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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56930

Title: Antifungal activity and antidiarrheal activity via antimotility mechanisms of (-)-fenchone in experimental models

Reviewer's code: 04162941
Position: Peer Reviewer
Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Brazil

Author's Country/Territory: Brazil

Manuscript submission date: 2020-05-25

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-05-26 07:06

Reviewer performed review: 2020-06-20 17:09

Review time: 25 Days and 10 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

I think the study is interesting. It gathers info about a specific compound in the context of gastrointestinal phenomena using classic approaches. A couple of mechanisms of action were suggested, and this could be further explored. Some alterations are necessary, both in format and content. I would also highlight that there might be a lack of novelty, as indicated by other studies with compounds from the same group that found similar findings. However, it is a novel compound and we could argue this study reinforces reproducibility, which is missing in science these days. It needs some English review by a native speaker. My specific thoughts: I think the title suggests antidiarrhea effect happens through the antimicrobial activity, and this is misleading. It should also specify antifungal effect instead of antimicrobial in the title. I think the authors should state in the abstract the no effect on bacteria, as these are major causes of diarrhea (more than fungi). Background is good, with the major info necessary for introducing the study, but I suggest the authors to include epidemiologic data indicating the burden of diarrhea in adults as well. Diarrhea in children from developing countries is mainly related to infections (and great proportion from bacteria) and undernutrition, so a target population for this drug could be adults from high income countries. The authors could highlight this population in the first paragraph. I think the bacteria testing should have been focused on the types that are associated with intestinal infections in humans: diarrheogenic E. coli, Salmonella, Shigella, Campylobacter, Yersinia. Staphyloccocus and Pseudomonas are associated with different contexts. This is a limitation. In general the methods are well explained as well as the results. I think the discussion is where it needs more revision. Overall this section is too long and the authors are often just describing info from the literature without linking it to the study findings. This needs to be revised. Sometimes I felt like reading a textbook. Authors must be more objective and focused on

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the discussion of their findings. If possible, the authors could identify what is needed for having a more complete understanding of why different terpenes show different effects. Is there any pattern? Could the authors suggest any approach to tackle this, such as comparison studies of terpenes? In the second paragraph, authors speculate whether the compound would show antisecretory effects. I think this is misleading as throughout the text they conclude there´s no antisecretory effects. This sentence should be deleted. Info citing studies that relate to a specific finding should be all in a single paragraph if the studies follow the same general logic of results among them. The paragraphs that describe muscle contraction/relaxation mechanisms and muscarinic/adrenergic receptors should just be deleted, in my view (this is the textbook feeling). Specific points giving rationale to a given approach is fair in the context of presenting and discussing your findings, but not like you did. The paragraph prior to the one you suggest that the compound influences the peristaltic movements should be shortened and linked to the one you discuss the data. Also, the following paragraph does not contribute for discussion. It would be good to speculate with literature´s help why this compound does not show antisecretory activities. There is a too large paragraph about microbiota, causes and treatment of diarrhea in the discussion. It is repetitive with the introduction. The lack of synergism with antifungals and the lack of antisecretory mechanisms put the study drug in disadvantage in comparison with other compounds from the same class? The authors should discuss about the translational potential of the findings. Is there any evidence in animals (including in your study) or humans to speculate whether the concentrations found could be safe? Important: It is necessary for the authors to highlight limitations of the study, such as potential other in vivo models of diarrhea that could help to reinforce these data, as well as other simple molecular marker analyses to characterize mechanisms. The lack of data on post-exposure treatment should be cited as well - Why was this not attempted? Also, it needs to address potential cytoxicity of the

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compound. In the context of novelty, the authors should defend why they think their findings are important for the literature.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56930

Title: Antifungal activity and antidiarrheal activity via antimotility mechanisms of (-)-fenchone in experimental models

Reviewer's code: 02921008
Position: Editorial Board
Academic degree: DDS

Professional title: Academic Research, Doctor

Reviewer's Country/Territory: Iran

Author's Country/Territory: Brazil

Manuscript submission date: 2020-05-25

Reviewer chosen by: Jia-Ping Yan

Reviewer accepted review: 2020-06-22 13:28

Reviewer performed review: 2020-06-22 13:45

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] 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) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

English needs revission.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56930

Title: Antifungal activity and antidiarrheal activity via antimotility mechanisms of (-)-fenchone in experimental models

Reviewer's code: 03486791
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: Brazil

Manuscript submission date: 2020-05-25

Reviewer chosen by: Jia-Ping Yan

Reviewer accepted review: 2020-06-21 03:07

Reviewer performed review: 2020-06-24 01:09

Review time: 2 Days and 22 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] 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
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Thanks for inviting me to review this paper. This is an interesting article and the results are attractive.However, the mechanism should be further proved.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56930

Title: Antifungal activity and antidiarrheal activity via antimotility mechanisms of (-)-fenchone in experimental models

Reviewer's code: 00038340
Position: Peer Reviewer
Academic degree: AGAF, PhD
Professional title: Associate Professor
Reviewer's Country/Territory: United States
Author's Country/Territory: Brazil

Manuscript submission date: 2020-05-25
Reviewer chosen by: Jia-Ping Yan
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Reviewer performed review: 2020-06-25 16:41
Review time: 3 Days and 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] 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) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

1. "In conclusion, the results of the present investigation indicate that (-)-fenchone has antidiarrheal activity, which is related to an anti-motility effect, through the participation of muscarinic, adrenergic, nitrergic pathways and KATP channels, not being related to antisecretory or pro-absorptive activities". To be able to confirm this statement very specific blockers or agonists should be used. The conclusion should be amended to say :(-)-fenchone has antidiarrheal activity, which is related to an anti-motility effect. This anti-motility effect can be blocked by α2 and β adrenergic receptor antagonists. It can also be blocked by L-Name indicating a possible role of NO. The same applies to glybenclamide. 2. In the section: "Effect of oral administration of (-)-fenchone after treatment with pilocarpine and yohimbine and on intestinal transit of mice". It is not clear if the difference between columns 1 and 4 (Pilocarpine and Pilocarpine+fenchone) is significant. If the difference is not significant it is not clear why the authors conclude that fenchone is acting via muscarinic receptors. The effect of pilocarpine is long lasting, in that group of mice were the animals exposed to pilocarpine once or twice? The description of each experiment should be more detailed. Were the groups treated as paired? 3. In the Introduction, the authors state that "Among the main classes of drugs used are antisecretory and motility suppressing agents, probiotics, enkephalinase inhibitors, bismuth compounds, α2-adrenergic receptor agonists, and muscarinic agonist". Muscarinic agonists usually enhance motility and secretion. If the authors think that a subtype of inhibitory muscarinic agonist is involved, they should specify it in this statement. Also when describing the microbiota they mention that "changes in microorganisms can cause motility disorders". This is not well established yet and the reference is not relevant. 4. The description of the methodology for the assessment of the anti-bacterial effect of Fenchone is lacking. The bacterial count or

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method of measurement should be described in detail. Minor 1. In the paragraph "Evaluation of the participation of muscarinic, adrenergic, nitrergic pathway and ATP-dependent potassium channels (KATP) in (-) fenchone antimotility mechanisms in the intestinal transit model" it is mentioned that after 30 min of "blockade" vehicle or fenchone is administered. It is not clear what "blockade" the authors are describing. The details of the steps of the experiments for each agent are lacking. 2. When describing the Results please describe the properties of each agent used (e.g. yohimbine is an α2 receptor antagonist) 3. Figure legend: n=8, does this number indicate the number of animals in each group? specify and indicate the numbers for each group in all the figures 4. Activated charcoal (10%) in gum arabic 5%. The description is lacking for the remaining compounds. 5. Please spell out abbreviations MIC, MCB and MFC in the text 6. CaV-L should be written Cav(L) 7. Referring to "test substance" is confusing because many compounds were used. Please indicate the name of the substance. 8. "Then, 100 µL of the substance was dispensed into the wells of the first line of the plate and by serial dilution at a ratio of two concentrations of 1024 µg/mL to 16 µg/mL were obtained. Finally, 10 µL of the suspensions of strains were added to the wells." The substance should be defined as well as the "suspension of strains". Please clarify the methods for this experiment 9. The bibliography should be reduced in number. 10. Figures 1 and 2, the columns in the graph should be textured

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56930

Title: Antifungal activity and antidiarrheal activity via antimotility mechanisms of (-)-fenchone in experimental models

Reviewer's code: 05088164
Position: Associate Editor
Academic degree: MD, PhD
Professional title: Associate Professor
Reviewer's Country/Territory: Romania
Author's Country/Territory: Brazil

Manuscript submission date: 2020-05-25
Reviewer chosen by: Jia-Ping Yan
Reviewer accepted review: 2020-06-20 12:39
Reviewer performed review: 2020-06-27 15:54
Review time: 7 Days and 3 Hours

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) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

The paper is presenting the results of a study on the anti-diarrheal activity of a bi-cyclic monoterpene compound from essential oils. before being published the paper needs some improvements. The title should include only the demonstrated effects, not antimicrobial, as the effect was demonstrated only for fungi. The background (introduction) include most important aspects of diarrhea (etiology, treatment, limitation of current methods and need for searching new alternatives). Many recent study tries to find if different species of plant compound could be used as treatment of gastrointestinal disorders. Material and methods are described correctly, the assays used give the possibility to evaluate the anti-diarrheal activity (evacuation index, percentage of liquid stools and diarrhea inhibition), gastric emptying, intestinal transit using activated charcoal (better use this wore all the times, not activated carbon), anti-motility action, anti-bacterial and anti-fungal activity. The results are presented in a convincing manner. I would change the figures 1,2,3 limiting the y-scale to 100%, as in figure 4 and 5. As the conclusions said, this compound has no antimicrobial activity and this should be emphasized, as more diarrhea cases are due to microbial agents than fungal agents. There is a need of check for English language for fine changes. Also some sentences are too long (even one paragraph long - 8 lines - ex. Muscarinic receptor agonists...)

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 56930

Title: Antifungal activity and antidiarrheal activity via antimotility mechanisms of (-)-fenchone in experimental models

Reviewer's code: 05088164
Position: Associate Editor
Academic degree: MD, PhD
Professional title: Associate Professor
Reviewer's Country/Territory: Romania
Author's Country/Territory: Brazil
Manuscript submission date: 2020-05-25
Reviewer chosen by: Jia-Ping Yan
Reviewer accepted review: 2020-08-13 17:08
Reviewer performed review: 2020-08-15 10:04
Review time: 1 Day and 16 Hours

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) [Y] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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Based on my comments and also the comments of other reviewers, the authors improved the manuscript. Still there are some minor changes that should be done and checked, but not some of substance or that could change the main aspects of the paper. - abstract: Aim: To investigate... ; Conclusion: could be without" hence, it is possible to infer that" ... my opinion is to write clear what was demonstrated. - Material and methods: on the paragraph about gastric emptying, please rephrase the sentence about " one zero-time control... "; also do not use abs if not explained before using in the formula. - Results: in the paragraph about the intestinal transit: please correct - results of this study showed that..., or the study proved that... - Association assay, please check the first phrase... both above and below? Based on these, I consider that the paper could be published after these minor changes would be done.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Manuscript NO: 56930

Title: Antifungal activity and antidiarrheal activity via antimotility mechanisms of (-)-fenchone in experimental models

Reviewer's code: 00038340
Position: Peer Reviewer
Academic degree: AGAF, PhD
Professional title: Associate Professor
Reviewer's Country/Territory: United States
Author's Country/Territory: Brazil

Manuscript submission date: 2020-05-25
Reviewer chosen by: Jia-Ping Yan
Reviewer accepted review: 2020-08-17 14:51
Reviewer performed review: 2020-08-17 15:42
Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] 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 statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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No further comments