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OPEN PEER REVIEW

Effects of Curcumin and Amla Co-supplementation on Lipid Profile, Glycemic Status, Antioxidant Indices, Inflammatory Factor, and Liver Enzymes in Type 2 Diabetes Patients: A Double-Blind, Randomized Controlled Trial Protocol

Maryam Behrouzi, Fatemeh Borazjani, Sima Jafarirad, Mehrnoosh Zakerkish, Krista Casazza, Kambiz Ahmadi Angali

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

More about open peer review: brieflands.com/knowledgebase/opr

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1 Original submission

3 comments · 10 Aug 2024 – 17 Aug 2024

Zahra Shokati Eshkiki Reviewer

MAJOR REVISION 10 Aug 2024

Dear Author,

Thank you for submitting your manuscript entitled "The Effect of Co-supplementation of Curcumin and Amla on lipid profile, Glycemic status, Antioxidant Indices, Inflammatory Factor, and Liver Enzymes in Patients with Type 2 Diabetes: A Protocol of Double-blinded, Randomized Controlled Trial;" to Jundishapur Journal of Natural Pharmaceutical Products. We need you to address the following issues:

Please follow the journal's instructions for manuscript writing:
1. The abstract of your manuscript is not in line with the journal's instructions: 1) Introduction (Background), 2) Material and methods, 3) Results, and 4) Conclusion, in that order. Why did you write about Ethics and Dissemination in the Abstract of the manuscript? It is not necessary to mention it in the abstract section.

2. Introduction: The introduction is written concisely, and it is expected that the first part will provide a detailed explanation of diabetes and its epidemiology, followed by more information about the importance and effectiveness of herbal medicines such as Curcumin and Amla in improving the lipid profile, glycemic status, antioxidant indices, inflammatory factors, and liver enzyme levels in patients with diabetes.

3&4. Methods and Results: You should completely separate these two parts from each other. Currently, there is no order or coherence in the above article. The methods and the results are intertwined, and there is no separate section under the title of Results at all. Please use similar articles and edit your manuscript according to the format of a scientific article.

5. Discussion: Please discuss your findings and compare them with those of other studies. You discussed the other studies' findings more than your own.

6. Please revise the English writing of the manuscript and try to improve it.

Thank you for submitting your work.

Soheil Abbaspour-Ravasjani Reviewer

MAJOR REVISION 15 Aug 2024

Title:
1. The title is clear but could be slightly rephrased for better readability and conciseness. Consider: Revised Title: "Effects of Curcumin and Amla Co-supplementation on Lipid Profile, Glycemic Status, Antioxidant Indices, Inflammatory Factors, and Liver Enzymes in Type 2 Diabetes Patients: A Double-blind, Randomized Controlled Trial Protocol"

Abstract:
2. The word "will" is overused; try rephrasing for a more active, present-tense description.
3. "This study follows Good Clinical Practice (GCP) and the Declaration of Helsinki" might be better placed in the "Methods" section for better flow.
4. The phrase "Due to access and treatment limitations" could be improved by specifying "limited access to treatments."
5. "Participants, aged 25-65 with a BMI of 25- 34.9" should use a range dash (–) instead of a hyphen (-).
6. There are some comma issues, such as the unnecessary comma before the phrase "with therapeutic properties."

7. Specify the rationale for choosing curcumin and Amla. While you mention their properties, briefly adding why their combination is being tested would enhance the abstract.
8. Mention any control factors for diet or medication use more explicitly.

Introduction:
9. Expand on why herbal supplements are becoming popular. Briefly mention the limitations of current therapies for T2DM to justify this.
10. "Curcumin may improve insulin sensitivity, reduce serum glucose and lipid levels, and lower inflammatory biomarkers," should be cited properly.
11. The paragraph on Amla could be expanded to include more specific studies or data supporting its use in T2DM.
12. The sentence "Diabetes, a widespread chronic disease, with over 90% being type 2 diabetes, poses a significant challenge in managing co-morbidities" would flow better as: "Diabetes is a widespread chronic disease, with over 90% of cases being type 2, posing significant challenges in managing comorbidities."
13. Consistent use of T2DM instead of "type 2 diabetes" will improve clarity and reduce redundancy.
14. The introduction could benefit from a brief explanation of the mechanisms through which curcumin and Amla exert their effects. For example, mention specific signaling pathways or antioxidant mechanisms.

Methods and Analyses:
Study Design:
15. Specify the inclusion criteria more clearly; the age range and BMI are currently missing in "aged xx-yy."
16. The sentence "presented in (Figs. 1 and 2)" should be integrated more smoothly into the text.
17. "This single-center randomized, double-blind, placebo-controlled, parallel-group study for 12 weeks..." is a bit cumbersome. Consider breaking it down: "This is a single-center, randomized, double-blind, placebo-controlled, parallel-group study lasting 12 weeks..."
18. Justify the choice of sample size (50 participants). How was this number determined?
19. Clarify whether there is any stratification during randomization to ensure balanced groups regarding potential confounders.

Primary Endpoints:
20. The description of primary endpoints is generally clear. However, "between groups" could be more specific: "differences between the intervention and control groups."
21. "A secondary endpoints is..." should be "Secondary endpoints are..."
22. Consider explaining why these particular endpoints were chosen. Are they the most relevant indicators for assessing the effects of curcumin and Amla?

Study Population and Settings:
23. Define the method for selecting the study population more clearly (e.g., convenience sampling, criteria for eligibility).
24. Remove the "…" after "social media app." It's better to list the apps if possible or use "such as."
25. It may be useful to mention the total population from which the sample is drawn to provide context for the sampling method.

Randomization and Blinding:
26. The process of randomization is clear but could benefit from a brief description of how blinding is maintained during data collection and analysis.
27. The phrase "Available [Online]" should be revised to just "Available online," or simply "available from."
28. Elaborate on how the randomization and blinding processes will ensure the study's rigor, particularly in avoiding bias.

Inclusion/Exclusion Criteria:
29. The criteria are well-defined but could be ordered to prioritize major inclusion/exclusion criteria first.
30. Use a consistent format for listing criteria (e.g., starting each criterion with a capital letter or maintaining the same tense throughout).
31. Consider adding any criteria related to the stability of participants' condition or their recent changes in medication to better control the study's internal validity.

Intervention:
32. Clearly specify the rationale behind the dosage and the composition of the capsules used.
33. The sentence "Both the study intervention and placebo capsules are visually identical, provided by Arjuna Natural Pvt. Ltd., India" could be rephrased for clarity: "The intervention and placebo capsules, which are visually identical, are provided by Arjuna Natural Pvt. Ltd., India."
34. Justify the choice of BCM-95®/Curcugreen® and the specific standardization percentages used in the study. Are these the most effective forms according to the literature?

Discontinuation of Treatment:
35. The discontinuation criteria are appropriate, but consider including a clause on how discontinuation data will be handled statistically.
36. The phrase "If non-cooperation is due to study intervention side effects..." could be clearer as "If non-cooperation results from side effects related to the study intervention..."
37. Mention any plans for follow-up on participants who discontinue the study to monitor potential long-term effects.

Outcome Measures:
38. "At the study's outset..." should be more precise. Consider specifying "At baseline and after 12 weeks of intervention..."
39. The structure of some sentences could be improved for clarity. For example, "smoking and alcohol consumption, family disease history, and dietary habits" should be "smoking, alcohol consumption, family disease history, and dietary habits."
40. The selection of biochemical markers should be justified with references to studies that highlight their relevance to curcumin and Amla's effects.

Conclusion:
41. Overall, the article is well-structured and detailed, but it would benefit from the following improvements:
42. Consistency in terminology and formatting throughout the text.
43. Clear justification for the methodological choices made, particularly regarding the sample size, inclusion/exclusion criteria, and specific biochemical markers selected.
44. Flow and readability improvements by restructuring sentences for clarity and conciseness.
45. Enhanced scientific rigor by citing relevant literature more extensively, especially regarding the mechanisms of action of curcumin and Amla in T2DM management.
Here is a useful reference for the authors' consideration:
https://www.thieme-connect.com/products/ejournals/abstract/10.1055/a-0646-3803

Associate Editor MAJOR REVISION 17 Aug 2024

Thank you for submitting your manuscript to Jundishapur Journal of Natural Pharmaceutical Products. Please address the questions of the reviewers in a thorough manner and highlight any changes in the text in order to make your manuscript suitable for publication.

It would also be an honor to have the author team contribute as reviewers for this journal.
Your assistance as a reviewer for Jundishapur Journal of Natural Pharmaceutical Products aids the editorial board in reaching a decision, and also enables the author(s) to disseminate their work at the highest possible quality.
Thank you in advance for your contribution and time.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

	Dear Editor and Reviewers, **Thank you for taking the time to review our manuscript. We sincerely appreciate your insightful comments and constructive feedback, which have significantly enhanced the quality of our work. Your expertise and suggestions were invaluable, and we have incorporated your recommendations into our revisions. We have provided a separate response addressing each of your comments.** **Thank you once again for your support.**
Reviewer 1	
Authors answer	Dear reviewer, we appreciate your expertise and constructive suggestions, to improve the work. We addressed the peer review comments one by one and incorporated them into the manuscript, highlighting the changes.
comment1	*Please follow the journal's instructions in manuscript writing:* *1. Abstract of your manuscript is not in line with the journals' instructions: 1) Introduction (Background), 2) Material and methods, 3) Results, and 4) Conclusion sequentially. Why did you write about Ethics and Dissemination in the Abstract of the manuscript? It is not necessary to mention it in the abstract section.*
Authors answer	Dear Reviewer, Thank you for your valuable feedback. We have revised the manuscript to align with the format of the latest published articles, which includes the following sections following the latest journal issues: 1) Background, 2) Objectives, 3) Methods, 4) Results, and 5) Conclusion. Please note that this study is a protocol for a randomized controlled clinical trial, as stated in the title, and therefore does not present any results at this time. We have also removed the "Ethics and Dissemination" section from the Abstract as requested.it was moved to the method section. Thank you once again for your input.
comment2	*Introduction: The introduction part is written concisely, and it is .2 expected that in the first part, a detailed explanation will be given about the disease of diabetes and its epidemiology and then some more about the importance and effectiveness of herbal medicines such as Curcumin and Amla in improving the lipid profile, glycemic status, antioxidant indices, .inflammatory factors, and liver enzyme levels in patients with diabetes*
Authors answer	Dear Reviewer, Thank you for your valuable comments. We have incorporated the requested information concerning diabetes, including relevant epidemiological data and the effectiveness of herbal medicines like Curcumin and Amla in improving lipid profiles, glycemic control, antioxidant indices, inflammatory markers, and liver enzyme levels in patients with diabetes. The revised sections are highlighted in the

	manuscript.
Comment3& 4	*Methods and Results: You should completely separate these two .4&3 parts from each other. Currently, there is no order and coherence in the above article. The method and the results are intertwined, and there is no separate section under the title of Results at all. Please use similar articles .and edit your manuscript according to the format of a scientific article*
Authors answer	Dear reviewer, thanks for the comments. The present manuscript is a protocol study of the randomized controlled double blinded clinical trial, as mentioned in the title. Therefore, there is no result. All the sections and subtitles have been selected following the requirements of the protocol study.
Comment5	*Discussion: Please discuss about your findings and compare them with .5 other studies. You discussed more about the other studies' findings instead .of yours*
Authors answer	Dear reviewer, Thank you for your comments. The current manuscript presents a protocol for a randomized controlled double-blind clinical trial, as indicated in the title. As such, there are no results to report at this stage. In the discussion section, we have provided a brief overview in line with common practices for protocol studies. Some published articles in this field opt to discuss findings from other studies, while others choose to omit a discussion section altogether. However we provide a discussion in brief.
Comment6	*Please revise the English writing of the manuscript and try to improve .6 .it*
Authors answer	Dear reviewer, thanks for the comment. We improved the level of manuscript language, hoping to complete the satisfaction.
Reviewer 2	
Authors answer	Dear reviewer, we are thankful for your thoughtful and constructive comments. Your insights and suggestions have been valuable in enhancing the quality of our manuscript. We addressed the peer review comments one by one and incorporated them into the manuscript, highlighting the changes.
comment1	*-The abstract is not written correctly and lacks method, results and conclusion sections.*
Authors answer	Dear reviewer, Thank you for your valuable comments. The current manuscript presents a protocol for a randomized controlled double-blind clinical trial, as indicated in the title. At this stage, there are no results and conclusion to report.

comment2	*The introduction is very short. The authors did not explain the background of the study.*
Authors answer	Dear reviewer, Thank you for your feedback. We have provided a more detailed context, including relevant literature and the rationale behind our research. Thank you again for your constructive comments.
comment3	*There are no results, neither in the abstract nor in the manuscript.*
Authors answer	Dear reviewer, thanks for the comment. The current manuscript is related to the protocol study of randomized controlled double-blind clinical trial, as indicated in the title. Therefore there is no result.
comment4	*The discussion is very short, incomplete and defective. there are no conclusions. limitations of the study are not mentioned, however, without the results of the study, the discussion is meaningless.* *In my opinion, this manuscript is not suitable for publication.*
Authors answer	Dear reviewer, thanks for the comment. The present manuscript is related to the protocol study of randomized controlled double-blind clinical trial, as indicated in the title. Hence, there is no result at this stage.
Reviewer 3	Dear reviewer, we sincerely appreciate the time and effort you considered in reviewing our manuscript. Your expertise has provided us with valuable insights and a fresh perspective on our work, significantly enhancing its quality. We addressed the peer review comments one by one and incorporated them into the manuscript, highlighting the changes.
Comment	*The title is clear but could be slightly rephrased for better readability .1 and conciseness. Consider: Revised Title: "Effects of Curcumin and Amla Co-supplementation on Lipid Profile, Glycemic Status, Antioxidant Indices, Inflammatory Factors, and Liver Enzymes in Type 2 Diabetes "Patients: A Double-blind, Randomized Controlled Trial Protocol*
Authors answer	Dear reviewer, Thank you for your valuable feedback. We have revised the title as suggested.
Comment	*Abstract:* *2. The word "will" is overused; try rephrasing for a more active and present description.* *3. "This study follows Good Clinical Practice (GCP) and the Declaration of Helsinki" might be better placed in the "Methods" section for better flow.* *4. The phrase "Due to access and treatment limitations" could be improved by specifying "limited access to treatments."* *5. "Participants, aged 25-65 with a BMI of 25- 34.9" should use a range dash (–) instead of a hyphen (-).* *6. There are some comma issues, such as before the phrase "with therapeutic properties" which isn't necessary.* *7. Specify the rationale for choosing curcumin and Amla. While you mention their properties, briefly adding why their combination is being*

	tested would enhance the abstract. *8. Mention any control factors for diet or medication use more explicitly.*
Authors answer	Dear reviewer, thanks for the precise comments. 2. We considered using present tense or more active verbs to reduce reliance on "will." 3. we moved the mention of Good Clinical Practice (GCP) and the Declaration of Helsinki in the "Methods" section to improve flow. 4. We changed "Due to access and treatment limitations" to " limited access to conventional treatments " for clarity. 5. We replaced the hyphen (-) with a range dash (–) in "aged 25-65 with a BMI of 25-34.9." 6. We removed unnecessary commas, such as before "with therapeutic properties." 7. We briefly explained why curcumin and Amla were chosen for testing their combination in the abstract. 8. We added a statement on control factors regarding diet or medication use.
Comment	*:Introduction* *Expand on why herbal supplements are becoming popular. Briefly .9 .mention the limitations of current therapies for T2DM to justify this* *Curcumin may improve insulin sensitivity, reduce serum glucose and " .10 lipid levels, and lower inflammatory biomarkers," should be cited .properly* *The paragraph on Amla could be expanded to include more specific .11 .studies or data supporting its use in T2DM* *The sentence "Diabetes, a widespread chronic disease, with over 90% .12 being type 2 diabetes, poses a significant challenge in managing co-morbidities" would flow better as: "Diabetes is a widespread chronic disease, with over 90% of cases being type 2, posing significant challenges ".in managing comorbidities* *Consistent use of T2DM instead of "type 2 diabetes" will improve .13 .clarity and reduce redundancy* *The introduction could benefit from a brief explanation of the .14 mechanisms through which curcumin and Amla exert their effects. For .example, mention specific signaling pathways or antioxidant mechanisms*
Authors answer	.Dear reviewer, thanks for the valuable feedback 9. the paragraph considered and referenced. 10. it has been properly cited following relevant literature to substantiate these claims. 11. a complete paragraph considered with the inclusion of Amla properties and clinical studies using the same herb. 12. The sentence has been revised for better clarity

	13. We have ensured the consistent use of "T2DM" throughout the manuscript instead of alternating with "type 2 diabetes 14. We have highlighted the key signaling pathways of both herbs.
Comment	*Methods and Analyses:* *Study Design:* *15. Specify the inclusion criteria more clearly; the age range and BMI are currently missing in "aged xx-yy."* *16. The sentence "presented in (Figs. 1 and 2)" should be integrated more smoothly into the text.* *17. "This single-center randomized, double-blind, placebo-controlled, parallel-group study for 12 weeks..." is a bit cumbersome. Consider breaking it down: "This is a single-center, randomized, double-blind, placebo-controlled, parallel-group study lasting 12 weeks..."* *18. Justify the choice of sample size (50 participants). How was this number determined?* *19. Clarify whether there is any stratification during randomization to ensure balanced groups regarding potential confounders.*
Authors answer	,Dear reviewer .Age range and BMI has been added .15 .integrated in the text of manuscript smoothly "(Figs. 1 and 2) .16 This statement replaced in the text of manuscript "*This is a single-* .17 *center, randomized, double-blind, placebo-controlled, parallel-group study "...lasting 12 weeks* the detail explanation with statistical formula have been included in the .18 "Method section in the subtitle of "sample size Patients are assigned to study groups using block randomization with a .19 block size of four to ensure equal proportions. They are stratified by age .and gender
Comment	*:Primary Endpoints* *The description of primary endpoints is generally clear. However, .20 "between groups" could be more specific: "differences between the ".intervention and control groups* *"...A secondary endpoints is..." should be "Secondary endpoints are" .21* *Consider explaining why these particular endpoints were chosen. Are .22 they the most relevant indicators for assessing the effects of curcumin and ?Amla*
Authors answer	.Dear reviewer, thanks for the comments

	differences between the intervention and control groups." It was " .20 .applied in the text highlighted .Secondary endpoints are..." It was applied in the text highlighted"21 *22.* These references will explain the importance of Amla and curcumin on T2DM. The highlighted references in the manuscript text list will also support the importance of these two herbs. -PMID: 36934568 -*Nutraceuticals* 2023, *3*(3), 329-352; https://doi.org/10.3390/nutraceuticals3030026 -PMID: 37748368 -Front. Endocrinol., 03 May 2021.Sec. Translational and Clinical Endocrinology Volume 12 - 2021 | https://doi.org/10.3389/fendo.2021.669448 - -Effects of curcumin/turmeric supplementation on glycemic indices in adults: A grade-assessed systematic review and dose–response meta-analysis of randomized controlled trials. Diabetes & Metabolic Syndrome: Clinical Research & Reviews Volume 17, Issue 10, October 2023, 102855
Comment	*:Study Population and Settings* *Define the method for selecting the study population more clearly .23* *.(e.g., convenience sampling, criteria for eligibility)* *Remove the "…" after "social media app." It's better to list the apps if .24* *".possible or use "such as* *It may be useful to mention the total population from which the sample .25* *.is drawn to provide context for the sampling method*
Authors , answer	.Dear reviewer, we appreciated for suggested comments the sampling method involves selecting participants based on .23 predefined inclusion criteria to ensure they meet specific characteristics relevant to the study. Patients are assigned to study groups using block randomization with a block size of four to ensure equal proportions. They are stratified by age and gender. The random number sequence is generated .by Sealed Envelope Ltd (2022), accessible online it was revised " Participants will be contacted via phone, text, or social .24 media Such as WhatsApp, telegram, or local application about the study

	”.and invited to an initial appointment for informed consent The flow diagram for the current protocol study is provided, but it does .25 not include exact numbers at either the baseline or the end of the study. Please note that this manuscript pertains to the protocol of a randomized .controlled trial (RCT)
Comment	*:Randomization and Blinding* *The process of randomization is clear but could benefit from a brief .26 description of how blinding is maintained during data collection and .analysis* *The phrase "Available [Online]" should be revised to just "Available .27 ".online," or simply "available from* *Elaborate on how the randomization and blinding processes will .28 .ensure the study's rigor, particularly in avoiding bias*
Authors answer	.Dear reviewer, thanks for the valuable comments 26. it was revised “ Patients are assigned to study groups using block randomization with a block size of four to ensure equal proportions. They are stratified by age and gender. The random number sequence is generated by Sealed Envelope Ltd (2022), accessible online. This study follows a double-blind design, with identical-looking intervention and placebo capsules. An independent individual codes the capsules (A and B), and both study research team and participants remain unaware of group assignments until the trial concludes to maintain blinding and ensure unbiased outcomes.” 27.it was revised. 28. In this randomized controlled trial (RCT), block randomization with a block size of four is used to ensure balanced participant distribution across study groups, helping to reduce selection bias. Participants are stratified by age and gender to comparability. An external service, Sealed Envelope Ltd, generates the random number sequence, ensuring a secure and unbiased process. Blinding is implemented for both participants, investigators, preventing knowledge of group assignments.
Comment	*:Inclusion/Exclusion Criteria* *The criteria are well-defined but could be ordered to prioritize major .29 .inclusion/exclusion criteria first* *Use a consistent format for listing criteria (e.g., starting each criterion .30 .with a capital letter or maintaining the same tense throughout)* *Consider adding any criteria related to the stability of participants' .31 condition or their recent changes in medication to better control the*

	" .*study's internal validity*
Authors answer	.Dear reviewer, thanks for the comments .the inclusion and exclusion criteria has been prioritized .29 . it was started each criterion with a capital letter.30 The internal validity of our study by ensuring that participants have .31 stable conditions and consistent medication regimens, as we considered in our exclusion criteria, Recent use of illicit or prescribed medications, which will help to control for confounding variables and better isolate the effects of the co-supplementation of Amla and Curcumin. Hence, .ultimately strengthens the reliability of the study's outcomes
Comment	*Intervention:* *32. Clearly specify the rationale behind the dosage and the composition of the capsules used.*
Authors answer	.Dear reviewer, Thank you for your valuable feedback 32.The rationale behind the dosage and composition of the capsules containing amla and curcumin was based on existing literature and previous research findings that suggest specific dosages for optimal efficacy. The chosen lower combined dosage of 250 mg Amla+curcumin250 mg per day, delivered in two capsules of 500 mg each, was selected to provide a clinically relevant amount of both amla and curcumin, ensuring sufficient bioactive compound intake to elicit the desired physiological effects. Amla (Phyllanthus emblica) is known for its high vitamin C content and antioxidant properties, which can support overall health. Curcumin (Curcuma longa), on the other hand, has been extensively studied for its anti-inflammatory and antioxidant effects. The combination of these two compounds is intended to leverage their synergistic effects. The composition was established considering safety, tolerability, and efficacy as reported in prior studies, ensuring that these dosages fall within acceptable ranges for human consumption.
Comment	*The sentence "Both the study intervention and placebo capsules are .33 visually identical, provided by Arjuna Natural Pvt. Ltd., India" could be rephrased for clarity: "The intervention and placebo capsules, which are*

	.'visually identical, are provided by Arjuna Natural Pvt. Ltd., India .
Authors answer	.Dear reviewer, thanks for the comment .it was revised and highlighted.33
Comment	*34. Justify the choice of BCM-95®/Curcugreen® and the specific standardization percentages used in the study. Are these the most effective forms according to the literature?*
Authors answer	Dear reviewer, Thank you for your insightful comment regarding the choice of BCM-95®/Curcugreen® and the standardization percentages employed in our study. 34.BCM-95®/Curcugreen® is a formulation of curcumin that has been shown to enhance bioavailability significantly compared to standard curcumin extracts. This particular formulation combines curcumin with essential oils derived from turmeric, which not only improves its solubility and absorption but also maintains its efficacy. The specific standardization percentages used in our study were informed by the existing literature, which indicates that higher concentrations of bioactive compounds in formulations like BCM-95® can lead to more pronounced therapeutic effects. For instance, studies have demonstrated that curcumin formulations that achieve at least 95% standardization can provide optimal health benefits, particularly with anti-inflammatory and antioxidant properties. Moreover, a review of recent clinical studies indicates that BCM-95®/Curcugreen® is one of the most effective forms of curcumin available, with data supporting its use in various health conditions. Our choice was grounded in the evidence demonstrating its enhanced absorption, effectiveness in achieving therapeutic outcomes, and safety profile. References: 1. Bioavailable turmeric extract for knee osteoarthritis: a randomized, non-inferiority trial versus paracetamol.*Trials* volume 22, Article number: 105 (2021)

	2. Highly Bioavailable Forms of Curcumin and Promising Avenues for Curcumin-Based Research and Application: A Review. *Molecules* 2020, *25*(6), 1397; https://doi.org/10.3390/molecules25061397 3. Ameliorative Effects of Curcumin on Type 2 Diabetes Mellitus. *Molecules* 2024, *29*(12), 2934; https://doi.org/10.3390/molecules29122934 4. The Effects of Curcumin on Diabetes Mellitus: A Systematic Review. Front. Endocrinol., 03 May 2021 5. Curcumin Formulations for Better Bioavailability: What We Learned from Clinical Trials Thus Far?ACS Omega. 2023 Mar 28; 8(12): 10713–10746. doi: 10.1021/acsomega.2c07326.PMCID: PMC10061533.PMID: 37008131
Comment	*Discontinuation of Treatment:* *35. The discontinuation criteria are appropriate but consider including a clause on how discontinuation data will be handled statistically.*
Authors answer	Dear reviewer, thanks for the comment. 35.To manage discontinuation data effectively, primarily, we will use Intention-to-Treat Analysis (ITT) to include all randomly assigned participants, minimizing bias from dropouts. Additionally, we will conduct sensitivity analyses to evaluate the robustness of our findings. We will provide descriptive statistics about participant dropout rates, and reasons for discontinuation. we will monitor and report compliance rates throughout the trial. This includes documenting the number of participants who adhered to the study protocol.
Comment	*The phrase "If non-cooperation is due to study intervention side .36 effects..." could be clearer as "If non-cooperation results from side effects "...related to the study intervention*
Authors answer	Dear reviewer, thanks for the comment. 36. it was revised : If non-cooperation results from side effects related to the study intervention side effects, necessary follow-up should continue until the patient's condition returns to normal.
Comment	*37. Mention any plans for follow-up on participants who discontinue the*

	study to monitor potential long-term effects.
Authors answer	Dear reviewer, thanks for the comment. 37.we will implement a follow-up via phone, for Participants who discontinue the study to assess their health status, dietary habits, and any relevant outcomes related to T2DM. We will specifically inquire about any changes in medication, lifestyle factors, and health status that may be influenced by the dietary supplements they received during the trial. Additionally, we will document and analyze the follow-up data to identify the impact of the supplementation, which will be included in the final study results and discussions. This comprehensive approach provides valuable insights into the sustainability of any observed benefits or outcomes associated with the interventions.
Comment	*:Outcome Measures* *At the study's outset..." should be more precise. Consider specifying " .38* *"..."At baseline and after 12 weeks of intervention* *The structure of some sentences could be improved for clarity. For .39* *example, "smoking and alcohol consumption, family disease history, and dietary habits" should be "smoking, alcohol consumption, family disease ".history, and dietary habits* *The selection of biochemical markers should be justified with .40* *references to studies that highlight their relevance to curcumin and Amla's .effects*
Authors answer	Dear reviewer, thanks for the comment. 38.it was revised and highlighted. 39. it was revised and highlighted. 40. These references will explain the importance of Amla and curcumin on T2DM. The highlighted references in the manuscript text list will also support the importance of these two herbs. -PMID: 36934568 -*Nutraceuticals* 2023, *3*(3), 329-352; https://doi.org/10.3390/nutraceuticals3030026 -PMID: 37748368 -Front. Endocrinol., 03 May 2021.Sec. Translational and Clinical

	Endocrinology Volume 12 - 2021 | https://doi.org/10.3389/fendo.2021.669448 -Effects of curcumin/turmeric supplementation on glycemic indices in adults: A grade-assessed systematic review and dose–response meta-analysis of randomized controlled trials. Diabetes & Metabolic Syndrome: Clinical Research & Reviews Volume 17, Issue 10, October 2023, 102855
Comment	*Conclusion:* *41. Overall, the article is well-structured and detailed, but it would benefit from the following improvements:* *42. Consistency in terminology and formatting throughout the text.* *43. Clear justification for the methodological choices made, particularly regarding the sample size, inclusion/exclusion criteria, and specific biochemical markers selected.* *44. Flow and readability improvements by restructuring sentences for clarity and conciseness.* *45. Enhanced scientific rigor by citing relevant literature more extensively, especially regarding the mechanisms of action of curcumin and Amla in T2DM management.* *Here is a useful reference for authors observation:* *https://www.thieme-connect.com/products/ejournals/abstract/10.1055/a-0646-3803*
Authors answer	.Dear reviewer, 41. Thanks for the comments we checked terminology and formatting throughout the text .42 we already applied in the text of the manuscript and answered .43 .separately we tried to improve the manuscript with the inclusion of necessary .44 .information the relevant references were added in the manuscript text to provide .45 more clarification of both herbs for the readers. additionally, thanks for the suggested link

2 Revision 1

1 comment · 27 Oct 2024

Soheil Abbaspour-Ravasjani Reviewer

ACCEPT 27 Oct 2024

Accepted for publication

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

	Dear Editor and Reviewers, **Thank you for taking the time to review our manuscript. We sincerely appreciate your insightful comments and constructive feedback, which have significantly enhanced the quality of our work. Your expertise and suggestions were invaluable, and we have incorporated your recommendations into our revisions. We have provided a separate response addressing each of your comments.** **Thank you once again for your support.**
Reviewer 1	
Authors answer	Dear reviewer, we appreciate your expertise and constructive suggestions, to improve the work. We addressed the peer review comments one by one and incorporated them into the manuscript, highlighting the changes.
comment1	*method:* *Why have you considered the age range of 20 to 25? Usually, in the studies conducted on adults, the age range of 18 to 65 is considered*
Authors answer	Dear Reviewer,Thank you for your valuable and precise feedback. We have already taken into account the age range of 25 to 65 years, as indicated in the highlighted sections of the abstract and methods in the present manuscript. This point has been rechecked.
comment2	*Those who entered the study had a stable diet. What do you mean by a ?stable diet* *?how did you do the random assignment* .

Authors answer	Dear Reviewer, Thank you for your insightful questions regarding our study. we refer to participants who consistently maintained their usual dietary intake without significant fluctuations in their eating habits in the weeks leading up to the study. This will assessed through a three-day 24-hr dietary recall questionnaire (one weekend day and two weekdays), which allow us to confirm that participants have a regular intake of macronutrients and micronutrients. In the method section has been already illustrated under subtitle “dietary assessment”.
Comment3	*In the section secondary endpoint and primary you said that you measure the markers. How practical and doable is this work? These tests are very expensive and very specialized*
Authors answer	Dear reviewer, We appreciate your valuable feedback regarding the practicality of measuring the markers in our study, recognizing the specialized and costly nature of tests for lipid profiles, glycemic status, antioxidant indices, inflammatory factors, and liver enzymes. To address these concerns, we have established partnerships with accredited laboratories to enhance measurement quality and potentially negotiate reduced testing rates. We have also prioritized biomarkers based on their relevance to our objectives, ensuring a strategic focus on the most critical assessments. Additionally, our budget accounts for these specialized testing costs, supported by a thorough financial analysis to secure adequate funding without compromising the integrity of our study. We are confident that these measures will ensure the feasibility and success of our research.
Comment4	*While you said in exclusion criteria smokers and alcoholics, are excluded from the study in outcome measure said again If you*

	reevaluate, please explain this part .
Authors answer	Dear reviewer, Thank you for your insightful comment. We have established clear exclusion criteria to maintain the integrity of our study by excluding individuals who smoke or consume alcohol, as these factors can significantly influence physiological and psychological outcomes. However, we aimed to assess whether there were any changes in these behaviors during the trial period, which could provide valuable data on the intervention's broader relevance and impact on lifestyle changes, even among initially excluded participants.

3 Revision 2

2 comments · 23 Nov 2024 – 23 Nov 2024

Referee 1 Reviewer

MINOR REVISION 23 Nov 2024

1- The abstract contains more than 250 words.
2- According to the clinical trial protocol compliance structure, the irct code should be included in the abstract.
3- It is better to mention which phase of clinical trial studies the protocol relates to.

Associate Editor

MINOR REVISION 23 Nov 2024

Please revise the manuscript and submit a point-by-point response to the reviewers' comments and concerns.

Please cite a reference indicating that the number of individuals in each group is statistically valid.

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Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewers' Comments:

Dear Editor and Reviewers,

Thank you very much for your valuable comments. We have addressed each comment individually, and our responses are highlighted in blue within the manuscript.

Best regards,

Borazjani Fatemeh

Reviewer 1:

1- The number of abstract words is more than 250 words

Author Answer: Dear reviewers, many thanks for the comments. The total number of abstract has been reduced to *223.*

2- According to the clinical trial protocol compliance structure, the irct code should be registered in abstract

Author Answer: Dear reviewers, many thanks for the comments. the IRCT cod and URL address has been added after abstract.

3- It is better to mention which phase of clinical trial studies the protocol is related to

Author answer: Dear reviewers, many thanks for the comments. the present study is the III phase of clinical trial that aimed to compares the co-supplementation of amla and curcumin to standard treatments among Diabetes type 2.

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4 Revision 3

0 comments

No public comments in this round.