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OPEN PEER REVIEW

Therapeutic Effects of *Pimpinella anisum* Fruit Extract on Polycystic Ovary Syndrome in a Rat Model: Emerging Role of Inflammatory Responses and Oxidative Stress

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About this report

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1 Original submission

3 comments · 17 Dec 2023 – 20 Dec 2023

Referee 1 Reviewer

REJECT 17 Dec 2023

I was not satisfied with the content. The manuscript suffers from poor novelty, poor design, and poor structure. Hence, I recommend rejection.

Referee 2 Reviewer

MINOR REVISION 20 Dec 2023

Dear Editor
This manuscript evaluates the therapeutic effects of Pimpinella anisum fruit extract on polycystic ovary syndrome. The manuscript contains valuable information. However, it needs some modifications as follows:
1) For the studied plant, “Herbarium number” should be provided.
2) The English grammar in this paper has to be improved before it can be reconsidered for publication. The manuscript is extremely poorly written and needs to be largely reworked.
3) Abbreviations are not defined in some places.
4) Figure 6b is not referred to in the main body of the text.
5) The discussion section has to be improved.

Associate Editor

MAJOR REVISION 20 Dec 2023

Please consider the reviewers' comments.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

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

Subject: Re-submission of a manuscript **(Manuscript ID: 143290)**

Title: Therapeutic effects of *Pimpinella anisum* fruit extract on polycystic ovary syndrome in a rat model: Emerging role of inflammatory responses and oxidative stress

Dear editor,

Thank you for the opportunity to revise our manuscript entitled “Therapeutic effects of *Pimpinella anisum* fruit extract on polycystic ovary syndrome in a rat model: Emerging role of inflammatory responses and oxidative stress”. We truly appreciate all the constructive comments and suggestions from the reviewers. With this letter, we will be submitting a revised version of the manuscript **(Manuscript ID: 143290).** Please kindly notice that one-by-one responses to the reviewers’ comments are provided in an MS Word file and that all the new changes and inclusions are in the main body of the manuscript. The changed parts are highlighted in yellow in the text.

We sincerely hope that the revised manuscript has been efficiently improved and reached the level of acceptance in the **Iranian Journal of Pharmaceutical Research**

:Reviewer #1

1. **Please check whole manuscript for English grammar and dictation**
   Response: We appreciate the reviewer for his valuable comment. The paper has been thoroughly edited and a number of words/sentences have been substituted or re-phrased appropriately.

2. **The scientific name of the plant should be written in italics throughout the text**
   Response: According to the reviewers' comment "Pimpinella anisum. L." in the text was written as follows: *Pimpinella anisum.* L.

3. **In some parts there is no need to refer many publications, for example, in the first sentence of the background, it is not necessary to refer 3 references**
   Response: The reviewer's valuable comment has been done.

4. **In second paragraph background;" These polyphenols, called Pimpinella anisum L. generally known as…" what is the meaning? Polyphenols are phytochemicals and Pimpinella anisum L. is the plant. Please clarify and correct.**
   Response: According to the respected reviewer's comment, the sentences in this paragraph have been rewritten (2st paragraph page 2, background section)

   Pimpinella anisum L. (*P. anisum*) commonly known as aniseed or anise, is an aromatic plant belonging to the Umbelliferae (Apiaceae) family that mainly grows in the Middle East, Asia Minor, and India. (20, 21).

5. **About anise phytochemicals (bioactive compounds) in the introduction, only essential oil compounds are written, while in this research, its extract was used**
   Response: The reviewer's valuable comment has been considered in the introduction section.

   Aniseed extract contains a range of compounds, including 1.5-6% essential oil (mainly trans-anethole), 8–11 % fatty acids (such as palmitic and oleic acids), 4 % carbohydrates, and 18 % protein, as well as considerable amounts of phenolic compounds including flavonoids, and phenolic acids. (2st paragraph page 2, background section)

6. **Although in this study, a more detailed phytochemical evaluation, (fractionation and isolation some active compounds), was not done, but as there are many publications in this regard, it is better to mention some of them in the discussion and discuss possible compounds associated with the biological effects observed in this study.**
Response: We have taken reviewer's comment in full consideration and it will be well reflected in the revised version of manuscript.

Other studies confirmed the anti-inflammatory activity of trans-anethole (45-47) and flavonoids (48, 49) as main compounds of *P. anisum* by inhibiting gene expression and release of inflammatory pathways such as IL-6, TNF-α, and nuclear factor kappa beta (NF-κB) *in vitro* and *in vivo* conditions (Page 10, line 2-6)

7. **In method section, many parts have no references, please check and correct.**
Response: As suggested by the respected reviewer, the references have been inserted in the methods section and highlighted.

Reviewer #2

1. **The country and company of all materials should be mentioned**
Response: "According to the reviewers' comment, we have added country and company of all materials in the methods section.

2. **The country and company of all instruments should be mentioned.**
Response: The reviewer's valuable comment has been done

3. **Please write in vitro, in vivo and P. anisum in italic all over the text including in Fig. 1.**
Response: According to the reviewer's suggestion, the words "P. anisum" and in vitro, in vivo in the text were written as follows: *P. anisum*, *in vitro*, *in vivo*

4. **The interval between P. anisum administration should be mentioned in text and figure.**
Response: With thanks to the reviewer's comment, the doses of *P. anisum* extract and the duration of treatment (interval) have been mentioned and highlighted in the text and figures.

Female Wistar rats were randomly assigned into four groups (n= 5/group), including: (I) Control group: Non-PCOS induced rats that received tap water and food; (II) polycystic ovary syndrome group (PCOS): PCOS rats that received 0.5 mL /day normal saline orally

(gavage) for 3 weeks; (III) polycystic ovary syndrome + *P. anisum* 200 mg/kg group (PCOS+ PA200): PCOS rats received extract PA at the dose of 200 mg/kg orally once daily for 3 weeks; (IV) polycystic ovary syndrome + *P. anisum* 400 mg/kg group (PCOS+ PA400): PCOS rats received extract *P. anisum* at the dose of 400 mg/kg orally once daily for 3 weeks (26). (Page 4, Experimental design)

5. **The method and time of tissue homogenization should be mentioned.**
Response: Thank you so much for your suggestion. It has been added

After 21 days of *P. anisum* administration, all animals were anesthetized with an intraperitoneal (IP) injection of ketamine/xylazine (80/10 mg/kg), and sacrificed by cervical dislocation. The liver and Ovaries of rats were isolated and weighed. The right ovary and liver were homogenized in lysis buffer, centrifuged at 1250×g for 30 min at 4°C (33), and the supernatants were collected and kept at − 80°C until analysis. The left ovaries were fixed in a formalin solution (10%) for histopathological examination. (Page 5, Tissue sampling)

6. **The data of table 2 were repeated in the text and table 2 can be omitted.**
Response: Sorry for the repetition and we have deleted it as suggested

7. **Please revise the following sentences:**
We might claim, the obtained results for DPPH radical scavenging activity were in line with our data for total phenolics and flavonoids contents, mentioning P. anisum fruits high contents of phenolics compounds being partly in charge of the revealed in vitro antioxidant activity.
Response: We appreciate the reviewer for his valuable comment., The sentence has been revised (Page 6, result section, "Phytochemical analysis")

8. **The authors claimed that the effect of Pimpinella anisum fruit extract on polycystic ovary syndrome is dose-dependent. The authors should explain in this regard in discussion section**
Response: Thank you to the reviewers for their excellent suggestions, we have mentioned it in the revised manuscript. (Page 10/line 18-21).

In this study, it is noteworthy that, treatment with *P. anisum* at a dose of 400 mg/kg was more effective than at a dose of 200 mg/kg. Together these findings suggest that extracts

with higher concentrations may contain higher levels of bioactive components. In other words, P. anisum can be considered as effective therapeutic option for PCOS.

9. **Please discussion more about the importance of IL-6 and TNF-α in pathology of PCOS in discussion section.**
Response: As suggested by the respected reviewer the following discussion on the mentioned issue has been added to the discussion section. (Discussion, 2st paragraph page 9).

The dysfunction in endocrine metabolism, abnormal androgen hormones, and chronic inflammation are observed in PCOS (8). Although many studies have examined the effect of hyperandrogenism on the pathological mechanisms of PCOS, mainly follicular dysplasia and anovulation. However, among the main factors contributing to PCOS pathophysiology, inflammation is one of the major critical risk factors (35, 36). Several studies indicated that PCOS is linked with progressive inflammation of the follicular ovaries and deterioration in ovarian performance (13, 37). It has been reported that IL-6 and TNF-α are important mediators of the inflammatory response and are involved in apoptosis or necrosis of ovarian follicles (38).

Reviewer #3

1. **For the studies plant "Herbarium number" should be provided.**
Response: According to the reviewers' comment the "herbarium number" of the plant was provided and highlighted in the Methods section (section 3.2./Plant material preparation)

Fruits of *P. anisum* were purchased from the local herbal market in Tabriz. After identification and confirmation of the plant materials by herbarium of the Department of Pharmacognosy, Faculty of Pharmacy, Tabriz University of Medical Sciences with voucher herbarium specimen (No. tbz-fph-45).

2. **The English grammar in this paper has to be improved for the reconsideration of publication. The manuscript is extremely poorly written and needs to be largely reworked.**
Response: We appreciate the reviewer for his valuable comment. The paper has been thoroughly edited and a number of words/sentences have been substituted or re-phrased appropriately.

3. **Abbreviation is not defined in some places.**

Response: The reviewer's valuable comment has been done:

- Tumor necrosis factor-α (TNF-α)
- Interleukin 6 (IL-6)
- Estradiol valerate (EV)

4. **Figure 6b is not referred to in the main body of the text.**
   Response: According to the respected reviewer's comment, Figure 6b has been referenced in the main text of the manuscript file (see result section).

5. **The discussion section has to be improved**
   Response: The reviewer's valuable comment has been done.

2 Revision 1

0 comments

No public comments in this round.