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PEER-REVIEW REPORT

Name of journal: *World Journal of Hepatology*

Manuscript NO: 70101

Title: Baicalin provides protection against fluoxetine-induced hepatotoxicity by modulation of oxidative stress and inflammation

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04047574
Position: Editorial Board
Academic degree: PharmD

Professional title: Academic Research, Director, Pharmacist, Professor, Senior Scientist

Reviewer's Country/Territory: Germany

Author's Country/Territory: India

Manuscript submission date: 2021-07-23

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-07-29 07:13

Reviewer performed review: 2021-07-29 07:54

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Aim of this manuscript was to evaluate the protective action of baicalin in fluoxetine induced liver toxicity and inflammation. The authors conclude from their experiments that co-application of baicalin protects against fluoxetine induced liver damage. Bailain is well known to protect against toxin-induced liver damage. Nevertheless, it is important to have many proves before translating these effects into the clinic. There are a number of questions that shall be addressed before publication - please see below: Main concern: The work is very solid and deserves publication BUT is is very descriptive. The mechanisms why it is inducing oxidative stress is somehow missing and would increase the value of the paper. Furthermore, the authors shall discuss that baicalin itself can act as an antidepressive agent. Others: There many small incorrect forms e.g. 100mg instead of 100 mg - between a number and a unit is almost always a space! Also check: between a word and a bracket belongs a space! Please check In the paper you write 'wistar' it should be 'Wistar' it is a proper Name and must be written with a capital 'W' The sentence 'This is probably the first study that assessed the alleviating effects of baicalin against fluoxetine induced hepatotoxicity, inflammation and oxidative stress.' must be changed since similar work is dealing with the subject - see missing published paper: The paper by Limanaqi and co-workers (Antioxidants 2020, 9, 234; doi:10.3390/antiox9030234) dealing with the same subject has neither cited nor discussed. In the same line of evidence, the authors shall cite and discuss the paper by Yang et al. (Front. Pharmacol., 11 February 2020 | https://doi.org/10.3389/fphar.2019.01685). These recent papers must be cited and discussed. Fig. 1 can be left out Table 1 should be rearranged - it is hard to read w/o the legend - but should be informative w/o the

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legend - only numbers.

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Peer-review model: Single blind

Reviewer's code: 05458463
Position: Peer Reviewer
Academic degree: PhD
Professional title: Assistant Professor
Reviewer's Country/Territory: Thailand
Author's Country/Territory: India

Manuscript submission date: 2021-07-23

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-07-26 06:33

Reviewer performed review: 2021-08-04 14:28

Review time: 9 Days and 7 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Fluoxetine is the prescription medication often used to treat a variety of neuropsychiatric disorders, including depression. However, some unwanted effects, including liver toxicity have been reported. This article was aimed to determine the preventive effect of baicalin against fluoxetine induced liver toxicity via the oxidative stress and inflammation status. Baicalin is one of the active compounds extracted from the root of Scutellaria baicalensis, which is an herb used in East Asian traditional medicine. Its pharmacological properties have been reported such as hepatoprotection, antioxidant, and neuroprotective effects. In addition, baicalin exhibits a variety effect on the central nervous system and shows antidepressant property. The results from this study demonstrated the positive effects of baicalin for prevention of fluoxetine-induced hepatotoxicity and liver injury in rat model. Parts of the mechanism are mediated by modulating the liver oxidative stress (SOD, CAT, GST, GSH, MDA and AOPP) and lowering the inflammatory cytokines levels (TNF-α, IL-6, IL-10 and IFN-γ). This report was interesting and can be further used in clinical approach, however, several issues should be addressed. 1. Baicalin has exhibited an antidepressant property as shown in various reports. The authors used the combination of baicalin and fluoxetine which is also an antidepressant medication in this model. Is it possible for the synergistic action of both compounds in term of neuropsychological or CNS effects may occur? How can the authors assure the safety of those amplification effects, if any? 2. The effect of treatment on BW. 2.1 The results of baicalin treated group (gr 6) and baicalin co-treatment with fluoxetine (gr 4) showed significant weight gain. However, there have been some reports for Baicalin to decrease appetite and reduce BW by modulating the

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orexigenic and anorexigenic signals, which is in disagreement with the results of this study. Please state this point in the discussion part. 2.2 It is difficult to understand the results in the line graph of BW in Fig 2, and some seems to be questionable. For example, at day 21 and 28, no significant symbols represented on gr 2 when compared with the control as well as no symbols showed on the other treatments when compared with gr 2. Is it better to represent the BW results in another format than in the line graph? 3. If fluoxetine can cause liver inflammation, would it be better to directly determine the inflammation cytokines in liver tissues? Serum levels of cytokines can represent the inflammation from other organs. 4. Overall results from gr 4 is not better than the results from gr 5 (fluoxetine+silymarin) which served as the positive control. It will make the manuscript more engaging if the authors discuss the benefit of using baicalin over silymarin in the discussion part. 5. Please clearly state the axis unit labels in the figures whether they are from serum or liver homogenates. If they are from the tissues, the results should be normalized with the liver proteins or weight and showed in the unit labels. 6. The histological sections of rat liver 6.1 Please replace the histological figures with the better-quality images. 6.2 It would be great if the authors add liver figures in all group of the treatment, including the positive controls. 7. Please take attention to the discussion part, no need to specify figures or tables or significant value at the end of the sentence. For example, Baicalin and silymarin administration did not produce significant change on IL-10 levels in groups 3, 4 and 5 and results were comparable to group 2 rats ($p > 0.005$).

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Position: Editorial Board
Academic degree: PharmD

Professional title: Academic Research, Director, Pharmacist, Professor, Senior Scientist

Reviewer's Country/Territory: Germany

Author's Country/Territory: India

Manuscript submission date: 2021-07-23

Reviewer chosen by: Jing-Jie Wang (Online Science Editor)

Reviewer accepted review: 2021-12-13 14:22

Reviewer performed review: 2021-12-13 14:31

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

No further comments; the authors have largely addressed my remarks