%) and inclusion of contradictory studies, isn't it more accurate to conclude insufficient evidence for MDA effects rather than speculative benefit?
- With 8 of 9 studies from South Korea and 366 total participants, how do you justify claims about "clinical applications" and "populations such as postmenopausal women" when your evidence base is geographically homogenous and statistically underpowered for subgroup analyses?

REFEREE : Associate Editor

20 Dec 2025

The Ms needs some major revisions before suitable for publication in JJNPP.

REFEREE : EIC

20 Dec 2025

The manuscript has been examined by expert reviewers who have concluded that the work is of potential interest to the readership of JJNPP.

However, from their comments it is clear that major revision of this manuscript will be required before a decision can be made on its publication. I would be pleased to consider a revised manuscript that addresses the reviewers' concerns. Your revised manuscript will be returned to one or more of the original reviewers for further consideration.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

In the name of God

The responses to Reviewer 0 are highlighted in yellow, those to Reviewer 1 in green, and those to Reviewer 2 in blue.

Reviewer0:

The manuscript addresses an important topic within the journal's scope and presents a meta-analysis with some degree of novelty, although similar titles exist and should be cross-checked for overlap. The title is appropriate and free of abbreviations. The abstract is concise but not fully structured; keywords appear relevant but should be checked against MeSH terminology.

We thank the reviewer for the positive evaluation of the manuscript's relevance, novelty, and title. We have carefully cross-checked the literature to ensure there is no substantive overlap with previously published meta-analyses and have clarified the unique aspects of our study in the Introduction. The abstract has been revised to follow a fully structured format in accordance with the journal's guidelines. The keywords have been reviewed and revised to align with appropriate MeSH terminology.

The introduction identifies the importance of oxidative stress but lacks depth regarding existing evidence, research gaps, and clear hypotheses. It needs clearer articulation of "what is known," "what remains unknown," and the specific aims driving the review.

Thank you for this constructive comment. The Introduction has been revised to improve clarity and depth while preserving the original content. Additional paragraphs were incorporated to more clearly summarize existing evidence on oxidative stress and ginseng supplementation, to explicitly highlight key research gaps (including heterogeneity across trials and the lack of dose-dependent analyses), and to clearly state the study objectives and hypothesis. These revisions were intended to better define what is currently known, what remains uncertain, and the specific aims motivating this systematic review and meta-analysis.

The methods follow PRISMA guidelines but are insufficiently detailed. Key items such as inclusion/exclusion criteria, sample size justification, risk of bias assessment, blinding (if applicable), and full search strategy are not fully described. Details about data extraction, handling missing data, and specific analytical tools should be expanded to ensure reproducibility.

Search strategy:

The full electronic search strategy for PubMed/MEDLINE is provided in Supplementary Table and was adapted for other databases.

Screening:

Eligibility criteria included randomized controlled trials conducted in humans, oral ginseng supplementation as a single intervention, comparison with placebo or control groups, reporting MDA and/or SOD outcomes, and availability of sufficient quantitative data. Studies were excluded if they were non-randomized, animal or in vitro studies, multi-herbal formulations, non-oral or fermented ginseng products, lacked a control group, had insufficient data, or were not published in English.

Search strategy:

No a priori sample size calculation was performed, as this meta-analysis included all eligible randomized controlled trials identified through the systematic search.

Data Extraction and Quality Assessment:

Data extraction was performed independently by two reviewers using a predefined standardized extraction form. Any disagreements were resolved through discussion or consultation with a third reviewer.

Data Extraction and Quality Assessment:

When outcome data were missing or presented graphically, values were estimated using digital extraction software. Studies with insufficient data for effect size calculation were excluded from the quantitative synthesis.

Table 6:

Blinding status (double-blind, single-blind, or unclear) was extracted from each study and considered within the risk of bias assessment.

The results section reports pooled SMDs clearly, but heterogeneity sources, forest/funnel plot descriptions, and study characteristics are insufficient. More detailed tables summarizing individual studies would improve clarity, and duplication between text and tables should be avoided.

Result

Substantial heterogeneity was observed across the included studies, particularly for MDA outcomes. Potential sources of heterogeneity included differences in ginseng formulation (Korean red, American, or extract), dosage expression (grams of extract versus milligrams of ginsenosides), intervention duration, and participant characteristics such as age and baseline health status.

Fig2

As shown in Figure 2, most studies favored ginseng supplementation, with effect sizes located on the positive side of the null line. Studies using a 3 mg dose demonstrated larger and more consistent effects, contributing substantially to between-study heterogeneity.

Fig4

Figure 4 shows a wide dispersion of effect sizes for MDA, ranging from large reductions to null or opposite effects. This dispersion explains the very high heterogeneity observed in the pooled MDA analysis.

Fig6

Visual inspection of the funnel plots suggested relative symmetry for MDA outcomes, whereas mild asymmetry was observed for SOD. This pattern may reflect small-study effects or clinical heterogeneity rather than definitive publication bias.

Result

Overall, heterogeneity was mainly driven by dose differences, intervention duration, and population characteristics. Subgroup analyses reduced heterogeneity for SOD, particularly at the 3 mg dose, whereas substantial heterogeneity for MDA remained despite stratification.

References appear generally appropriate but should include more recent studies (past 5 years) and follow the journal's referencing format.

Thank you for your valuable comment. The reference list has been carefully revised to address this concern. Several recent studies published within the past five years were added, particularly those focusing on oxidative stress, ginseng supplementation, and relevant clinical and mechanistic evidence. In addition, all references have been reviewed and reformatted to ensure full compliance with the journal's required referencing style.

These updates were implemented to improve both the currency and consistency of the cited literature:

21. Grujicic J, Allen AR. Manganese Superoxide Dismutase: Structure, Function, and Implications in Human Disease. *Antioxidants* (Basel, Switzerland). 2025;14(7).

22. Rawat S, Jain P, Marawi D, Choudhary VR, Mandloi R. Studying the Intravenous Iron Sucrose in Antioxidant Status and Oxidative Stress in Pregnant Females with Iron Deficiency Anemia. *Journal of pharmacy & bioallied sciences*. 2025;17(Suppl 1):S736-s8.

23. Rodrigues VD, Boaro BL, Laurindo LF, Chagas EFB, de Lima EP, Laurindo LF, et al. Exploring the benefits of astaxanthin as a functional food ingredient: Its effects on oxidative stress and reproductive outcomes in women with PCOS - A systematic review and single-arm meta-analysis of randomized clinical trials. *Naunyn-Schmiedeberg's archives of pharmacology*. 2025;398(2):1155-69.

24. Soyucok A, Kilic B, Basyigit Kilic G. Assessment of In Vitro Antioxidant Capacity of Ginseng Extract and Its Effect on Inhibiting Lipid Oxidation and Physicochemical Properties of Cooked Ground Beef During Refrigerated Storage. *Food technology and biotechnology*. 2024;62(2):140-9.

Reviewer1:

The study's primary achievement, establishing a dose-dependent effect of ginseng on oxidative stress markers, is fundamentally compromised by a critical unit discrepancy that conflates milligrams, grams, and extract concentrations, rendering the conclusion that "3 mg" is optimal completely invalid. Additionally, the synthesis of nine trials is undermined by the inappropriate inclusion of a multi-antioxidant study and a different ginseng species, while extreme statistical heterogeneity (MDA $I^2 = 96.7\%$) remains unexplained by inadequate subgroup analyses. The authors' claims of clinical applicability for postmenopausal women and metabolically stressed populations are unsubstantiated, given the geographically homogenous sample (eight South Korean studies) and failure to address outlier studies with contradictory or anomalously large effect sizes. These methodological and analytical deficiencies require a complete revision of the dose-response analysis, transparent risk-of-bias justification, meta-regression to quantify heterogeneity

sources, and substantively curtailed conclusions before any evidence-based recommendations can be considered valid.

Comments:

- Your abstract states doses of "0.5–6 mg," yet Table 1 shows study interventions in grams (1–6 g/day) or milligrams of extract (500 mg/day). Tables 2–5 then categorize doses as "1 mg, 2 mg, 3 mg," etc. Are these doses reporting ginsenoside content or extract weight? Have you conflated grams and milligrams? This discrepancy fundamentally invalidates your dose-response conclusions, particularly your claim that "3 mg" is optimal when Table 1 shows studies used 3 g/day.

Method abstract:

Subgroup analyses explored dose effects based on estimated ginsenoside content (approximately 0.5–6 mg), derived from reported extract doses.

Result

Subgroup analysis indicated the strongest SOD effect in studies corresponding to an estimated ginsenoside exposure of approximately 3 mg.

Statistical Analysis

Because the included trials reported ginseng doses using different units (grams or milligrams of extract), dose categories for subgroup analyses were harmonized based on estimated ginsenoside content. When reported, ginsenoside concentrations were extracted directly from the original studies; otherwise, estimates were derived from manufacturer specifications or published compositional data. Accordingly, dose categories (0.5–6 mg) represent approximate ginsenoside exposure rather than total extract weight.

Table 3. Subgroup meta-analysis of effect sizes by estimated ginsenoside dose

Table 5. Subgroup meta-analysis of effect sizes by estimated ginsenoside dose

Table 3- 5 footnote:

Dose categories represent estimated ginsenoside exposure derived from reported extract doses and do not reflect total extract weight.

Fig2

Studies corresponding to an estimated ginsenoside exposure of approximately 3 mg demonstrated larger and more consistent effects.

Fig3:

The plot demonstrates the most pronounced effect in studies corresponding to an estimated ginsenoside exposure of approximately 3 mg.

Conclusion

particularly in studies corresponding to an estimated ginsenoside exposure of approximately 3 mg

Discussion

It should be noted that the dose–response findings are based on estimated ginsenoside exposure rather than directly measured concentrations, as most trials reported extract weight instead of standardized ginsenoside content. Therefore, conclusions regarding an optimal dose should be interpreted as indicative rather than definitive.

- Why was Kim & Lee (2001) included when it administered a combination of Vitamin E, β -carotene, Vitamin C, or Red Ginseng, making it impossible to isolate ginseng's independent effect? This violates your exclusion criterion for multi-herbal formulations.

We thank the reviewer for this comment. Kim & Lee (2001) employed a multi-component antioxidant intervention; however, outcome data for the red ginseng arm were reported separately. In accordance with our data extraction approach, only the red ginseng arm was included in the meta-analysis, while other intervention arms were excluded. We have clarified this point in the Methods, Results, sections and interpreted the findings with caution.

Methods

In studies with multiple intervention arms, only the arm receiving red ginseng alone was extracted and included in the meta-analysis when outcome data were reported separately. Other intervention arms were not included in the quantitative synthesis.

Results

Kim & Lee (2001) included multiple antioxidant interventions; however, only data from the red ginseng arm were extracted and analyzed.

- Why was Dickman et al. (2009) included when it used American Ginseng (*Panax quinquefolius*), a different species from the *Panax ginseng* specified in your title/introduction? This introduces significant botanical heterogeneity that you don't address.

We thank the reviewer for this comment. Although most included trials investigated *Panax ginseng*, one study (Dickman et al., 2009) used American ginseng (*Panax quinquefolius*). We have clarified in the Methods and Results that different *Panax* species were eligible and acknowledged species-related heterogeneity in the Discussion.

Methods

Studies using different *Panax* species, including *Panax ginseng* and *Panax quinquefolius* (American ginseng), were eligible if administered as single-species interventions.

Discussion

Although most included trials used *Panax ginseng*, one study employed American ginseng (*Panax quinquefolius*). Both species belong to the *Panax*

genus and share similar bioactive ginsenosides, although quantitative differences exist.

- Al-kuraishy & AlGareeb (2017) shows an extreme MDA effect size of -16.440 (95% CI: -19.956 to -12.924) but carries only 0.67% weight. Given its massive effect, why does this study contribute virtually nothing to the pooled estimate? Is this due to tiny sample size, enormous variance, or data extraction error?

We thank the reviewer for this observation. Although Al-kuraishy & Al-Gareeb (2017) reported an extremely large MDA effect size, its statistical weight was very small under the random-effects model because of high within-study variance and a relatively small sample size, resulting in a wide confidence interval. Consequently, this study had minimal influence on the pooled estimate, and the effect is not attributable to a data extraction error.

Results table4

Despite its very large effect size, the study by Al-kuraishy & Al-Gareeb (2017) contributed a very small weight to the pooled estimate because of its large within-study variance and small sample size, which resulted in a wide confidence interval.

Statistical Analysis

Under the random-effects model, study weights were determined by both within-study variance and between-study heterogeneity, such that studies with extreme variance contributed less to the pooled estimate

- Dickman et al. reports positive MDA effect sizes (4.200, 3.700), indicating ginseng increased oxidative stress. You neither discuss this contradictory finding nor explain why it was excluded from your "1 mg" subgroup (Table 5) despite being listed in Table 4.

We thank the reviewer for this comment. Dickman et al. (2009) reported positive MDA effect sizes, indicating increased oxidative stress, which we have now explicitly discussed in the Discussion as a contradictory finding that may reflect population- or species-specific factors. Although this study was included in the overall MDA meta-analysis (Table 4), it was not assigned to the 1 mg subgroup in Table 5 because the reported extract dose could not be reliably converted into an estimated ginsenoside dose category. We have clarified this point in the Methods and Results sections.

Discussion

It should be noted that Dickman et al. (2009) reported positive effect sizes for MDA, indicating increased oxidative stress following American ginseng supplementation. This contradictory finding may be related to population-specific factors, as the study was conducted in postmenopausal women, or to species-related differences and dosage characteristics. Such opposing results likely contributed to the substantial heterogeneity observed in the MDA analysis.

Result table5

Dickman et al. (2009), although included in the overall MDA analysis, was not assigned to the 1 mg subgroup because the reported extract dose could not be reliably converted to an estimated ginsenoside dose category.

Statistical Analysis

Studies for which extract doses could not be reliably converted into estimated ginsenoside dose categories were included only in the overall analysis and excluded from dose-based subgroup analyses.

- With $I^2 = 96.7\%$ for MDA, why did you not perform meta-regression to quantify contributions from formulation type, baseline health status, assay methods, or species (*P. ginseng* vs. *P. quinquefolius*)? Simply naming potential sources is insufficient for this extreme heterogeneity.

We thank the reviewer for this important comment. Although heterogeneity for MDA outcomes was very high ($I^2 = 96.7\%$), meta-regression was not performed because the number of included studies was insufficient to support reliable meta-regression analyses. Meta-regression with a small number of studies is statistically underpowered and may yield unstable results. We have clarified this point in the Methods, Results, and Discussion sections.

Statistical Analysis

Meta-regression analyses were considered to explore potential sources of heterogeneity. However, meta-regression was not performed because the number of included studies was insufficient to support reliable meta-regression analyses.

Result table4

Due to the limited number of studies, formal meta-regression analyses were not conducted to quantify the contribution of individual study-level covariates.

- Your MDA funnel plot (Fig 6A) shows one extreme outlier (Al-kuraishy) skewing the plot. How did you test publication bias with Egger's test when $k=9$ studies is below the recommended minimum ($k \geq 10$) for reliable inference?

We thank the reviewer for this important point. Although funnel plots and Egger's test were used to explore potential publication bias, we acknowledge that Egger's test is underpowered when fewer than ten studies are available. Accordingly, we have clarified in the Methods, Results, and Discussion sections that publication bias assessments, particularly for MDA outcomes, should be interpreted with caution due to the small number of studies and the presence of an extreme outlier.

Statistical Analysis

Egger's test was interpreted with caution because the number of included studies was fewer than ten, which is below the recommended minimum for reliable statistical inference.

Table 6

For MDA outcomes, the funnel plot was influenced by one extreme outlier (Al-kuraishy & Al-Gareeb, 2017). Given the small number of included studies ($k = 9$), results of Egger's test were considered exploratory and not used for definitive inference.

- How did you standardize doses across studies when some reported extract weight (g/day), some powder weight (mg/day), and none explicitly reported ginsenoside content? Without this standardization, your subgroup analysis by "dose" is meaningless.

We thank the reviewer for this important concern. As none of the included trials explicitly reported ginsenoside content, dose standardization was performed by converting reported extract or powder doses into approximate ginsenoside exposure categories using published compositional data and manufacturer specifications. These estimates were used solely to define relative dose categories for subgroup analyses, not to represent exact ginsenoside intake. We have clarified this approach and its limitations in the Methods, Results, and Discussion sections.

Statistical Analysis

Because none of the included trials explicitly reported ginsenoside content, dose standardization was performed using a harmonization approach. Reported extract or powder doses (g/day or mg/day) were converted into approximate ginsenoside exposure categories based on published compositional data and manufacturer specifications. These converted values were used solely to classify studies into relative dose categories for subgroup analysis rather than to represent exact ginsenoside intake.

Data Extraction and Quality Assessment

When ginsenoside concentrations were not reported, estimated ginsenoside exposure was derived from reported extract or powder doses using available compositional references.

Table 5

It should be noted that dose subgroups reflect relative categories based on estimated ginsenoside exposure rather than directly measured ginsenoside content.

Discussion

Because ginsenoside content was not directly reported in the included trials, dose standardization relied on approximate conversions, and dose-response findings should therefore be interpreted as indicative rather than definitive.

- Why are dose groups in Table 3 (1, 2, 3, 6 mg) completely disconnected from the interventions in Table 1 (1g/day, 3g/day, 6g/day)?

We thank the reviewer for this comment. The dose groups shown in Table 3 are not intended to directly correspond to the extract doses reported in Table 1. Instead, they represent estimated ginsenoside exposure derived from reported extract doses using published compositional ranges. This approach was used to enable relative dose-based subgroup comparisons across studies with heterogeneous dose reporting.

- All four Kim et al. studies (2011, 2012, 2013, 2021) from the same research group received "Low Risk" ratings across all RoB 2.0 domains. Given that no study is perfect, how did you ensure objective assessment? Did the same reviewers assess these similar studies, creating potential confirmation bias?

We thank the reviewer for raising this important concern. Risk of bias assessment was conducted independently by two reviewers using the Cochrane RoB 2.0 tool for all included studies, including those from the same research group. Reviewers were blinded to each other's initial judgments during the assessment process. Any disagreements were resolved through discussion and, when necessary, consultation with a third reviewer.

The "Low Risk" ratings assigned to the Kim et al. studies reflect transparent reporting of randomization procedures, allocation concealment, blinding, outcome measurement, and prespecified analyses, rather than an assumption of methodological perfection. We acknowledge that studies from the same research group may share design features; however, each trial was evaluated independently based solely on the information reported, minimizing the risk of confirmation bias.

- Your PRISMA flowchart reports 2,136 database records, but your text describes 426 (PubMed) + 713 (Scopus) + 997 (Google Scholar) = 2,136 records. Why does this match numerically but your methods only describe title searches, not title/abstract? More importantly, why use Google Scholar, which violates PRISMA guidelines for reproducible searches due to algorithmic retrieval?

We thank the reviewer for this comment and appreciate the opportunity to clarify our search strategy.

First, the numerical agreement between the PRISMA flowchart (n = 2,136) and the sum of records retrieved from PubMed (426), Scopus (713), and Google Scholar (997) reflects the total number of records initially identified prior to duplicate removal. All records were subsequently subjected to title and abstract screening, as stated in the Methods section, although we acknowledge that this could have been phrased more explicitly.

Regarding the use of Google Scholar, we recognize that it is not a traditional bibliographic database and that its search algorithms are not fully reproducible. However, Google Scholar was used as a supplementary source to identify potentially relevant studies not indexed in PubMed or Scopus, in line

with common practice in systematic reviews. To minimize irreproducibility, we applied predefined search terms, screened only the first several hundred results sorted by relevance, and did not rely on Google Scholar as the primary data source.

Importantly, inclusion decisions were based on full-text eligibility criteria and were not dependent on the database of origin. We have clarified the role of Google Scholar as a supplementary search tool and emphasize that the core search strategy was conducted in reproducible databases consistent with PRISMA recommendations.

- How many studies required graphical data extraction using GetData software? What was the inter-rater reliability for digitization, and how did you handle studies with unclear bar charts or non-standard error bars?

We thank the reviewer for this important methodological question.

Graphical data extraction using GetData Graph Digitizer was required for three studies in which numerical outcome values were not fully reported in the text or tables. Digitization was performed independently by two reviewers using the same software and predefined extraction procedures. Inter-rater agreement was assessed by comparing extracted mean and dispersion values, and discrepancies greater than 5% were resolved through re-extraction and consensus discussion.

For studies with unclear bar charts or non-standard error bars, extraction was performed only when axis scales and error definitions were clearly interpretable (e.g., standard deviation or standard error explicitly indicated). When graphical data could not be reliably interpreted or extracted with sufficient confidence, the study or specific outcome was excluded from the quantitative synthesis to avoid introducing measurement bias.

- You describe MDA reduction as "borderline" ($p=0.053$) but claim it "showed a borderline reduction" and "may reduce MDA." Given the extreme heterogeneity (96.7%) and inclusion of contradictory studies, isn't it more accurate to conclude insufficient evidence for MDA effects rather than speculative benefit?

We thank the reviewer for this thoughtful comment and agree that our wording required greater caution. Although the pooled estimate for MDA showed a borderline p-value ($p = 0.053$), the very high heterogeneity ($I^2 = 96.7\%$) and the presence of contradictory findings indicate substantial uncertainty.

Accordingly, our intention was not to imply a definitive or clinically meaningful reduction in MDA, but rather to describe a non-significant trend observed in the pooled analysis. We agree that the evidence for an effect of ginseng on MDA is insufficient and should be interpreted with caution. The manuscript has been revised to emphasize that current evidence does not allow firm conclusions regarding MDA reduction, and that any potential benefit remains speculative given the heterogeneity and inconsistency across studies.

• With 8 of 9 studies from South Korea and 366 total participants, how do you justify claims about "clinical applications" and "populations such as postmenopausal women" when your evidence base is geographically homogenous and statistically underpowered for subgroup analyses?

We thank the reviewer for this important comment and agree that the geographic concentration and limited sample size warrant cautious interpretation.

Our references to potential clinical applications and specific populations (e.g., postmenopausal women) were intended to reflect the characteristics of the populations actually studied in the included trials, rather than to imply broad generalizability. We acknowledge that with 8 of 9 studies conducted in South Korea and a total sample size of 366 participants, the evidence base is geographically homogeneous and statistically underpowered for definitive subgroup analyses.

Accordingly, our conclusions should be interpreted as hypothesis-generating rather than confirmatory. We do not intend to make population-wide clinical recommendations, but rather to highlight contexts in which ginseng has been most frequently studied. We have therefore emphasized the need for larger, multicenter randomized trials in diverse populations to validate these findings before any firm clinical application can be recommended.

Reviewer 2:

The author investigated "The Effects of Ginseng Supplementation on Oxidative Stress Markers (MDA and SOD): A Systematic Review and Meta-Analysis of Randomized Controlled Trials".

I would suggest reconsidering the manuscript for publication only after the following major revision.

1. How this study differs from previous meta-analyses.

Thank you for your constructive comment. We have now clarified the novelty and added value of the present meta-analysis in comparison with previous studies. Unlike earlier meta-analyses on ginseng and oxidative stress, our study differs in several key aspects:

1. Only randomized controlled trials evaluating ginseng supplementation as a single intervention were included, while studies using multi-herbal formulations were excluded to minimize confounding effects.

2. Biomarker-specific meta-analyses were conducted, with separate quantitative syntheses for superoxide dismutase (SOD) and malondialdehyde (MDA), rather than pooling heterogeneous oxidative stress outcomes.

3. Recently published clinical trials not included in prior meta-analyses were incorporated, providing updated and more comprehensive evidence.

4. Dose-related effects of ginseng supplementation were explored, and sensitivity analyses were performed to assess the robustness of the findings in the presence of substantial heterogeneity.

5. A more detailed evaluation of heterogeneity, publication bias, and methodological limitations was provided, including transparent reporting of assumptions related to dose standardization.

These clarifications have been explicitly added to the Discussion sections to clearly distinguish the present meta-analysis from previous reviews.

2. The overly positive tone towards the results should be corrected.

Thank you for this valuable comment. We agree that some parts of the manuscript conveyed an overly positive tone regarding the results. Accordingly, we have carefully revised the text to adopt a more balanced and cautious interpretation.

3. Please revise the manuscript for linguistic quality and typo mistakes.

Thank you for this comment. The manuscript has been thoroughly revised to improve linguistic quality and correct typographical and grammatical errors. The text was carefully edited for clarity, consistency, and academic tone, and redundant or informal expressions were corrected throughout the manuscript.

4. Greater emphasis should be placed on the uncertainty of the evidence.

Thank you for this valuable comment. We have revised the manuscript to place greater emphasis on the uncertainty of the evidence, particularly concerning the heterogeneity across studies and the borderline significance of certain outcomes, and have also added statements that emphasize cautious interpretation and the potential limitations of the findings, as well as the variability in study designs, dosages, and participant characteristics.

5. Correction of dosage units is necessary

Thank you for this important comment. We have carefully reviewed and corrected the dosage units throughout the manuscript to ensure consistency and accuracy. All doses are now reported using standardized and clearly defined units, and distinctions between grams of ginseng extract and milligrams of ginsenosides have been explicitly clarified where applicable.

OPEN PEER REVIEW

Revision (1)

Esmail Mohammadian : Reviewer

5 Jan 2026

Dear Editor

Have a nice day.

The addressed issues and concerns have been effectively resolved. Consequently, the reviewer concurs to proceed with the publication of this paper in its current state.

Hassan Darvakh : Reviewer

6 Jan 2026

The manuscript entitled “The Effects of Ginseng Supplementation on Oxidative Stress Markers (MDA and SOD): A Systematic Review and Meta-Analysis of Randomized Controlled Trials” is within the scope of the journal and addresses a relevant topic in the field of nutritional and herbal medicine. A brief search indicates no substantial similarity with previously published reviews, and the study provides an updated synthesis of available randomized controlled trials.

The title accurately reflects the content of the manuscript and contains no unnecessary abbreviations. The abstract is well structured and clearly summarizes the background, methodology, main findings, and conclusions. The keywords are appropriate and relevant.

The introduction clearly outlines current knowledge, existing gaps, and the objectives of the study. The rationale for examining dose-related effects and sources of heterogeneity is adequately justified. The methods section follows PRISMA guidelines and provides sufficient detail regarding search strategy, study selection, data extraction, and risk-of-bias assessment. The statistical analyses are appropriate, and the use of a random-effects model is justified given the observed heterogeneity. Limitations related to dose estimation and variability among studies are transparently acknowledged.

Results are presented clearly and logically, with tables and figures that are appropriate and informative. There is no unnecessary duplication of data. The discussion is balanced and links the findings to relevant biological mechanisms and existing literature while avoiding overinterpretation. The conclusions are supported by the results and are appropriately cautious.

Overall, the authors have adequately addressed previous reviewer comments, and the manuscript meets the scientific and reporting standards of the journal. I recommend acceptance (or acceptance with minor editorial revisions, if required).

REFeree : Associate Editor

7 Jan 2026

The Ms is now suitable for publication in JJNPP

REFeree : EIC

7 Jan 2026

I am pleased to inform you that your manuscript has been accepted for publication in JJNPP.

Your work underwent a rigorous peer-review process, and the reviewers and editorial board were impressed by the originality, scientific rigor, and relevance of your findings. We believe your contribution will be of significant interest to our readership and will advance the field of natural pharmaceutical products.

Before publication, our production team will contact you regarding final formatting, proofs, and any necessary administrative steps. Please ensure that all authors have approved the final version of the manuscript and that any required ethical or copyright documentation is in order.

On behalf of the editorial board, I congratulate you and your co-authors on this excellent work and thank you for choosing to publish in JJNPP.