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OPEN PEER REVIEW

Effects of Ellagic Acid Supplementation on Antioxidant Status and Symptom Improvement in Patients with Major Depressive Disorder: A Double-blind Randomized Clinical Trial

Seyed Hamzeh Hosseini, Mehran Zarghami, Hossein Khadem Haghighian, Amirhosein Babaie Roochi, Saeid Abediankenari, Saeed Kargar-Soleimanabad, Gholamreza Houshmand

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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

4 comments · 13 Mar 2024 – 22 Apr 2024

Referee 1 Reviewer

MAJOR REVISION 13 Mar 2024

I appreciate the efforts put into this study on the effects of ellagic acid supplementation in patients with major depression. The findings have the potential to contribute significantly to our understanding of alternative treatment options for depression. However, I would like to highlight several points that need to be addressed in a major revision:

Basic points

1. Inappropriate use of matching: There are various methods available to control confounding factors during the study design phase, including randomization, matching, and restriction. However, the best method to control confounding, which is only feasible in experimental studies, is randomization, and in such studies, there is no need for matching. Nonetheless, in this study, the samples were matched for age, gender, and height, which reduces generalizability and study power.
2. Small sample size: The study only included a total of 40 patients diagnosed with major depressive disorder. A larger sample size would provide more robust and generalizable results.
3. Short study duration: The study lasted for only 8 weeks. A longer duration would provide a better understanding of the long-term effects of ellagic acid supplementation on depressive symptoms and antioxidant status.
4. Lack of placebo blinding: The placebo group received a capsule containing wheat flour, which was identical in appearance to the intervention substance. However, the study does not specify whether the participants and researchers were blinded to the treatment allocation. Lack of blinding can introduce information bias and affect the study outcomes.
5. Lack of comparison with conventional antidepressant treatment: The study does not include a comparison group receiving only conventional antidepressant treatment. A comparison with standard treatment would provide a better understanding of the additive effects of ellagic acid supplementation.
6. Lack of mention of side effects: The study does not mention any potential side effects or adverse reactions associated with ellagic acid supplementation. It is important to consider and discuss the safety profile of the intervention to provide a balanced assessment of its benefits and risks.

Abstract

7. Insufficient contextual information: The abstract does not provide sufficient background information about major depressive disorder, ellagic acid, or the current understanding of the relationship between antioxidant status and depressive symptoms.
8. Limited information in methods: The methods section of the abstract does not provide information about the sampling methods, type of randomization, study design, demographic characteristics of the sample (e.g., age, gender, ethnicity), blinding, statistical methods, or the significance level.
9. Incomplete reporting of the results: The abstract offers a concise summary of the study's findings; however, it could be improved by including specific numerical values and effect sizes. Furthermore, instead of reporting p-values as "less than 0.05" or "less than 0.01," it is preferable to provide the exact p-values. Additionally, it does not mention whether the observed changes were statistically significant when compared to the placebo group.
10. Lack of key words specificity: The chosen keywords lack specificity and do not provide specific details about the study. To improve specificity, consider adding more specific terms related to the study's focus, design, measurement methods, outcomes, and demographic characteristics of the participants.

Methods

11. Incomplete description of the study design: The provided description lacks specific details about the randomization procedure, blinding methods, and allocation concealment.
12. Inadequate reporting of ethical approval: The study does not provide sufficient information about the ethics committee responsible for the approval, the date of approval, or any additional ethical considerations.
13. Lack of information on sample size calculation: The methods section does not mention how the sample size was determined. It is important to justify the chosen sample size based on statistical power calculations, anticipated effect sizes, and the desired level of significance.
14. Insufficient details on intervention and placebo: The description of the intervention and placebo is limited. It does not provide information about the composition, appearance, or administration of the ellagic acid supplement and placebo.
15. Lack of information on outcome assessments: The methods section does not provide enough details about the assessment methods for measuring oxidative stress indices, depression severity, and nutritional factors. Specific measurement tools, protocols, and the timing of assessments should be clearly described to ensure the reliability and validity of the results.
16. Absence of reporting on missing data and dropout rates: The methods section does not mention how missing data or participant dropout was handled in the analysis.
17. Lack of blinding assessment: The methods section does not mention any assessment or validation of the blinding effectiveness.
18. Incomplete disclosure of conflicts of interest: The methods section does not provide information about any conflicts of interest among the researchers or funding sources.

Results

19. Inadequate reporting of demographic characteristics: The Results section provides limited information about the demographic characteristics of the participants. Although the mean age is reported for each group, there is no information about the standard deviation or range. Additionally, the number of male and female participants is mentioned, but specific numbers (X and Y) are not provided, making it difficult to assess the gender distribution accurately.
20. Insufficient reporting of dietary comparison results: The Results section states that there was no significant difference in dietary intake between the two groups at the beginning of the study and no significant change during the study. However, no statistical analysis results or p-values are provided to support these statements. It is important to report the statistical tests used and the corresponding p-values.
21. Lack of clarity in reporting depression scores: Although the Results section mentions a significant decrease in depression scores in the ellagic acid group and non-significant reductions in the placebo group, it does not provide specific values or measures of effect size. The percentage reductions in Beck's depression inventory and Hamilton's depression scale are mentioned but without the corresponding baseline values. This lack of specific data makes it difficult to fully assess and interpret the findings.
22. Incomplete reporting of oxidant and antioxidant evaluation: The Results section provides limited information about the results of the oxidant and antioxidant evaluation. Although it mentions a significant increase in total antioxidant capacity (TAC) and a significant decrease in the malondialdehyde (MDA) level in the ellagic acid group, it does not provide specific values, measures of effect size, or the statistical tests used. Additionally, it does not mention the baseline values or the absolute changes in TAC and MDA levels. These details are necessary for a comprehensive understanding of the results.
23. Insufficient reporting of statistical significance: The Results section mentions statistical significance ($p < 0.05$) for some findings but does not report the exact p-values or the statistical tests used. It is essential to provide the actual p-values to allow readers to assess the strength of the evidence and determine the statistical significance of the results.

Discussion

24. Lack of comparison with previous studies: Although the Discussion section briefly mentions a few studies that investigated the effects of ellagic acid, it does not provide a thorough comparison of the current study's findings with previous research. It is important to discuss similarities, differences, and potential explanations for any discrepancies between the studies to provide a broader understanding of the topic.
25. Absence of mechanistic explanations: The Discussion section does not explore potential underlying mechanisms by which ellagic acid may exert its effects. It merely mentions different pathways and systems without discussing how they might be involved in the observed outcomes. Providing mechanistic insights can help readers understand the biological rationale behind the findings.
26. Incomplete consideration of alternative explanations: The Discussion section does not thoroughly consider alternative explanations for the observed effects. It does not discuss other factors that could have influenced the outcomes or potential confounding variables that were not accounted for in the study design. Addressing alternative explanations strengthens the validity of the results.
27. Insufficient discussion of limitations: The Discussion section does not adequately address the limitations of the study. It does not mention any potential confounding factors, sources of bias, or other limitations that may affect the generalizability or reliability of the findings. Discussing limitations is essential for providing a balanced view of the study's strengths and weaknesses.

Conclusion

28. Overgeneralization: The conclusion makes broad statements about the effects of ellagic acid supplementation without considering the limitations and specific conditions of the study. It claims that the supplement has "desirable effects" in reducing symptoms of depression and improving antioxidant capacity in (all) patients with major depression. However, the study might have specific inclusion criteria or limitations that restrict the generalizability of these findings to a broader population.
29. Limited consideration of alternative explanations: The conclusion does not thoroughly address potential alternative explanations for the observed effects. It does not discuss whether other factors, such as placebo effects or lifestyle changes, could have contributed to the observed improvements. Considering alternative explanations helps provide a more comprehensive understanding of the results.

Thank you for considering these suggestions, and I look forward to reviewing the revised version.

Referee 2 Reviewer

MINOR REVISION 8 Apr 2024

Considering the interesting title and the strengths, as I read the manuscript, I found some areas in which I would have appreciated greater clarity. I believe the paper could be further strengthened by adding information about:

Abstract

Comment 1: The abstract needs to be more concise. In addition, the conclusion of the abstract shouldn't be very long. It seems necessary to modify the conclusion.
Comment 2: Please note the sentence “venous blood samples were collected before and after the study from 10 individuals” …
As stated in the abstract, the number of patients is 40. Why did you mention that the samples were taken from 10 individuals?

Introduction

Comment 3: Reference No. 6 should be corrected or replaced with a more accurate and relevant reference.

Method:

Comment 4: In the study design section, it is not appropriate to include such a long link in a manuscript.

Comment 5: A psychiatric clinic? Why was the name of the clinic not mentioned?
Comment 6: What was the reason for choosing a dosage of 200 mg/day as an effective therapeutic dose of ellagic acid for patients with Major Depressive Disorder? Please state the reason for choosing this dose in this project, citing the relevant reference.
Comment 7: Please state in the manuscript where the ellagic acid capsule was purchased.

Results:
Comment 8: Demographic Characteristics: Why is the gender of male and female patients not specified in the study? They are described as "X patients were male and Y patients were female". Please correct the related sentence.
Comment 9: Please write captions for all tables.
Comment 10: The p values in table No. 3 for the significant reduction in depression scores (Depression-Beck and Depression-Hamilton) in the ellagic treatment group are reported as 0.001, while $p<0.05$ is reported in the results and also in the abstract, which is inconsistent. Please correct them in table No. 3, the results, and the abstract.

Discussion:
Comment 11: Although reference No. 26 by Bedel et al. indicated that ellagic acid has antioxidant effects in an animal model, the mechanism of its effects is different from that in the present study and is not in line with yours. Considering the research by Bedel et al., the proposed mechanism should be explained and discussed in more detail.
Comment 12: Reference No. 27 by Dhingra et al. showed that the substance ellagic acid exerts its antidepressant effects by stimulating and activating the adrenergic and serotonergic systems. Considering the different mechanisms in the present study and the study by Dhingra et al., stating that the results of your study are consistent with those of their study is not correct. A more appropriate explanation should be provided and discussed.
Comment 13: Ref. No. 30 investigated the mechanisms of chronic administration of ellagic acid in the improvement of cognition in middle-aged overweight men. It seems that comparing the manuscript with the mentioned paper is not correct.
Instead, consider referring to the work of Hajiluian et al. (2023) entitled " The effects of Ellagic acid supplementation on neurotrophic, inflammation, and oxidative stress factors, and indoleamine 2, 3-dioxygenase gene expression in multiple sclerosis patients with mild to moderate depressive symptoms: A randomized, triple-blind, placebo-controlled trial".

References:
Comment 14: Please provide some up-to-date references.

Ramin Ataee Reviewer

MINOR REVISION 14 Apr 2024

dear author
I think this manuscript is good, with nice methods and a good message, but some comments and questions are relevant. Please reply.
1-Why was elagic acid selected? Were there any previous reports of an antidepressant effect? We have not seen enough previous animal studies on its antidepressant effect.
2-How did you determine the sample size? This has not been explained in the methods.
3-Why was only the MDA marker assayed, and why were other markers, such as SOD, CAT, and GSH, not studied?
4-Why did you not use a routine antidepressant as a positive control for comparison?

5-It would be better to add some graphs in the results to compare groups.
6-In the discussion, please explain more about the similarities and differences between this study and others.

Associate Editor MAJOR REVISION 22 Apr 2024

Dear authors,
Thanks for submitting your paper to IJPBS. According to the reviewers' comments, this paper needs a major revision.
Best

2

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 Dr…

Editor-in-Chief of IJ Psychiatry and Behavioral Sciences

Thank you for giving us the opportunity to submit a revised draft of my manuscript titled" Effects of Ellagic Acid Supplementation on Antioxidant Status and Symptom Improvement in Patients with Major Depressive Disorder: A double-blind randomized clinical trial" to your esteemed journal, IJ Psychiatry and Behavioral Sciences. We appreciate the time and effort that you and the reviewers have dedicated to providing your valuable feedback on our manuscript. We are grateful to the reviewers for their insightful comments on our paper. We have been able to incorporate changes to reflect most of the suggestions provided by the reviewers. We have highlighted the changes within the manuscript.

Sincerely,

Corresponding

***Here is a point-by-point response to the reviewers' comments and concerns.

Reviewers' Comments:

Reviewer 1:

I appreciate the efforts put into this study on the effects of ellagic acid supplementation in patients with major depression. The findings have the potential to contribute significantly to our understanding of alternative treatment options for depression. However, I would like to highlight several points that need to be addressed in a major revision:

Basic points

Comment 1: Inappropriate use of matching: There are various methods available to control confounding factors during the study design phase, including randomization, matching, and restriction. However, the best method to control confounding, which is only feasible in experimental studies, is randomization, and in such studies, there is no need for matching. Nonetheless, in this study, the samples were matched for age, gender, and height, which reduces generalizability and study power.

Answer: Based on the search in scientific databases, this clinical study was designed and conducted for the first time. Unfortunately, due to the lack of financial resources, it was not possible to recruit a large sample size and evaluate different doses. Therefore, due to the low sample size and the heterogeneity of the samples, matching was done and the results of the study were reported statistically, therefore, other studies with a higher sample size are needed for clinical conclusions.

Comment 2: Small sample size: The study only included a total of 40 patients diagnosed with major depressive disorder. A larger sample size would provide more robust and generalizable results.

Answer: Thank you for pointing this out. You are right and this may be one of the limitations of our study. However, this research was a preliminary study and we hope to conduct a cohort study to investigated more detailed effects of ellagic acid and its underlying mechanisms on MDD patients. Similar studies in term of sample size are listed below.

DOI: 10.7762/cnr.2022.11.2.98; **DOI:** 10.1002/ptr.6867; **DOI:** 10.1016/j.phymed.2023.155094

Comment 3: Short study duration: The study lasted for only 8 weeks. A longer duration would provide a better understanding of the long-term effects of ellagic acid supplementation on depressive symptoms and antioxidant status.

Answer: Thank you for pointing this out. However, in clinical trials investigating the effects of ellagic acid in trials, the desirable antioxidant effects of ellagic acid have been observed even in the short study period. Similar studies in term of the duration of study are listed below.

Doi:10.1002/ptr.6867; **DOI:** 10.7762/cnr.2022.11.2.98; DOI:

Comment 4: Lack of placebo blinding: The placebo group received a capsule containing wheat flour, which was identical in appearance to the intervention substance. However, it does not specify if the participants and researchers were blinded to the treatment allocation. Lack of blinding can introduce information bias and affect the study outcomes.

Answer: In this study, the investigational drug and placebo were visually identical, with no difference between the two groups.

Comment 5: Lack of comparison with conventional antidepressant treatment: The study does not include a comparison group receiving only conventional antidepressant treatment. A comparison with standard treatment would provide a better understanding of the additive effects of ellagic acid supplementation.

Answer: Thank you for the constructive comment. In this study, both groups were taking anti-depressant medication, and stopping the medication of one group and being satisfied with receiving a placebo harmed the methodology of the article and was not ethically correct. However, the aim of the present study was to investigate the effects of Ellagic acid on antioxidant status and symptom improvement in patients with major depressive disorder. Although a comparison with standard treatment would provide a better understanding of the additive effects of ellagic acid supplementation, the lack of a group receiving only conventional antidepressant treatment dose not substantially affect the results.

Articles similar to our work are listed below.

DOI: 10.1002/ptr.6867; **DOI:** 10.1016/j.phymed.2023.155094; **DOI:** org/10.7762/cnr.2022.11.2.98

Comment 6: Lack of mention of side effects: The study does not mention any potential side effects or adverse reactions associated with ellagic acid supplementation. It is important to consider and discuss the safety profile of the intervention to provide a balanced assessment of its benefits and risks.

Answer: Thank you for pointing this out. No side effects were reported in the study. Also, there were no cointerventions in this study. This part was added and highlighted in the revised manuscript.

Abstract

Comment 7: Insufficient contextual information: The abstract does not provide sufficient background information about major depressive disorder, ellagic acid, or the current understanding of the relationship between antioxidant status and depressive symptoms.

Answer: Thank you for your comment. The sufficient background information about major depressive disorder, ellagic acid, or the current understanding of the relationship between antioxidant status and depressive symptoms.

Comment 8: Limited information in methods: The abstract methods does not provide information about the sampling methods, type of randomization, study design, samples demographic (e.g., age, gender, ethnicity), blinding, statistical methods or the significance level.

Answer: In the methods section of the abstract, the type of study, intervention, number of patients, evaluation outcomes, and overall idea of the design are presented.

Comment 9: Incomplete reporting of the results: The abstract offers a concise summary of the study's findings; however, it could be improved by including specific numerical values and effect sizes. Furthermore, instead of reporting p-values as "less than 0.05" or "less than 0.01," it is preferable to provide the exact p-values. Additionally, it does not mention whether the observed changes were statistically significant when compared to the placebo group.

Answer: Thank you for your comment. The exact p-values are provided. Also, the comparison of intervention group with placebo group was added and highlighted in revised manuscript.

Comment 10: Lack of key words specificity: The chosen keywords lack specificity and do not provide specific details about the study. To improve specificity, consider adding more specific terms related to the study's focus, design, measurement methods, outcomes, and demographic characteristics of the participants.

Answer: Thank you for your comment. According to your valuable comment, Keywords were revised and highlighted in the new manuscript.

Methods

Comment 11: Incomplete description of the study design: The provided description lacks specific details about the randomization procedure, blinding methods, and allocation concealment.

Answer: Done, this part added to the method

Comment 12: Inadequate reporting of ethical approval: The study does not provide sufficient information about the ethics committee responsible for the approval, the date of approval, or any additional ethical considerations.

Answer: Thank you for your suggestion. According to your valuable comment, the ethics committee responsible for the approval, the date of approval, or any additional ethical considerations was added in revised manuscript.

Comment 13: Lack of information on sample size calculation: The methods section does not mention how the sample size was determined. It is important to justify the chosen sample size based on statistical power calculations, anticipated effect sizes, and desired level of significance.

Answer: The sample size method was added to the method section.

Comment 14: Insufficient details on intervention and placebo: The description of the intervention and placebo is limited. It does not provide information about the composition, appearance, or administration of the ellagic acid supplement and placebo.

Answer: Thank you for your recommendation. The required information was included and highlighted in the revised manuscript.

Comment 15: Lack of information on outcome assessments: The methods section does not provide enough details about the assessment methods for measuring oxidative stress indices, depression severity, and nutritional factors. Specific measurement tools, protocols, and the timing of assessments should be clearly described to ensure the reliability and validity of the results.

Answer: Thank you for your recommendation. The required information was included and highlighted in the revised manuscript.

Comment 16: Absence of reporting on missing data and dropout rates: The methods section does not mention how missing data or participant dropout was handled in the analysis.

Answer: The report of the number of participants and people who were excluded from the study was added to the results section.

Comment 17: Lack of blinding assessment: The methods section does not mention any assessment or validation of the blinding effectiveness.

Answer: Done, this part added to the method

Comment 18: Incomplete disclosure of conflicts of interest: The methods section does not provide information about any conflicts of interest among the researchers or funding sources.

Answer: Thank you for your recommendation. However, disclosure of conflicts of interest is written at the end of the manuscript.

Results

Comment 19: Inadequate reporting of demographic characteristics: The Results section provides limited information about the demographic characteristics of the participants. Although the mean age is reported for each group, there is no information about the standard deviation or range. Additionally, the number of male and female participants is mentioned, but specific numbers (X and Y) are not provided, making it difficult to assess the gender distribution accurately.

Answer: The mentioned part was modified and rewritten based on the reviewer's opinion.

Comment 20: Insufficient reporting of dietary comparison results: The Results section states that there was no significant difference in dietary intake between the two groups at the beginning of the study and no significant change during the study. However, no statistical analysis results or p-

values are provided to support these statements. It is important to report the statistical tests used and the corresponding p-values.

Answer: Since a large number of dietary factors have been evaluated in this section including protein consumption, fat, carbohydrates, fiber, vitamin C, vitamin E, and selenium, none of which showed any significant differences. Therefore, mentioning p-values for each was not feasible separately, and further details are presented in Table 2 in a comma-separated format.

Comment 21: Lack of clarity in reporting depression scores: Although the Results section mentions a significant decrease in depression scores in the ellagic acid group and non-significant reductions in the placebo group, it does not provide specific values or measures of effect size. The percentage reductions in Beck's depression inventory and Hamilton's depression scale are mentioned but without the corresponding baseline values. This lack of specific data makes it difficult to fully assess and interpret the findings.

Answer: Based on the search in scientific databases, this clinical study was designed and conducted for the first time. Unfortunately, due to the lack of financial resources, it was not possible to recruit a large sample size and evaluate different doses. Therefore, due to the low sample size and the heterogeneity of the samples, matching was done and the results of the study were reported statistically, therefore, other studies with a higher sample size are needed for clinical conclusions.

Comment 22: Incomplete reporting of oxidant and antioxidant evaluation: The Results section provides limited information about the results of the oxidant and antioxidant evaluation. Although it mentions a significant increase in total antioxidant capacity (TAC) and a significant decrease in malondialdehyde (MDA) level in the ellagic acid group, it does not provide specific values, measures of effect size, or the statistical tests used. Additionally, it does not mention the baseline values or the absolute changes in TAC and MDA levels. These details are necessary for a comprehensive understanding of the results.

Answer: All results related to oxidants and antioxidants are fully described in the results section, as well as base levels, the extent of changes, and the significance level of each change are also fully explained in Table 4.

Comment 23: Insufficient reporting of statistical significance: The Results section mentions statistical significance ($p < 0.05$) for some findings but does not report the exact p-values or the statistical tests used. It is essential to provide the actual p-values to allow readers to assess the strength of the evidence and determine the statistical significance of the results.

Answer: In all 3 sections, Depression score and oxidant and antioxidant evaluation, all changes are mentioned with their corresponding p-values.

Discussion

Comment 24: Lack of comparison with previous studies: Although the Discussion section briefly mentions a few studies that investigated the effects of ellagic acid, it does not provide a thorough comparison of the current study's findings with previous research. It is important to discuss similarities, differences, and potential explanations for any discrepancies between the studies to provide a broader understanding of the topic.

Answer: Thank you for your recommendation. Thorough comparison of the current study's findings with previous research was included and highlighted in the revised manuscript. This discussion is considered to be our first report in major depression in clinical trial, and due to few similar articles, writing discussion is limited. However, according to your comment, the discussion has been rewritten and an attempt has been made to discuss it more deeply.

Comment 25: Absence of mechanistic explanations: The Discussion section does not explore potential underlying mechanisms by which ellagic acid may exert its effects. It merely mentions different pathways and systems without discussing how they might be involved in the observed outcomes. Providing mechanistic insights can help readers understand the biological rationale behind the findings.

Answer: Thank you for your recommendation. Required changes have been made in the revised manuscript.

Comment 26: Incomplete consideration of alternative explanations: The Discussion section does not thoroughly consider alternative explanations for the observed effects. It does not discuss other factors that could have influenced the outcomes or potential confounding variables that were not accounted for in the study design. Addressing alternative explanations strengthens the validity of the results.

Answer: Thank you for your recommendation. Required changes have been made in the revised manuscript.

Comment 27: Insufficient discussion of limitations: The Discussion section does not adequately address the limitations of the study. It does not mention any potential confounding factors, sources of bias, or other limitations that may affect the generalizability or reliability of the findings. Discussing limitations is essential for providing a balanced view of the study's strengths and weaknesses.

Answer: Thank you for your recommendation. Required changes have been made in the revised manuscript.

Conclusion

Comment 28: Overgeneralization: The conclusion makes broad statements about the effects of ellagic acid supplementation without considering the limitations and specific conditions of the study. It claims that the supplement has "desirable effects" in reducing symptoms of depression and improving antioxidant capacity in (all) patients with major depression. However, the study might have specific inclusion criteria or limitations that restrict the generalizability of these findings to a broader population.

Answer: Thank you for your recommendation. Required changes have been made in the revised manuscript.

Comment 29: Limited consideration of alternative explanations: The conclusion does not thoroughly address potential alternative explanations for the observed effects. It does not discuss

whether other factors, such as placebo effects or lifestyle changes, could have contributed to the observed improvements. Considering alternative explanations helps provide a more comprehensive understanding of the results.

Answer: Thank you for your recommendation. Required changes have been made in the revised manuscript.

Thank you for considering these suggestions, and I look forward to reviewing the revised version.

Reviewer 2:

With thanks and appreciation for your time and effort in writing the manuscript. Please find my comments below.

Comment 1: A double-blind randomized clinical trial or A Double-Blind Clinical Trial? Please check the title.

Answer: Thank you for your recommendation. The current study is a double-blind randomized clinical trial. Required changes have been made in the revised manuscript.

Comment 2: Incomplete reporting of results in the abstract: The results do not provide information on the specific statistical tests or models used for comparing between two groups, especially effect sizes and p-value, etc.

Answer: In this section, all relevant aspects of the results have been included based on the limited number of words available in the abstract.

Comment 3: How is the sample size determined? Please cite the reference paper to determine the effect size!

Answer: The mentioned part was modified and rewritten based on the reviewer's opinion.

Comment 4: Please describe the method of random allocation completely.

Answer: Done, this part added to the method.

Comment 5: Incomplete reporting of results: The result section provides incomplete results. It mentions some findings without providing any effect sizes and statistical tests. Please report effect sizes in the results. In my opinion, the results focus more on intra-group changes, while the purpose of the study is to compare two groups under study.

Answer: Based on the search in scientific databases, this clinical study was designed and conducted for the first time. Unfortunately, due to the lack of financial resources, it was not possible to recruit a large sample size and evaluate different doses. Therefore, due to the low sample size and the heterogeneity of the samples, the results of the study were reported statistically, and the effect size report will not be very helpful in this case. Therefore, other studies with a higher sample size are needed for clinical conclusions.

Comment 6: Has the ANCOVA model been used? Please report the parameter estimate results here such as coefficients, 95% confidence intervals, and p-values, and interpret them completely.

Answer: Because in this study, we have tried to control the confounding factors as much as possible, and at the beginning of the study, there was no significant difference in the average of these factors between the two groups, so the mentioned test was not used.

Comment 7: Have the variables of oxidant and antioxidant been compared between the control and intervention groups? In the results, only changes within the group have been discussed, but no results have been presented for comparison between the two groups.

Answer: The indicated factors are presented in full in the relevant table, and due to the observance of abbreviations, they are only mentioned in summary form in the results section.

Reviewer 3:

Considering the interesting title and the strengths, as I read the manuscript, I found some areas in which I would have appreciated greater clarity. I believe the paper could be further strengthened by adding information about:

Abstract

Comment 1: The abstract needs to be more summary. In addition, the conclusion of abstract shouldn't be very long. It seems necessary to modify the conclusion.

Answer: Thank you for pointing this out. According your valuable comment, conclusion was modified and highlighted in the revised manuscript.

Comment 2: Please notice the sentence “venous blood samples were collected before and after the study from 10 individuals” …

As stated in the abstract, the number of patients is 40. Why did you mentioned that the samples were taken from 10 individuals?

Answer: Thank you for pointing this out. According your valuable comment, this part was corrected and highlighted in the revised manuscript.

Introduction

Comment 3: Reference No. 6 should be corrected or replaced with a more correct and relevant reference.

Answer: Thank you for pointing this out. According your valuable comment, this part was corrected and highlighted in the revised manuscript.

Method:

Comment 4: In the study design section, it is not captivating to include such a long link in a manuscript.

Answer: Thank you for pointing this out. According your valuable comment, this part was corrected and highlighted in the revised manuscript.

Comment 5: A psychiatric clinic? Why was the name of the clinic not mentioned?

Answer: Thank you for pointing this out. Considering the double-blind nature of the journal, any names of clinics, hospitals, cities, states, etc., should be removed from the text, and only referred to as "general".

Comment 6: What was the reason for choosing a dosage of 200 mg/day as an effective therapeutic dose of ellagic acid for patients with Major Depressive Disorder? Please write the reason for choosing this dose in this project by mentioning the relevant reference.

Answer: Thank you for pointing this out. This dosage was chosen based on similar reports. the relevant reference has mentioned in the revised manuscript.

Comment 7: Please write in the manuscript, where was the ellagic acid capsule purchased from?

Answer: Thank you for pointing this out. The name of the company is mentioned and highlighted in the revised manuscript.

Results:

Comment 8: Demographic Characteristics; Why the gender of male and female patients is not specified in the study. They are expressed as “X patients were male and Y patients were female”. Please correct the related sentence.

Answer: This part was modified based on the results presented in the table.

Comment 9: Please write captions for all tables.

Answer: Thank you for your comment. all tables have captions now.

Comment 10: The p values in table No. 3 for the significant reduction of depression score (Depression-Beck and Depression-Hamilton) in the ellagic treatment group is reported as 0.001, while $p<0.05$ is reported in the results and also in the abstract, which are not in line. Please correct them in table No. 3, results and the abstract.

Answer: Thank you for your comment. According to your valuable comment, this part was corrected and highlighted in the revised manuscript.

Discussion:

Comment 11: Although reference No. 26 by Bedel et al indicated that ellagic acid has antioxidant effects in an animal model, the mechanism of its effects is different from present study and is not in

line with yours. Considering the research by Bedel et al, the explanation of the proposed mechanism should be more detailed and discussed.

Answer: Thank you for your comment. According to your valuable comment, this part was corrected and highlighted in the revised manuscript.

Comment 12: Reference No. 27, by Dhingra et al showed that the substance ellagic acid exerts its antidepressant effects based on stimulating and activating the adrenergic and serotonergic systems. Considering different mechanisms between the present study and Dhingra et al, comparing that the results of your study are consistent with their study is not correct. More appropriate explanation should be provided and discussed.

Answer: Thank you for your comment. According to your valuable comment, this part was corrected and highlighted in the revised manuscript.

Comment 13: Ref. No. 30 investigated the mechanisms of chronic administration of ellagic acid in the improvement of the cognition in middle-aged overweight men. It seems that comparing the manuscript with the mentioned paper is not correct. Instead, consider referring to the work of Hajiluian et al. (2023) entitled" The effects of Ellagic acid supplementation on neurotrophic, inflammation, and oxidative stress factors, and indoleamine 2, 3-dioxygenase gene expression in multiple sclerosis patients with mild to moderate depressive symptoms: A randomized, triple-blind, placebo-controlled trial"

Answer: Thank you for your comment. According to your valuable comment, this part was corrected and highlighted in the revised manuscript.

References:

Comment 14: Please provide some up-to-date references.

Answer: Thank you for your comment. According to your valuable comment, this part was corrected and highlighted in the revised manuscript.

Reviewer 4:

dear author

I think this manuscript is good with nice methods and good message but some comments and questions are relevant please reply

Comment 1: -why elagic acid was selected if any antidepressant report was before as we have not seen enough studies in animal before for antidepressant effect.

Answer: Thank you for your comment. There are some studies in animals that discussed the effect of ellagic acid on depression. Moreover, one previous study was conducted to effects of ellagic acid in depression. However, one important factor in the pathogenies of depression is oxidative stress. Considering that the antioxidant effects of ellagic acid have been stated in many studies, this study was conducted to evaluate the effects of ellagic acid supplementation on antioxidant status and symptom improvement in patients with major depressive disorder, taking into account the antioxidant capabilities of ellagic acid.
In vivo studies:
doi.org/10.1016/j.npep.2019.04.003;doi.org/10.1016/j.ejphar.2012.02.034;doi.org/10.1016/S1734-1140(12)708757;doi.org/10.1002/pca.2429;doi.org/10.3389/fnbeh.2022.836681; etc.

Clinical trial: doi.org/10.1016/j.phymed.2023.155094

Comment 2: how you have determined sample size it has not explained in methods

Answer: The sample size calculation section was modified and rewritten.

Comment 3-why only MDA marker was assayed? and other markers as SOD ,CAT,GSH has not been studied?

Answer: Based on the search in scientific databases, this clinical study was designed and conducted for the first time. Unfortunately, due to the lack of financial resources, it was not possible to recruit a large sample size and evaluate different doses. Also, this lack of budget also affected the selection of measured factors and only one case of oxidant index and one case of antioxidant index was evaluated.

Comment 4-why you have not used positive control as routine antidepressant for comparison

Answer: The aim of the present study was to investigate the effects of Ellagic acid on antioxidant status and symptom improvement in patients with major depressive disorder. Although a comparison with standard treatment would provide a better understanding of the additive effects of ellagic acid supplementation, the lack of a group receiving only conventional antidepressant treatment dose not substantially affect the results. Due to low referrals, it was not possible for us to include an additional group. Articles similar to our work are listed below.

DOI: 10.1002/ptr.6867; **DOI:** 10.1016/j.phymed.2023.155094; **DOI:** org/10.7762/cnr.2022.11.2.98

Comment 5-it is better to add some graphs in results for comparing groups

Answer: Due to the existence of two groups (intervention and control) in the study and limited data and their presentation in the table, their presentation in the graph will cause repetition.

Comment 6-in discussion please explain more about similarities and differences of this study with others

Answer: Thank you for your comment. According to your valuable comment, the discussion section was thoroughly discussed and revised in the revised manuscript.

2 Revision 1

4 comments · 17 Jun 2024 – 24 Jun 2024

Sajedeh Seyed-Alipour Reviewer

MINOR REVISION 17 Jun 2024

Thanks for the opportunity to study the manuscript.
It is well edited according to the first reviewers' comments.
39 of the 48 references are from more than 5 years ago; please update the references.
Please write the keywords in alphabetic order.
I can only see one table in the uploaded file, and other referenced tables are not in the file.

Referee 3 Reviewer

MINOR REVISION 20 Jun 2024

Thank you for the revision.
Here are some comments to improve the quality of the manuscript:
Because of the matching, the study cannot be a randomized study.
The conclusion is not consistent with the results and is overgeneralized.
The abstract should be concise.
There are two abstracts in the manuscript that are different from each other.
The 1st and 2nd paragraphs should be shortened due to the journal's audience. These details aren't needed.
The 3rd and 4th paragraphs have a lot of unnecessary information.
The introduction should focus on the topic of the manuscript and any effects of Ellagic acid on depression, but we cannot see any.
In the objective of the manuscript, the clinical trial should be cited.
Explain the double-blind method.
The brand of Ellagic used should be cited.
The time and date of the study are not clear.
Line 115: A depression score above 20—with which score?
The dose of fluoxetine used was analyzed between the two groups. What is the result, and what was the duration of fluoxetine use?
Illnesses described as acute, such as CVD, Cancer, and others, are chronic conditions.
The psychometric properties of the Persian versions of the tools should be addressed, with references.
Also, SCID should be described.
The manuscript is required to explain how many participants were excluded during the study and why.
Lines 25 to 258 should be cited in the introduction, not in the discussion.

Associate Editor

ACCEPT 21 Jun 2024

Dear authors
Two of the three reviewers believe that this paper needs a minor revision. However, I think these corrections could be made during the publication process. Therefore, my position is acceptance, and I ask the authors to pay attention to the reviewers' comments and make improvements in the next steps.
Best

Editor-in-Chief ACCEPT 24 Jun 2024

We have completed our review of your manuscript and are pleased to inform you that it is being considered for publication in the IJPBS. Note that the publication of your article will only be finalized upon your cooperation in the editorial process.
Thank you for your fine contribution. On behalf of the Editors of IJPBS, we look forward to your continued contributions to the Journal.