

No.: 33523

Title: Hepatoprotective Effects of *Foeniculum vulgare* root barks extract on Carbon Tetrachloride Induced-Hepatic Fibrosis in mice

Dear reviewers,

We would like to thank you for giving us a chance to resubmit our manuscript entitled “Hepatoprotective Effects of *Foeniculum vulgare* root barks extract on Carbon Tetrachloride Induced-Hepatic Fibrosis in mice”. We also thank you for your attention constructive comments. Those valuable comments are very helpful for revising and improving our paper. The manuscript has been modified according to the reviewers’ suggestions. All amendments are highlighted by red font in the revised manuscript.

Thank you again for your attention to our manuscript. If there are any requests, please feel free to contact us.

Sincerely yours.

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The following is a point-to-point response to the reviewer’s comments.

Reviewer #1:

The authors's aim were to investigate hepatoprtoeczive effects of *Foeniculum vulgare*

root barks on carbon tetrachloride-induced hepatic fibrosis in mice. The methods are appropriate, the results are moderate.

Comment 1: The article is a well-written but the authors would have considered more references.

Response to comment 1: Thank you very much for your attention to our manuscript. Following the reviews' suggestion, we have added four references in the revised manuscript.

- 22 **Sun Y**, Jia L, Huang Z, Wang J, Lu J, Li J. Hepatoprotective effect against CCl₄-induced acute liver damage in mice and High-performance liquid chromatography mass spectrometric method for analysis of the constituents of extract of *Rubus crataegifolius*. *Nat Prod Res* 2017; 1-5 [PMID: 28322066 DOI: 10.1080/14786419.2017.1292264]
- 23 **Pareek A**, Godavarthi A, Issarani R, Nagori BP. Antioxidant and hepatoprotective activity of *Fagonia schweinfurthii* (Hadidi) Hadidi extract in carbon tetrachloride induced hepatotoxicity in HepG2 cell line and rats. *J Ethnopharmacol* 2013; **150**: 973-981 [PMID: 24140589 DOI: 10.1016/j.jep.2013.09.048]
- 24 **Vladimir-Knezevic S**, Cvijanovic O, Blazekovic B, Kindl M, Stefan MB, Domitrovic R. Hepatoprotective effects of *Micromeria croatica* ethanolic extract against CCl₄-induced liver injury in mice. *BMC Complement Altern Med* 2015; **15**: 233 [PMID: 26174335 DOI: 10.1186/s12906-015-0763-8]
- 25 **Wahid A**, Hamed AN, Eltahir HM, Abouzied MM. Hepatoprotective activity of ethanolic extract of *Salix subserata* against CCl₄-induced chronic hepatotoxicity in rats. *BMC Complement Altern Med* 2016; **16**: 263 [PMID: 27473536 DOI: 10.1186/s12906-016-1238-2]

Comment 2: The authors have to rewrite the discussion part and give credits to more authors who considered natural plants hepatoprotective effects

Response to comment 2: Thank you very much for your helpful suggestion. Following the reviews' suggestion, we have rewritten the discussion part.

There are evidences that natural substances may have a protective role against CCl₄-induced liver injury[22, 23]. Considerable efforts have been made in the study of natural products with hepatoprotective activities[24, 25].

- 22 **Sun Y**, Jia L, Huang Z, Wang J, Lu J, Li J. Hepatoprotective effect against CCl₄-induced acute liver damage in mice and High-performance liquid chromatography mass spectrometric method for analysis of the constituents of extract of *Rubus crataegifolius*. *Nat Prod Res* 2017; 1-5 [PMID: 28322066 DOI: 10.1080/14786419.2017.1292264]
- 23 **Pareek A**, Godavarthi A, Issarani R, Nagori BP. Antioxidant and hepatoprotective activity of *Fagonia schweinfurthii* (Hadidi) Hadidi extract in carbon tetrachloride induced hepatotoxicity in HepG2 cell line and rats. *J Ethnopharmacol* 2013; **150**: 973-981 [PMID: 24140589 DOI: 10.1016/j.jep.2013.09.048]
- 24 **Vladimir-Knezevic S**, Cvijanovic O, Blazekovic B, Kindl M, Stefan MB, Domitrovic R. Hepatoprotective effects of *Micromeria croatica* ethanolic extract against CCl₄-induced liver injury in mice. *BMC Complement Altern Med* 2015; **15**: 233 [PMID: 26174335 DOI: 10.1186/s12906-015-0763-8]
- 25 **Wahid A**, Hamed AN, Eltahir HM, Abouzied MM. Hepatoprotective activity of ethanolic extract of *Salix subserrata* against CCl₄-induced chronic hepatotoxicity in rats. *BMC Complement Altern Med* 2016; **16**: 263 [PMID: 27473536 DOI: 10.1186/s12906-016-1238-2]

Comment 3: Questions: Why did you select olive oil for APIs?

Response to comment 2: Thank you very much for your attention to our manuscript. The reagent has a good solubility in olive oil. Also, olive oil itself is non-toxic and does not interfere with hepatoprotective effects of *Foeniculum vulgare* root barks. Therefore, olive oil were selected for APIs.

We have studied comments carefully and tried our best to improve the manuscript. We appreciate for the reviewer's hard work and hope that the correction will meet with approval. Once again, thank you very much for your valuable comments and suggestions.