

Response to Reviewer 1's Comments

1. Summary

Thank you very much for taking the time to review this manuscript. Please find the detailed responses below and the corresponding revisions/corrections highlighted/in tracked changes in the re-submitted files.

2. Questions for General Evaluation	Reviewer's Evaluation	Response and Revisions
Is the work a significant contribution to the field?		
Is the work well organized and comprehensively described?		
Is the work scientifically sound and not misleading?		
Are there appropriate and adequate references to related and previous work?		
Is the English used correct and readable?		

3. Point-by-Point Response to Comments and Suggestions for Authors

Although the content of this manuscript is not very much different from a recent review (DOI: 10.3390/ijms23031333) which seemed to address a similar problem, it is needed in the field. The authors have demonstrated some form of understanding in how review articles are written. For instance, the introduction section highlights the aim of the review and how the review was done. Also, at each stage of the review, the authors tried to make deductions, which reflect a good review manuscript. Regardless of this, I have some issues with this manuscript which I believe, if addressed, will improve its quality.

Comments 1: Minor grammatical errors are seen in the abstract and the entire manuscript, and should be rechecked.

Response 1: Thank you for pointing this out. We have made English revisions to this article and corrected minor grammatical errors in Abstract and the entire manuscript. Please refer to the revised manuscript for details.

Comments 2: While the clinical implications of P4 in PE have been clarified in this review, the pathophysiological role of P4 in PE has not been substantiated. Hence, the title of this manuscript is misleading.

Response 2: Thank you for your suggestion; we have modified the title of this manuscript.

Comments 3: In line 43, “determine” should be replaced with “characterize” since this is not a research article but a review of available findings to make a claim.

Response 3: Thank you for pointing out this error; we have made revisions in the text. Please refer to the revised manuscript for details.

Comments 4: Some unnecessary paragraphing are also seen in this manuscript. For instance, the paragraph created at line 74 is a mistake. From line 62 to 82, the authors were trying to synthesize a common information. So, no paragraphing is needed there. Authors should note that in scientific writing, a deduction made at the end of a paragraph is about that paragraph not about other paragraphs. So, the deductions they made in line 81 will be mistaken for only the information presented from lines 74 to 79. However, it is obvious that it is also applicable to the preceding paragraph. The entire manuscript should be devoid of such paragraphing anomalies.

Response 4: Thank you for pointing out this issue; we have made revisions in the text and checked other paragraphs. Please refer to the revised manuscript for details.

Comments 5: In line 263, the authors wrote the heading “P4 protects against PE by regulating vascular endothelial function”. This is a serious claim which, unfortunately, is not supported by the references cited. None of the references is about PE.

Response 5: Thank you for raising this question. We have changed the heading. Please refer to the revised manuscript for details.

Comments 6: In line 268, the authors wrote a bold statement that “P4 protects against PE by regulating VEGF signaling”. Surprisingly, none of their references supports this claim, and still the authors had the courage to propose a mechanism about this. Wow! While the references point to a potential role of P4 in VEGF signaling, none of the studies was about PE. The same problem is associated with the heading “P4 protects against PE by regulating eNOS/NO expression” and the references cited in its support.

Response 6: Thank you for raising this question. We have changed the heading and added a paragraph on the effect of VEGF in PE, and a paragraph on the effect of eNOS/NO in PE, hoping to solve this problem. Please refer to the revised manuscript for details.

Comments 7: In line 433, the authors wrote that “P4 protects against PE by regulating trophoblast invasion”. To substantiate this bold claim, they cited papers with opposing findings. In those studies, cell lines, such as HTR8/SVneo and JEG3, which do not closely mimic trophoblast development were employed. So, even if the findings had been consistent across the studies, the results could still not be extrapolated to the ideal process of placentation in humans. Since those cell lines do not yield reliable experimental results and besides the findings are conflicting, the conclusion of the authors is dangerously misleading. They must consider deleting that paragraph or

rephrasing everything into a hypothetical message and requesting prospective studies to address that gap in knowledge. It is premature to make any meaningful deduction since the available evidence is not enough.

Response 7: Thank you for your suggestion. We have deleted this paragraph from the text. Please refer to the revised manuscript for details.

Comments 8: In line 449, the authors wrote the heading “P4 protects against PE by promoting trophoblast proliferation and adhesion”. While the findings support the potential role of P4 in trophoblast proliferation, none of the studies was done in relation to PE. The role of P4 in trophoblast adhesion could also not be clarified with enough evidence. What authors can do is to also explain how proliferation and adhesion associate with PE, and then cite the ideal references. Until this is done, the statement made in the heading cannot be seen to be correct.

Response 8: Thank you for pointing out this issue. We explain how proliferation and adhesion associate with PE and then cite the ideal references. Please refer to the revised manuscript for details.

Comments 9: From line 462 to 522, the authors reviewed the association between P4 supplementation and PE development. They first presented findings about humans and then moved on to findings about animals. In scientific reports, in vitro studies are first reported, followed by animal studies and then human studies because once findings about humans are concluded, findings from in vitro and animal studies are no longer relevant. In this review, it would have been ideal to present the findings about animals before the findings about humans. Truly, even if the findings about animals are deleted, it won't change anything. After all, the authors have enough human studies to substantiate their claim. Apart from this, it would have been ideal to present these clinical findings ahead of the mechanistic findings that began from line 263. To the best of my knowledge, association findings are first reported before mechanistic findings are brought in to clarify the underlying pharmacological mechanisms.

Response 9: Thank you for your suggestion. We have presented the findings about animals ahead of the findings about humans, and presented these clinical findings ahead of the mechanistic findings. Please refer to the revised manuscript for details.

Comments 10: Due to the issues I have already raised, the conclusions of this review cannot be trusted. Authors are to rewrite the manuscript to reflect the hypothetical stance of their message and then revise the conclusions in a similar way.

Response 10: Thank you for your suggestion. We have modified the manuscript and rewritten the conclusion of this review.

Comments 11: My final words to the authors is that in literature review, you don't have to only look at the findings of a study but also the methodology used. If a research work has a questionable methodology, the findings should not be taken seriously as that can affect the deductions made in a review.

Response 11: Thank you very much for your comments and suggestions, which have

taught me a lot.

4. Response to Comments on the Quality of English Language

Point 1: The grammar is good but not excellent. Grammar check is needed to improve the overall quality of the manuscript.

Response 1: We have made English revisions to this article.

5. Additional clarifications

None.