Author’s response to reviews

Title: Effect of a multi-ingredient based food supplement on sexual function in women with low sexual desire. Pilot study.

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Version: 2 Date: 14 Jan 2019

Author’s response to reviews:

Reviewer reports:

Alan W Shindel (Reviewer 1):

1) The principle and most important limitation of this study is absence of a control group. This, with small sample sizes, renders this study at best pilot data and not truly demonstrative of a clinical effect. This may indeed be a good treatment for women in the future, but this study alone cannot justify widespread use. The authors must make this explicit in the abstract conclusion and the conclusions section of the paper.

We would like to thank the reviewer for this comment. We have not changed the abstract conclusion section because it is already explicit that this is a pilot study and we think the concept you ask for it is covered by the sentence: “Further studies must be conducted to confirm these exciting results. We have added a similar sentence in the conclusions section of the manuscript.

2) The authors should consider stating in the manuscript itself that one author has financial ties with Procare.

Many thanks for the note. We have already mentioned that Santiago Palacio and Fernando Losa are part of Procare Health Iberia's scientific board. In addition, we added a new author to the
paper, Mr. Danial Khorsandi, who works as a scientific researcher and medical affair in Procare Health Iberia.

3) I don't fully understand the low sexual desire cut off. I have traditionally seen the FSFI-total cut off of 26.55 promoted as the cut off for risk of sexual dysfunction, where did 25.83 come from?

1. For our study, we took the cut-off point from the results of the group with sexual dysfunction in Rosen's study (attached, ref 20). We added the average score of the FSFI (19.2) plus the standard deviation (6.63) trying to ensure that we did not leave out any patient who might have sexual dysfunction: 19.2 + 6.63 = 25.83. In fact, the 2 figures are similar.


4) The authors should also clarify in the abstract hat the 25.83 is not specific to sexual desire but rather to sexual dysfunction more broadly. MOST IMPORTANTLY, sexual dysfunction cannot be diagnosed by the FSFI as it does not contain a distress component in assessment. The authors can speak of RISK of sexual dysfunction but should use caution in making an actual diagnosis.

We acknowledge these comments: we have changed “desire” by “dysfunction” in the abstract and we have revised the concept of “RISK of sexual dysfunction” along the manuscript.

5) The authors should also include several more citations in the methods to bolster their claims about the capabilities of the FSFI.

We added these references:


6) This study is hampered by absence of a control group.

We would like to thank the reviewer for this comment. We have already mentioned in discussion section that "The study has two limitations: it is a pilot study with small number of women and there is no control or placebo group."

7) A domain specific analysis should be considered and reported in the abstract; what specifically got better for these women?

Many thanks for this comment; we added the following sentence in the abstract:

“All FSFI domains, except dyspareunia, showed significant increases. The highest increase was observed in desire domain (p=0.0004).”

8) The units of testosterone measurement are unusual. Typically, ng/dL or nmol/L are utilized as units, please consider.

It is true that serum testosterone levels can be expressed in ng/ml or nmol/L, but also in pg/ml. In fact, in Europe this measure is widely used. We include a couple of recent references.


9) Please provide a citation for the statement that women produce higher amounts of estrogens than androgens. I would also take issue with the statement that this fact demonstrates how important androgens are; this is supposition.
There are numerous references in the literature that show that the quantity of androgens produced in women is greater than estrogen one. We include two review articles.


10) The authors should condense their background references in the introduction; one or two paragraphs can make the case for how prevalent the problem is. The DSM section could similarly be shortened. What should receive more attention is the data to suggest that these herbal preparations are helpful. Please discuss these in more detail, do not simply refer to existing studies en bloc and say they are helpful, provide the data to support this study on their efficacy in women. Please state a testable hypothesis in the introduction.

We acknowledge this comment and we have revised all these suggestions in the manuscript.

11) Please provide more information about this herbal product. How is quality control maintained? What is the dosing of these different components? From what source are they obtained? Why these particular components and not others?

The quality control is maintained by the technical director of Procare Health Iberia S.L.

We have added a table (table 1) indicating the dosing details. The components were chosen due to the traditional use and because they have clinical data publications in sexual disorders.

12) Were all participants heterosexual? YES

Was this a requirement? NO

What requirements existed regarding partner sexual function? Stable couples with habitual sexual availability (at least 15 days per month) are involved in this study.

13) How as normality of data determined? This is essential to deciding between parametric and non-parametric statistical tests.

A descriptive analysis of the variables included in the study was carried out. We present the measures of central tendency and dispersion, that is, mean, standard deviation (SD), median,
percentiles 25 and 75 (P25 and P75, respectively), minimum and maximum (min and max, respectively) of the quantitative variables. The distributions of absolute (n) and relative (%) frequencies of the qualitative variables are presented. It was not planned to allocate the unavailable data, which were simply described as lost data.

For the analysis of the evolution / change throughout the study, parametric tests were used for continuous variables (Student's T test for paired samples) and / or non-parametric tests (Wilcoxon).

For the comparison analysis between 2 groups, parametric tests were used for continuous variables (Student's T test for 2 independent samples) or nonparametric tests (Mann-Whitney U test); For categorical variables, the Chi-square Test or Fisher's Test was used.

14) I believe "two tailed" is a better term than "bilateral" for hypothesis testing in the stats section.

We acknowledge this comment and this is revised

15) Be aware of and correct run on sentences. The first, third, and fourth sentences of the discussion is an example, they need to be sub-divided. In general, it is not a good idea to have two or more commas in a sentence, unless one is making a list of considerations (e.g. as above when I state the specific problematic sentences).

We acknowledge this comment and this is revised.

16) What does this study add to existing literature? The authors cite prior work that articulates the purported benefits of these herbals in women; so what makes this current work novel and/or important?

This is a very good comment. In this study, we evaluated a new product, which contains different traditional used ingredients with a recognized effect to improve sexual function.

17) The specific limitations should be a separate paragraph, not buried at the end of a paragraph on hormone biology. The authors should expound on what could be done in the future to rectify these limitations in future work.

We acknowledge this comment and this is revised.
18) The authors are making an assumption about how this compound works in the second to last paragraph of the discussion; are they certain that the "Domino effect" and increasing free T and vasodilation are the drivers of these effects? Without a specific study on the components they cannot attribute specific actions to the particular components of this herbal. They may speculate but must be clear that it is speculation, not fact.

We would like to thank the reviewer for this comment. We have used the word "May" to show our speculation. In addition, the references (12-19) have provided and cited at the end of the paragraph to claim the speculation.

19) I would also recommend more caution about the "truly objective" hormonal results. Measurement of androgens in women is fraught with potential for error given low concentrations and variation. Until a control group of women is included the authors cannot conclusively demonstrate that their results are not all driven in some fashion by placebo effect.

We acknowledge this comment and this is revised.

20) Units must be included in table 1 (e.g. years, kg, centimeters, etc). Since all women were Caucasian this could however be eliminated and just stated in text.

We acknowledge this comment and this is revised.

21) What is meant by "studies" in table 1?

We acknowledge this comment and this is revised.

22) Were all women post-menopausal? This was not made clear. Table 1 implies that all women had undergone menopause, how was this determined?

Thanks for the observation, we now add in the text

Those eligible for inclusion were healthy, postmenopausal women aged 45–65 years with no natural menses for at least 1 year. Hysterectomized patients should have an FSH above 40 IU.
23) The "no hysterectomy" row could be omitted as it is implied from the prior line.

We acknowledge this comment and this is revised.

24) Was number of pregnancies assessed? Number of deliveries may be better presented as whole numbers or even median, depending on normality of data.

We acknowledge this comment and this is revised.

25) The pie chart in figure 1 is relatively uninteresting. Would be better to include a domain-specific detail of FSFI changes.

We acknowledge this comment and this is revised.

26) Consider changing the y axis in the chart on testosterone levels, a maximum of 1 pg/mL would permit more distinction

We acknowledge this comment and this is revised.

C Rusike (Reviewer 2):

GENERAL: Authors investigated the effect of a Trigonella foenum graecum-based food supplement on sexual function in women with low sexual desire. Testosterone levels were measured. As a pilot, this study addresses an important problem. The paper is well written in good English and is easy to follow.

1) Plant names should be given in Italics.

Thanks for the comment. This is revised.

2) Title: What percent of Libicare® is Trigonella foenum graecum - seeing there are other plants namely - Turnera diffusa, Tribulus terrestris, and Ginkgo biloba - some of which have been shown to have testosterone enhancing effects. I ask for clarity - if Trigonella forms the main plant - then I suppose it is alright to call Libicare® Trigonella-based - otherwise it may
be prudent to leave title as "polyherbal food supplement" without pointing out this particular plant.

Thanks for the suggestion and we have made the appropriate modifications, among them we have changed the title.

ABSTRACT

3) Postmenopausal (spelling in introduction).

Thanks for the comment. This is revised.

4) Too many unexplained abbreviations in the abstract. Need to be given in full first

Thanks for the comment. This is revised.

INTRODUCTION: Adequate background is given to motivate for this study. Arguments are clear and relevant to the problem being addressed.

5) More could have been said about the timing of testosterone levels within the cycle relative to sexual desire and possible mechanisms of action in sexual desire (local vs central effects?).

Thank you very much for the comment However, although due to the characteristics of the study (observational and with a food supplement) we consider that talking about the mechanism of action of testosterone in the introduction section would not be appropriate, since it would have to be treated very superficially, when it is a complex issue and also that it is not completely known. Nevertheless, we have added some sentences on the mechanism of action in the discussion section.

METHODS: Methods are clearly explained with inclusion and exclusion criteria clearly outline.

6) The proportion contribution of plants in Libicare® should be indicated.

May thanks for this comment, the table containing the herbal compounds has been added to the manuscript (table 1).
7) There has to be clarity as to what day of menstrual cycle blood was collected to measure testosterone and SHBG since both vary over the menstrual cycle. Was menstrual timing similar for the whole cohort or was it per individual. I would be wary of blood collection at random days not synchronised by cycle day.

May thanks for this comment. We apologize because we have not clarified that they were all postmenopausal women. That is why we have added this data in the inclusion criteria

RESULTS: Results are clearly presented and are consistent with objectives of study and methods.

DISCUSSION

8) Some discussion of mechanisms of action were expected here (testosterone, flibanserin). What are treatment options targeting mechanistically?

We have added this:

The hormones that influence female sexuality are estrogens and androgens. Several studies have shown that the reduction in testosterone level is directly related to the decrease in sexual activity in postmenopausal women (9,10). However, it is also true that other studies have shown that the level of testosterone is not related to sexual performance (25,26). On the other hand, there is more and more data that point to a possible role of androgens on neurotransmitters, dopamine and serotonin (27,28). Dopamine plays an essential role in the modulation of desire sexual; it seems to increase sexual desire, the subjective sensation of excitement and the desire to continue sexual activity once the stimulation has begun (28,29).


As mentioned earlier, authors continually attribute observed effects to Trigonella - yet this is multi-herbal intervention. Indeed authors allude to studies with Tribulus terrestris as possessing hypoactive sexual desire improving effects and Gingko biloba and Turnera diffusa also playing a role. This reviewer therefore feels that authors should discuss Libicare® in its entirety without necessarily attributing observed effects to just the one plant - Trigonella.

Many thanks for this comment. This is revised.

Spelling errors

There are several spelling errors in the document e.g. Methods (Laboratory tests) sex hormone blinding globulin (should be binding). Results - different **ducational and economic backgrounds (missing an 'e')

We acknowledge the reviewer for this comment. This is revised.