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Jundishapur Journal of Natural Pharmaceutical Products
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Peer Review Report for "In Vitro Enzyme Inhibitory and Antioxidant Properties, Cytotoxicity, and LC-DAD-ESI-MS/MS Profile of Extracts from the Halophyte *Lotus creticus* L."

Author(s): Chloe Placines, Viana Castaneda-Loaiza, Maria J. Rodrigues, Catarina G. Pereira, Jose Paulo da Silva, Gokhan Zengin, Luísa Custódio

Review Timeline:

Submit Date: 9 Feb 2020
Revised Date: 18 Jul 2020
Accepted Date: 9 Sep 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) — 11 Feb 2020

Dear author;

I have read your manuscript precisely and found it interesting. I came to the conclusion that it is worth publishing following some minor corrections. The conclusion is supported by the amassed data very well. I have annotated the manuscript in the attached file. Please address all comments.

Good Luck!

Mohammadreza Rashidi Nooshabadi: Reviewer | Revision (0) — 7 Jun 2020

Dear author;

Thank you for choosing JJNPP for publishing your manuscript. Please do consider the following comments;

1- what idea or thoughts did make you decide to investigate enzymes inhibition of creta trefoli?
2- Insert a reference referred to acetyl- and butyrylcholinesterase inhibition and using galantamin as standard.

Good Luck!

Asadollah Salarabadi: Reviewer | **Revision (0)** 11 Jul 2020

Dear author;
Thank you for choosing JJNPP for publishing your manuscript.

The manuscript discusses about the edible halophyte Lotus creticus L. (creta trefoil). The main contribution of the paper is to display the importance of plants to humans' health and life.

I recommend that this paper be accepted after some revisions as coming below;

-Major comments:

1. Material and methods:
The word "in vitro" is written in Italic in some sections and non-italic elsewhere. Why? Correct it if applicable.

2. References:
There are a lot of old references.
The reference no. 1, 10, 11, 16, 17, 18, 19, 21, 22, 23, 27, 30, 32, 33, 34 and 35 should be replaced with the references related to the last five years.

-Minor comments:

1. Title:
This title is not appropriate, select a simple and understandable title.

2. Keywords:
Please provide two more keywords based on MESH (https://www.ncbi.nlm.nih.gov/mesh).

Good Luck!

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.

Dear **Editor in Chief of the Journal 'Jundishapur Journal of Natural Pharmaceutical Products'**

Please find enclosed the revised version of the manuscript 'A first approach to explore the edible halophyte *Lotus creticus* L. (creta trefoil) as a source of bioactive natural products: *in vitro* enzyme inhibitory and antioxidant properties, cytotoxicity and LC-DAD-ESI-MS/MS profile' (Placines et al).

We are grateful for the revisions and comments made by the reviewers and the editorial office. All the changes were made to address the questions and comments raised by them, in track changes mode.

I hope that this version is now suitable for publication.

Best regards
Luísa Custódio



ANSWERS TO THE REVIEWERS

Reviewer 1:

Comments: I have read with much interest the MS. I came to the conclusion it is worth to be published following some minor comments.The conclusion is supported by the data amassed. I have annotated the file. Please address all comments.

Answers: We are grateful for the valuable comments nd suggestions made by the reviewer. All the modifications were addressed in the paper, in red.

Reviewer 2:

Comments: Please explain:

1- what idea or thoughts caused you decide to investigate enzymes inhibition characteristics of creta trefoli?

2- About Acetyl- and butyrylcholinesterase inhibition and use of galantamin as standard, enter reference?

3-Acetyl- and butyrylcholinesterase inhibition in medicine, at where it is important and valuable?\

Answers: We are grateful for the comments made by the reviewer. Please find bellow the answers for your questions.

1 – In our lab, we search for possible medicinal applications of natural extracts. Those appplications include, for example, antioxidant, anti inflammatory, and inhibition of enzymes relevant for the management of human diseases, such as neurodegeneration(inhibition of AChE and BuChE), Type 2 diabetes mellitus (inhibition of α-glucosidase and α-amylase) and hyperpigmentation (inhibition of tyrosinase). This is based on the fact that a high number of drugs used in clinical practices for the management of such diseases are inhibitors of referred enzymes (Ferreri et al., 2006; McDermott et al., 2012; Jiang et al., 2017;).

2 and 3 – The medicinal importance of the use of AChE and BuChE inhibitors is explained in lines 187-192. The reference for the use of galantamine as a standard is referred on the text (reference number 24, Zengin et al., 2016).

References

Ferreri F, Agbokou C, Gauthier S. Cognitive dysfunctions in schizophrenia: potential benefits of cholinesterase inhibitor adjunctive therapy. *Journal of Psychiatry and Neuroscience*. 2006,31(6):369.

Jiang Y, Gao H, Turdu G. Traditional Chinese medicinal herbs as potential AChE inhibitors for anti-Alzheimer's disease: a review. *Bioorganic chemistry*. 2017,75:50-61.

McDermott CL, Gray SL. Cholinesterase inhibitor adjunctive therapy for cognitive impairment and depressive symptoms in older adults with depression. *Annals of Pharmacotherapy*. 2012,46(4):599-605.

Zengin G. A study on in vitro enzyme inhibitory properties of *Asphodeline anatolica*: new sources of natural inhibitors for public health problems. *Industrial Crops and Products*. 2016,83:39-43.

Reviewer 3:

This paper discusses on to explore the edible halophyte Lotus creticus L. (creta trefoil). The main contribution of the paper is to display the importance of plants to humans' health and life.

I recommend that this paper be accepted after minor revision.

Major comments:

1. Material and methods:

The word "in vitro" is written in Italic in some sections and simply written elsewhere. Why is there a difference?

2. References:

There are a lot of old references.

The reference no. 1, 10, 11, 16, 17, 18, 19, 21, 22, 23, 27, 30, 32, 33, 34 and 35 should be replaced with the references for the last five years.

Answers: We are grateful for the comments made by the reviewer. Please find bellow the aswers for the questions. All the modifications were addressed in the paper, in red.

1. Material and methods: This was corrected.

2. References: References were replaced for relevant and most recent ones, except for references number 10, 11, 16-16, 21-23. Those references refer to biological properties of Lotus species, and to the best of our knowledge, there are no similar and more recent ones.

Minor comments:

1. Title:

This title is not appropriate, select a simple and understandable title.

2. Keywords:

Please provide two more keywords based on MESH (https://www.ncbi.nlm.nih.gov/mesh).

Answers: We are grateful for the comments made by the reviewer. Please find bellow the aswers for the questions. All the modifications were addressed in the paper, in red.

1. Title: As suggested the title was replaced by **“**In vitro enzyme inhibitory and antioxidant properties, cytotoxicity and LC-DAD-ESI-MS/MS profile of extracts from the halophyte Lotus creticus L.”

2. Keywords: More keywords were provides, as requested.

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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) 25 Jul 2020

Dear EIC;

The authors have revised the MS in line with comments sent by reviewers. The corrections have now improved the MS significantly. I am satisfied with corrections undertaken. The paper can be accepted.

With Best Wishes!

REFEREE: Reviewer | **Revision** (1) 31 Aug 2020

Dear EIC;

I think This manuscript is suitable for publication, but there is a comment;

In discussion: adding possible pathways of cholinergic effects & antioxidant properties, as well as the cytotoxicity of halophyte Lotus creticus L. extracts can make a more powerful discussion.

sincerely yours!