PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>The effects of Eurycoma longifolia Jack standardised water extract (Physta®) on well-being of peri and postmenopausal women: Protocol for a randomized, double-blinded, placebo-controlled, parallel group study</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Muniandy, Subashini; Yahya, Hanis Mastura; Shahar, Suzana; Kamisan @ Atan, Ixora; Mahdy, Zaleha; Rajab, Nor Fadilah; George, Annie; Chinnappan, Sasikala M</td>
</tr>
</tbody>
</table>

VERSION 1 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Aryaeian, Naheed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iran University of Medical Sciences, Nutrition</td>
</tr>
<tr>
<td>REVIEW RETURNED</td>
<td>06-Apr-2023</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GENERAL COMMENTS</th>
<th>Dear authors,</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Add more about the novelty of your work, because there are similar works to your research. You have mentioned in Introduction the RCT studies involving women and Eurycoma longifolia to date are Limited. Please mention them. Please explain the mechanisms of Eurycoma longifolia effects on Hormonal level modification in the Introduction. You will exclude 4) B Complex, Vitamin C, Vitamin E, Vitamin A, and Vitamin B6 supplements intake what about omega 3 fatty acids, selenium, ca, Zinc, and Iron supplements? Also, you must exclude those who consume medications that affect the lipids profile, Blood sugar, Mood, sleep, and other metabolic effects. Please add Nutritional intake and physical activity assessment to your study. Please add the randomization method and compliance of your study. Please add the normality determination and control of confounding factors in statistical analysis methods, If the data are not normal what change in your statistical methods will you carry out?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Rezai, Arezou</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Damghan University</td>
</tr>
<tr>
<td>REVIEW RETURNED</td>
<td>05-Jul-2023</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GENERAL COMMENTS</th>
<th>Dear authors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First of all, please accept my possible delay in reviewing your manuscript. I was really busy with various tasks. I have read the manuscript carefully. This is a valuable ethnopharmacological study. However, some editing will enhance</td>
</tr>
</tbody>
</table>
your work. Please find my comments in sticky boxes in the main text. In addition, some new parameters are proposed for measurement, if there is no budget constraint. Apparently, the esteemed authors will know me, accordingly I suggest they read our publications on Elaeagnus angustifolia L. and Post-Menopausal Women. I hope you find it helpful.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1: Dr. Naheed Aryaeian, Iran University of Medical Sciences

Thank you very much for your insightful review and valuable feedback on our manuscript. Your comments are greatly appreciated and have provided us with valuable perspectives to further improve the quality of our research. We have addressed them all carefully and the responses for the comments are provide as below:

1. **Comment:** Add more about the novelty of your work, because there are similar works to your research. You have mentioned in Introduction the RCT studies involving women and Eurycoma longifolia to date are Limited. Please mention them. Please explain the mechanisms of Eurycoma longifolia effects on Hormonal level modification in the Introduction.

   **Response:** Thank you for the constructive suggestions. To add more novelty to our study and to explain the mechanism of Eurycoma longifolia on hormonal level modification, we have included in the introduction details of RCT studies conducted on males and females using Eurycoma longifolia that showed positive outcomes. We have addressed these comments precisely in introduction as below:

   ‘EL has shown a great potential to be explored for menopausal symptom management as its one of the most versatile and safe to be consumed. Besides the available scientific data available, more evidence-based studies need to be conducted to establish proper clinical guidelines for safer utilisation of EL. As its exclusive benefits on enhancing sexuality and fertility mainly among male population, the research studies involving women and EL to date are limited. In a randomised clinical trial (RCT) study carried out on 119 healthy women in Canada aged 41 to 55 years old with peri- and postmenopausal symptoms, supplementation of herbal formulation consists of both Labisia pumila and EL, has reported to be well tolerated for consumption and has potential in supporting reduction of hot flushes, improves their hormone and lipid profile. Nevertheless, past studies testing intake of EL on males and females with moderate stress problems have reported that it has improved their stress hormone profiles and certain mood state parameters. Moreover, the alkaloids and triterpenes found in this root has proven to act as effective antioxidants that reduces bone loss and maintain the rate of bone formation in men. A recent animal study done on ovariectomised rats has shown that intake of EL has improved hormonal levels caused by ovariectomy, an animal model resembling menopause. These attributes align with our study aim of investigating the effects of Physta® on menopausal symptoms in peri-post menopausal women.’ (Page 5)

2. **Comment:** You will exclude “4) B Complex, Vitamin C, Vitamin E, Vitamin A, and Vitamin B6 supplements intake what about omega 3 fatty acids, selenium, ca, Zinc, and Iron supplements? Also, you must exclude those who consume medications that affect the lipids profile, Blood sugar, Mood, sleep, and other metabolic effects.

   **Response:** Thank you for the suggestions. We have revised the list of prohibited concomitant medications as below: (Page 9)

   The following concomitant medications and interventions are not permitted while the participants are on trial:

   (1) Dexamethasone systemic medication
   (2) Cortisone systemic medication
   (3) Adrenal supplements
B Complex, Vitamin C, Vitamin E, Vitamin A, Vitamin B6, Omega 3 fatty acids, Selenium, Calcium, Zinc, and Iron supplements
Herbal products that may contain androgenic/anxiolytic activity
Any supplement which can influence women reproductive hormones, lipid profile, blood sugar levels, mood, sleep, or other metabolic functions
Any product containing Eurycoma longifolia

Comment: Please add Nutritional intake and physical activity assessment to your study.
Response: We sincerely appreciate the reviewers’ insightful suggestions to further strengthen the study through the inclusion of detailed nutritional intake and objective physical activity assessments. While we recognize the potential benefits of such additions, we regret to inform the reviewers that due to resource and time constraints, these specific assessments cannot be incorporated into the current study. The study design and data collection procedures were established based on available resources and the predefined scope of the research. Introducing comprehensive nutritional intake and objective physical activity assessments would require significant additional resources, time, and logistical considerations that are beyond the scope of the present study. We understand the importance of these assessments in enhancing the depth of our findings, and we acknowledge that their absence is a limitation of the current study. We are committed to addressing this limitation in future research endeavours where additional resources and time can be allocated to ensure the inclusion of these assessments.

Comment: Please add the randomization method and compliance of your study
Response: For your kind information, these details has been included already in the main text under intervention and randomisation (Page 7), blinding (Page 8) and ‘assessment of compliance (Page 9)’.

Comment: Please add the normality determination and control of confounding factors in statistical analysis methods, If the data are not normal what change in your statistical methods will you carry out?
Response: Thank you for the suggestion, we have considered adding on the type of normality test we are planning to use and proposed test to be used in case the data is not normally distributed. In the statistical analysis part, we have added these information as:

‘Data of subjects who have consumed more than 70% of study product with out any major protocol deviation and completed all study visits will be used for primary endpoint analysis. Dependent variables will be tested for normality using Shapiro-Wil test and non-normal variables will be analysed using non-parametric analysis.’ (Page 11)

Reviewer 2: Dr. Arezou Rezaei, Damghan University
Thank you very much for your insightful review and valuable feedback on our manuscript. Your comments are greatly appreciated and have provided us with valuable perspectives to further improve the quality of our research. We have addressed them all carefully and the responses for the comments are provide as below:

1. Comment: Please cite the scientific name of the herb. The plant's scientific name consists of three parts: 1- the genus name or generic name, 2- the specific epithet or species epithet, and 3- the author's name. In the genus name, the first letter is always capitalized, and the remaining letters are lowercase.
Response: We appreciate your attention to detail. We have revised the name of the herb as suggested. The name is corrected as ‘Eurycoma longifolia Jack water extract (Physta®),’ we have amended this detail in the title of the article as well.

2. Comment: People's expertise is not clear. At least one gynecologist, one Neurologists, and one biostatistician should be in the group.
Response: Thank you for your valuable input regarding the composition of our research team. We truly appreciate your concern about having diverse expertise, and we want to clarify our rationale for the current team composition:

Firstly, our team already includes professional gynaecologists and authors who are highly experienced in data analysis and statistical methods. Their expertise ensures that we can effectively handle the participant screening and data analysis aspects of our study. The roles have been added accordingly in the ‘author’s contribution’ section as ‘SM conducting the participant recruitment under supervision of HMY, SS and IKA. IKA and ZAM are the gynaecologists who performs the transabdominal uterus scan for participant eligibility assessment. For data analysis using SPSS software, HMY, SS and NFR will guide SM with their knowledge and experience in performing statistical analysis.’ (Page 12)

Secondly, regarding the role of a neurologist, we would like to clarify that our study does not involve the assessment of any nerve-related parameters or conditions. As such, the scope of our research does not necessitate the involvement of a neurologist. Rest assured; we believe our team is well-equipped to manage the overall flow of this RCT study.

3. Comment: Please be sure that MeSH (Medical Subject Headings) terms are used as keywords whenever is possible.
Response: We sincerely appreciate your attention to detail and your emphasis on utilizing MeSH (Medical Subject Headings) terms as keywords. We have carefully reviewed our manuscript and made the necessary adjustments to incorporate MeSH terms as keywords wherever applicable.

4. Comment: For the first mention, the three-part scientific name (Eurycoma longifolia Jack) is required. then it is sufficient to mention E. longifolia. Even you may use EL as an abbreviation for the herb.
Response: Revised as suggested, changed to ‘Eurycoma longifolia Jack’

5. Comment: “medicinal herb” or “herbal medicine” is self-explanatory.
Response: Revised as suggested, changed to ‘a medicinal herb’ (Page 3)

6. Comment: How do you discriminate between peri- and post menopause? What is the ratio of peri- to post- menopausal participants in each group? Are the groups similar according to this ratio? The physiology and metabolism differ between peri- and post-menopausal women. Accordingly, I think it should be focused on just peri- or post menopause not both of them. My suggestion is perimenopause, However you may decide based on the number of the referees to your hospital or clinic. To be sure, please consult a gynaecologist and biostatistician.
Response: Thank you for providing additional context about the scope of our study and the inclusion criteria. Your clarification is greatly appreciated. We sincerely appreciate your thoughtful consideration of the physiological differences between peri- and post-menopausal women. We want to clarify that our study design encompasses women aged 40 to 55, without specific differentiation between peri- and post-menopausal stages. Our intention is to capture a broad age range of women within this age range, acknowledging that individual variations in menopausal status may exist. Moreover, due to the natural course of post-menopause, some may have experienced symptom relief, making it challenging for us to identify individuals who meet the specified MENQOL questionnaire score criteria. This could cause challenges in our participant recruitment later as well as impact our ability to observe significant changes in symptoms post-supplement intervention. Additionally, we will emphasize the study’s objectives during the recruitment phase to ensure potential participants understand the importance of capturing a range of symptom experiences.
Your insights are invaluable in helping us anticipate and address potential limitations, and we are committed to achieve meaningful and relevant outcomes. Thank you once again.

7. Comment: If there are no word limits, please write the full names for all abbreviations.  
Response: Revised as suggested, have included the full names of the abbreviations as 'Profile of mood State (POMS), Menopause-Specific Quality of Life (MENQOL), Chalder Fatigue Scale (CFQ), Pittsburgh Sleep Quality Index (PSQI), Female Sexual Function Index (FSFI) and the Brief Pain Inventory (BPI) questionnaires.' (Page 3)

8. Comment: Please also name the possible obstacles on your way.  
Response: Added as suggested under ‘strength and limitations’ as:  
• The limitation of this 12 weeks study is loss to follow up and missing data points that would challenge the validity of reported results during data analysis.  
• The study acknowledges the lack of nutritional intake information, which can be a limitation for a comprehensive analysis of the potential influence of dietary factors on the observed outcomes. (Page 3)

9. Comment: Is there any data available on the herbs used for menopausal complications? Please write about the traditional herbs prescribing in Malaysia for menopause and explain the reason for choosing E. longifolia. You may mention other herbal management of peri-post menopausal complications and name the strength of your study.  
Response: We sincerely appreciate your thoughtful question. Indeed, there is a growing body of literature exploring the potential benefits of various herbal interventions for addressing peri-post menopausal symptoms. We managed to address some of them in the introduction as ‘Herbal supplements of black cohosh, evening primrose oil, maca, pollen extracts, curcumin, bitter orange, phytoestrogen rich soy and red clovers are the common herbal dietary supplements used in treating menopausal symptoms among women globally. Particularly in Malaysia, local herbs like Pucuk sendap (Arcypteris irregularis), Tongkat Ali (Eurycoma longifolia Jack) (EL), Bunga pakma (Rafflesia hasseltii), and Kacip Fatimah (Labisia pumila) are generally used in rural areas to alleviate menopausal symptoms.’ (Page 5)

10. Comment: Is it also traditionally prescribed for women in your country? Otherwise, preclinical studies are required.  
Response: Yes, its prescribed among women as well, we have added the information as ‘Nonetheless, its consumed as a power tonic to curb postpartum depression and fatigue among women after childbirth as EL possesses great antioxidative properties due to presence of high concentrations of superoxide dismutase’ in introduction. (Page 4)

11. Comment: Which parts (leaves, stems, roots) and how is Tongkat Ali traditionally used (raw, cooked, soaked, brewed) in Malaysia?  
Response: Thank you for your question regarding the traditional usage of Tongkat Ali in Malaysia. One prevalent method of preparation involves brewing Tongkat Ali root in hot water to create herbal infusion or tea. This method allows the bioactive compounds in the root to be extracted into the water. We have included information about this as suggested in the introduction as ‘Locally recognized as ‘Tongkat Ali’ in Malaysia, its roots are boiled traditionally to prepare energy decoctions which predominantly used to treat impotency and decreased virility among men’ (Page 4)

12. Comment: Please also provide detailed phytochemical information on E. longifolia and its active ingredient(s) which focus on known biological activities relevant to your research objective.  
Response: Our study focuses on evaluating the efficacy of Physta®, a standardized extract derived from Tongkat Ali roots. While Physta® contains a range of bioactive compounds, its quassinoid content is of particular interest due to its potential influence on hormone regulation, mood, and overall well-being. These attributes align with our research objective of investigating the effects of Physta®
on menopausal symptoms in peri-post menopausal women. Background information on these phytochemicals is included in the introduction as:

‘This herb is known for its anti-pyretic, anti-malarial, antibacterial, antidiabetic properties since ancient times due to the presence of numerous bioactive compounds such as alkaloids, quassinoids, peptides, eurycolactone and eurycomalactone in the plant’s roots’ (Page 4)

and

‘Moreover, the alkaloids and triterpenes found in this root has proven to act as effective antioxidants that reduces bone loss and maintain the rate of bone formation in men’. (Page 5)

13. Comment: Please identify the kind of the cited studies (clinical trials on male, female, or both, animal studies, ..) in the research background.
Response: Apologies for the insufficient references on previous studies. In introduction, we have carefully cited a range of studies to support the rationale for our investigation as suggested. The cited studies encompass a variety of research designs, including clinical trials involving both male and female participants as well as animal studies as below:

‘In a randomised clinical trial (RCT) study carried out on 119 healthy women in Canada aged 41 to 55 years old with peri- and postmenopausal symptoms, supplementation of herbal formulation consists of both Labisia pumila and EL, has reported to be well tolerated for consumption and has potential in supporting reduction of hot flushes, improves their hormone and lipid profile. Nevertheless, past studies testing intake of EL on males and females with moderate stress problems have reported that it has improved their stress hormone profiles and certain mood state parameters. Moreover, the alkaloids and triterpenes found in this root has proven to act as effective antioxidants that reduces bone loss and maintain the rate of bone formation in men. A recent animal study done on ovariectomised rats has shown that intake of EL has improved hormonal levels caused by ovirectomy, an animal model resembling menopause.’ (Page 5)

14. Comment: Please write the full names of all abbreviations in the first mention.
Response: Revised as suggested, RCT is changed to ‘Randomised clinical trial (RCT)’ (Page 5)

15. Comment: Why water extract not alcoholic, acidic, .. extracts? Is water extract the main route of traditional usage of this herb?
Response: Thank you for your thoughtful inquiry regarding the choice of water extract over other extraction methods for our study. In our study, we opted for a water extract of the herb, which aligns with the traditional route of usage for Tongkat Ali (Eurycoma longifolia) in Malaysia. Historically, water-based preparations, such as herbal infusions and teas, have been a prevalent method of consuming Tongkat Ali. This traditional approach allows for the extraction of a broad spectrum of bioactive compounds that are water-soluble and that mirror the way the herb has been used by local communities for generations.

16. Comment: Clinical trials should follow the CONSORT 2010 checklist of clinical trials.
Response: Thank you for your comment and your emphasis on adherence to reporting guidelines for clinical trials. In our study, we have diligently followed the SPIRIT (Standard Protocol Items for Recommendations for Interventional Trials) checklist, as recommended by the authors’ hub of BMJ Open. While we understand the importance of CONSORT guidelines, the SPIRIT checklist serves as a comprehensive guide for transparently detailing the essential components of our study protocol. We greatly appreciate your consideration of our adherence to reporting guidelines.
17. Comment: Serum cholesterol levels between 200 and 300 mg/ml without the need for medication may be considered as a criterion.
Response: Thank you for your clarification regarding the rationale for not including serum cholesterol levels as an eligibility criterion. While serum cholesterol levels are relevant to our study's outcomes, we understand that including them as eligibility criteria could potentially confound the outcome.

18. Comment: Are people with controlled hypertension, diabetes, or thyroid disorders who receive medications included?
Response: Thank you for seeking clarity on our participant eligibility criteria. In our study, participants with controlled hypertension and diabetes who receive medications are included in the study (Page 6). We recognize the importance of studying the effects of interventions in individuals who manage these conditions within a controlled range. However, participants with thyroid disorders, regardless of medication use, are excluded from our study.

19. Comment: Are subjects using supplements such as multivitamins other herbal medicines or other kinds of complementary and traditional medicine eligible?
Response: Participants who are currently using supplements such as multivitamins, other herbal medicines, or other forms of complementary and traditional medicine are not eligible for inclusion. We have established this criterion to minimize potential confounding factors that could influence the outcomes of our research. By excluding participants who use these supplements, we aim to isolate the effects of the Physta® supplement and enhance the internal validity of our findings. The list of prohibited concomitant medications has been included in the main text.

20. Comment: 1- Why is maltodextrin used?
2- Doesn't maltodextrin have any effects on the studied parameters?
3- Why is the weight of maltodextrin different between three groups?
4- Are the capsules prepared in your lab or shopped? How are they given to the participants (e.g. all in a package or were packaged separately like modern medications)?
5- Please provide details and cite to relevant references, if possible.
Response: Thank you for your thorough questions regarding the use of maltodextrin in our study. Maltodextrin is commonly used as a bulking agent and excipient. In our study, maltodextrin is employed as a carrier for the active ingredient, Physta®. The variation in the weight of maltodextrin among the study groups is due to the specific formulation requirements of each dosage. The bulk density of maltodextrin is higher compared to the bulk density of Physta® (the active ingredient). Therefore, the amount of maltodextrin in each product is adjusted accordingly to fit a fixed size capsule. The capsules used in our study are prepared by Biotropics Malaysia Berhad, the respective sponsor of the study. They are carefully encapsulated to ensure uniformity in dosage and quality.

21. Comment: How many of the capsules per day are taken by the participants?
When do they use their treatments (e.g. morning, noon,...), with their meals, fasting, ..?
How will they use their treatments, e.g. with milk, water, ...
Response: Thank you for your attention to these logistical elements. We have revised and added the required details as ‘All the eligible participants will be randomized to receive one capsule daily with water in the morning after the first meal of the day consistently for 12 weeks.’ (Page 8)

22. Comment: Numbers less than 10 should be written as words, not numerals
Response: Revised as suggested, ‘2’ is changed to ‘two’ (Page 8)

23. Comment: Please consider the following references:


Response: Thank you for the suggestions. We have added the papers suggested as below to add more depth to our introduction.

‘Nevertheless, past studies testing intake of EL on healthy males and females with moderate stress problems have reported that it has improved their stress hormone profiles and certain mood state parameters’ – (Page 5) George A, Udani J, Abidin NZ, Yusof A. Efficacy and safety of Eurycoma longifolia (Physta®) water extract plus multivitamins on quality of life, mood and stress: a randomized placebo-controlled and parallel study. Food & nutrition research. 2018;62.


24. Comment: Investigators should not be aware of the coding before doing statistical analysis of data.
Response: Thank you for highlighting a crucial aspect of maintaining the integrity and objectivity of data analysis in our study. To address this concern, we have revised the sentence as ‘the allocation codes will only be disclosed at the end of the data analysis’ (Page 7)

25. Comment: If you don’t have a problem with funding, please consider Dehydroepiandrosterone (DHEA) as a parameter; its measurement will be helpful.
Response: Thank you for your valuable suggestion regarding the inclusion of Dehydroepiandrosterone (DHEA) as a parameter in our study. While we appreciate your recognition of the potential importance of DHEA measurement, we want to acknowledge that our study design and available resources have been carefully planned to focus on specific outcome measures related to menopausal symptoms. Unfortunately, due to budget constraints and the established scope of our research, we may not be able to incorporate additional parameters such as DHEA at this time.

26. Comments: Where will the questionnaires be completed? Where will the clinical tests be done?
Response: Added the information required as ‘All the questionnaire and clinical assessments will be conducted at the Clinical Trial Ward of Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia.’ (Page 8)

27. Comment: How is it confirmed that the participants are menopausal at the beginning of the study? FSH measurement is suggested
Response: In our study, we indeed include FSH measurement as a pivotal component of our participant selection process as well as in all other face-to-face visits. We also would like to share that although we measure the levels of FSH under reproductive hormone profile, we do not use FSH as
the main inclusion or exclusion criteria. We aim to conduct this study without classification of per- or postmenopausal women and solely based on their symptom severity.

28. Comment: Measuring of BMI is also suggested.
Response: Yes, indeed we measure the BMI of the participants at all visits, apologies for missing out this crucial point. Have revised and included it in the main text as ‘. Anthropometric measurements which included the measurement of height (cm), weight (kgs) and body mass index (BMI) calculation, will be taken at all visits’ under clinical assessment section. (Page 8)

29. Comment: Insulin and HbA1C are also recommended.
Response: Thank you for your valuable recommendation to incorporate insulin and HbA1c measurements in our study. While we recognize the significance of insulin and HbA1c assessments in elucidating diabetes-related implications, I would like to mention that our study currently operates under budget constraints that influence the scope of measurements we can feasibly include. Our resources have been allocated to focus on the primary outcome measures related to menopausal symptoms.

30. Comment: Please exactly name the parameters of the lipid profile.
Response: Apologies for missing out this crucial information. We have now clearly stated the parameters of lipid profile measured under the clinical assessment section as ‘lipid profile (total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol and triglycerides)’ (Page 8)

31. Comment: prolactin is also suggested.
Response: Regrettably, due to resource constraints and the specific scope of our research, we may not be able to incorporate additional parameters such as prolactin at this time. However, we will certainly consider your recommendation for future research endeavours, especially if funding and study design permit.

32. Comment: How often will the subjects be visited and will adverse effects be checked?
Response: Added as suggested as ‘Frequency, intensity, and severity of AEs’ will be recorded in detail, based on the participants’ feedbacks at all 4 visits including week 2.’ (Page 9)

33. Comment: Please cite relevant citations for adverse effects of the herb, if available.
Response: As of our knowledge, there is a limited number of studies reporting adverse effects directly linked to Physta. The available literature suggests that it has a favourable safety profile when used within recommended dosages. Our informed consent process will clearly outline potential adverse effects that participants might possibly experience as stated in the participant’s information sheet as below:

Side effects and risks:
You may or may not experience side effects. Side effects may include a decreased blood cortisol level, medication discontinuation syndrome, weight gain and gastrointestinal symptoms. If this happens, you should notify the researcher immediately of any side effects experienced by you by calling the phone number listed below. (Participant information sheet)

34. Comments: The reason for not assessing some parameters on the 2nd week?
Response: Thank you for seeking clarification on the absence of certain assessments during the second week of the study. During the second week of the study, we have opted for a self-administered questionnaire assessment, which participants will complete at home. This approach contrasts with face-to-face visits, considering their convenience and minimisation of bias. The initial
two-week period is intended to allow participants to acclimate to the intervention and by delaying assessments, we believe we can capture more accurate data and reduce the potential for confounding due to immediate responses.

35. Comment: Which spss version?
Response: Added as ‘IBM SPSS Statistics version 29 will be used to run all descriptive and inferential analyses for all endpoints.’ (Page 10)

36. Comment: For the provided ID, it has been mentioned Not yet recruiting. Please update the information on ANZCTR.
Response: Thank you for bringing to our attention the status of the provided ID on the ANZCTR registry. Our apologies, we will promptly review and update the information on the ANZCTR registry to accurately reflect the current status of our study in future.

37. Comment: Who are the gynecologist and the Statistics Consultant?
Response: Already responded in query no. 2.

38. Comment: I think it is better not to mention the nature of the herb. It is sufficient to say that it is herbal medicine and for the research protocol it is better that participants not be aware of the nature of the herb till the end of the study.
Response: Thank you for clarifying your stance on mentioning the name of the herb to participants. We understand that participants have a genuine interest in knowing the supplement's name, and we respect their curiosity. Considering your recommendation for blinding and research protocol, we will indeed disclose the specific name of the herb to participants as part of our informed consent process. This approach aligns with maintaining ethical communication while ensuring participants are fully aware of the intervention they will receive.

39. Comment: Be sure that the participants are explained that they may receive placebo not a medication.
Response: Thank you for underscoring the importance of transparent communication with our participants regarding the possibility of receiving a placebo rather than an active medication. We want to assure you that our informed consent process is designed to provide participants with a clear understanding of the study procedures, including the potential of receiving a placebo. This is accompanied by the participant's information sheet where we have clearly stated about the possibility of receiving a placebo as ‘This study requires you to take either Tongkat Ali extract dose 1, Tongkat Ali extract dose 2 or placebo (a substance that has no therapeutic effect, used as a control).’
(Participant information sheet)

40. Comment: Benefits or possible side effects?
Response: Apologies for the mistake, we have revised it as below:

Benefits:
The benefits you will receive if you participate in this study may not be direct. The Tongkat Ali supplement given has the potential to provide energy to the study subjects who received this supplement.

Possible side effects and risks:
You may or may not experience side effects. Side effects may include a decreased blood cortisol level, medication discontinuation syndrome, weight gain and gastrointestinal symptoms. If this happens, you should notify the researcher immediately of any side effects experienced by you by calling the phone number listed below. (Participant information sheet)
41. Are the participants asked not to share their experience with other participants or in media till the end of the trial?
Response: We appreciate your question on this as we get a point to include in our information sheet. We have revised the participant information sheet as ‘We also appreciate your cooperation in not to sharing your potential experience with other participants or in any kind of social platform or media till the end of the trial.’ (Participant information sheet)

42. Will they be compensated for which kind of complications? I mean they are aware that the treatments may have some possible adverse effects.
Response: Yes, we maintain a comprehensive informed consent process that outlines potential adverse effects, their likelihood, and the steps we have taken to ensure participant safety. Participants in our study will be compensated to offset any inconvenience they may experience during the study period.

43. Comment: Are the participants free to leave the experiment any time they wish for any reason?
Response: Yes, they are free to leave the study whenever they wish for any reasons of their concern. We have clearly stated this in the participant information sheet.

In conclusion, we believe that the revised manuscript has substantially improved in response to the reviewers’ comments. We hope that our responses and revisions demonstrate our commitment to enhancing the quality and significance of the research. We kindly request that you consider the revised manuscript for publication in BMJ Open.