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Peer Review Report for "*Teucrium polium* Alters the Vascular Branching Pattern and VEGF-A Expression in the Chick Extra-Embryonic Membrane Model"

Author(s): Elahe Moeini, Hadi Tavakkoli

Review Timeline:

Submit Date:	22 Jun 2019
Revised Date:	5 Nov 2019
Accepted Date:	7 Jan 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0)

5 Aug 2019

Dear editor-in-Chief;

The manuscript entitled"Teucrium polium alters vascular branching pattern and VEGF-A expression in the chick's extra-embryonic membrane model" is extremely poorly written and needs to be largely revised. Below you can see some comments which need author's attention:

1- A good abstract should reflect background, objectives, methodology and results in the most summarized form to give readers a complete view of the study; please provide readers some information about Teucrium polium.
Writers talked about herb side effects but which kind of side effects?

2- Did you use three image analyzer software? why?

the paper is potentially interesting to the readers of JJNPP, but it needs to be rewritten.

Best regards!

REFEREE: Reviewer | **Revision** (0) 9 Aug 2019

Dear author;

Thank you for choosing JJNPP for publishing your article. There are some comments that need your attention:

1. It has numerous spelling mistakes..
2. Why the authors have not used other models of angiogenesis (such as Cornea angiogenesis assay or In vivo matrix invasion assays) to have more accurate results?

With best wishes!

REFEREE: Reviewer | **Revision** (0) 30 Sep 2019

Dear Editor-in-Chief;

The mentioned manuscript describes a valuable research project, but needs some revisions:

1- Authors have mentioned that “the eggs were treated with 50 µl of either a T. polium extract or sterile phosphate buffered saline (PBS) as a sham control”. This should be described as (how many mg or µg/50 µl). What is the volume of solution in treated doses (3 or 6 mg/kg)?

2- X axis labels should be clear In figures 3 and 4 .

With best wishes!

REFEREE: Associate Editor | **Revision** (0) 30 Sep 2019

Major Revision

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Responses to Reviewers' Comments:

Dear Editor

The reviewers' comments are accepted and corrected.

Sincerely yours,

Reviewer 1:

1- Authors have mentioned that “the eggs were treated with 50 µl of either a T. polium extract or sterile phosphate buffered saline (PBS) as a sham control”. In this way describe the right dose of extract (how many mg or µg/50 µl). What is the volume of solution in treated doses (3 or 6 mg/kg).

The doses of extract were as follows:

Group 2: embryonated eggs were treated with *T. polium* extract at dosage of 3 mg/kg egg weight (150 µg/50 µl).

Group 3: embryonated eggs were treated with *T. polium* extract at dosage of 6 mg/kg egg weight (300 µg/50 µl).

The volume of solution in treated doses was 50 µl. These data were added to the text.

2- In figures 3 and 4, X axis labels should be fully presented.

It was corrected.

3- Given that the plant is used as a medicine in humans, extend the data from this study to humans.

This issue was added in conclusion section.

Reviewer 2:

1. It has numerous spelling mistakes

The paper was edited for language and grammar based on attached certification.

2. Why the authors have not used other models of angiogenesis (such as Cornea angiogenesis assay or In vivo matrix invasion assays) to verify more accurately.

The chick embryo model is frequently used for preclinical evaluation of drug delivery systems such as activity, toxicity, biodistribution and pharmacokinetics. It is also promoted and validated to investigate the effects of drugs on pathways, which are associated with vessel genesis and regression. Therefore, in this paper this model was used. On the other hand, the authors are expert in this model and some methods such as cornea angiogenesis involved limitations such as ethical and legal aspects. (Mousa, Yalcin et al. 2017; Ribatti 2017; Khosravi, Sharifi et al. 2018; Khosravi, Sharifi et al. 2018; Morgan, Keen et al. 2018; Raval, Khunt et al. 2018; Seifaddinipour, Farghadani et al. 2018; Tavakkoli, Attaran et al. 2019)

Khosravi, A., I. Sharifi, et al. (2018). "Embryonic toxico-pathological effects of meglumine antimoniate using a chick embryo model." PLoS ONE **13**(5): e0196424.

Khosravi, A., I. Sharifi, et al. (2018). "Vascular apoptosis associated with meglumine antimoniate: In vivo investigation of a chick embryo model." Biochemical and Biophysical Research Communications **505**(3): 794-800.

Morgan, R., J. Keen, et al. (2018). "Species-specific regulation of angiogenesis by glucocorticoids reveals contrasting effects on inflammatory and angiogenic pathways." PloS one **13**(2): e0192746.

Mousa, S. A., M. Yalcin, et al. (2017). Models for Assessing Anti-Angiogenesis Agents: Appraisal of Current Techniques. Anti-Angiogenesis Strategies in Cancer Therapeutics, Elsevier**:** 21-38.

Raval, N., D. Khunt, et al. (2018). "Microemulsion based delivery of Triamcinolone acetonide to posterior segment of eye using Chitosan and butter oil as permeation enhancer: An in vitro and in vivo investigation." Journal of Microencapsulation(just-accepted): 1-37.

Ribatti, D. (2017). "The chick embryo chorioallantoic membrane (CAM) assay." Reproductive Toxicology **70**: 97-101.

Seifaddinipour, M., R. Farghadani, et al. (2018). "Cytotoxic Effects and Anti-Angiogenesis Potential of Pistachio (Pistacia vera L.) Hulls against MCF-7 Human Breast Cancer Cells." Molecules **23**(1): 110.

Tavakkoli, H., R. Attaran, et al. (2019). "Vascular alteration in relation to fosfomycine: In silico and in vivo investigations using a chick embryo model." Biomedicine and Pharmacotherapy **118**: 109240.

Reviewer 3:

1- A good abstract should reflect background, objectives, methodology and results in a most summarized form to give readers a complete view of the work. for example provide readers some information about Teucrium polium. writers talked about herb side effects but which kind of side effects? and.....

It is corrected.

2- did you use three image analyzer software? why?

Each software has its specific limitations in image analysis. Therefore, three image analyzer software were used to computerized analysis of image.

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Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) 28 Nov 2019

Dear author;

1. Given that the present study is very similar to the following study: “Al-Qahdi SS, Alzohari N, Alsaid AY, et al. Teucrium polium plant extract provokes substantial cytotoxicity at the early stage of embryonic development. Bosnian journal of basic medical sciences. 2019;19(1):67.”, please refer to similar studies and the above mentioned study in the discussion section. What is the author's justification for ensuring that the principle of novelty is respected? Discuss the differences between the two studies in different ways.

Best regards!

REFEREE: Reviewer | **Revision** (1) 30 Nov 2019

Dear editor-in-Chief;

Thank you for considering me as a reviewer for this publication in your journal JJNPP.
In my opinion, the manuscript is well written and now is suitable for publication.

Best regards!