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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 78405

Title: Safety and efficacy of purified clinoptilolite-tuff treatment in patients with irritable bowel syndrome with diarrhea: Randomized controlled trial

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05864829
Position: Peer Reviewer
Academic degree: BMed, MM, PhD
Professional title: Academic Editor, Statistician
Reviewer's Country/Territory: China
Author's Country/Territory: Austria

Manuscript submission date: 2022-06-27

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-07-04 05:20

Reviewer performed review: 2022-07-04 06:12

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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

SPECIFIC COMMENTS TO AUTHORS

The authors conducted a pilot randomized controlled trial to assess the safety and efficacy of purified clinoptilolite tuff treatment in IBS-D patients. Overall, the manuscript is well writen and organized with abundant data. The current report is consistent with the previously published study protocol which make it reliable. Before it could be finally published I have several comments for the authors' reference. Major concern 1. Regarding the primary outcome, after 12 weeks of treatment the proportion of responders according to the SGA of Relief was 21% (n=3) in the G-PUR® group and 25% (n=4) in the placebo group (p=1.0; Table 2). It is obviously that G-PUR is not superiority to the placebo pill at the end of treatment from whether clinically or statistically aspect. Herein, I cannot agree with the authors who drew the current conclusion that "In this randomized, placebo-controlled study, the purified clinoptilolite tuff product G-PUR® demonstrated safety and clinical benefit in patients with IBS-D, representing a promising novel treatment option for these patients". Although you set more than 10 secondary outcomes and some of them indeed showed a positive results, it cannot change the conclusion that G-PUR is not better than placebo. Authors, please draw the conclusion again. Minor concenrs 1. For most RCT with moderate or more sample size, there is no necessary to provide p-value in demographic characteristics. However, as this is a pilot study with only 30 participants, I noticed that some baseline variable between groups may not comparable (such as duration of IBS, metabolism disorders, gastrointerstinal disorders, etc.). Please add p-value for table 1. 2. Current Table 2 is not acceptable. Please add more statistical information including RD (risk difference) and its 95%CI (confidence interval) for the response analysis of primary outcome and secondary

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outcomes that have similar data pattern. For the continuous outcomes (such as IBS-SSS, SF-12, PSQ) please provide MD (mean difference) and its 95%CI. 3. How you handle with the missing data, I did not locate this in the current manuscript. Five patients in total withdrew from the study before the end of treatment. Considering the small sample size, data from each person is vital for results. 4. Why you chose IDO as an exploratory end?

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Peer-review model: Single blind

Reviewer's code: 05452471
Position: Editorial Board
Academic degree: PhD

Professional title: Associate Professor, Senior Scientist

Reviewer's Country/Territory: Russia

Author's Country/Territory: Austria

Manuscript submission date: 2022-06-27

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-07-25 04:36

Reviewer performed review: 2022-07-29 07:34

Review time: 4 Days and 2 Hours

Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] 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	[ ] Yes [Y] No

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

SPECIFIC COMMENTS TO AUTHORS

The article under review is a randomized controlled trial analyzing the safety and efficacy of purified clinoptilolite tuff treatment in patients with irritable bowel syndrome and diarrhea. The authors present the results of a completed study conducted in accordance with the norms and requirements of the law. All necessary documents have been presented by the authors in full. The studies were conducted on a small sample of 30 patients. A formal calculation of the sample size was not carried out due to the design of the pilot study. I have the following remarks on the operation and presentation of data. 1. Notes on files posted on the site: Forms, 78405-Institutional Review Board Approval Form or Document and 78405-Non-Native Speakers of English Editing Certificate contain the same information. It is desirable for the authors to clarify the correctness of the information in the attached documents. 2. Introduction: it is necessary to clarify the correctness of quoting some reference, for example. 15. 3. Materials and methods; in the section The following variables were assessed as exploratory endpoints before and after 12 weeks of treatment: you must add references to sources that explain how these variables were studied. 4. Figure 1. It is unclear why, if the early withdrawal of patients from the study, why the final analysis was carried out for the primary number of patients. 5. Table 1. Clarify data on the duration of IBS since symptom onset (years) presented in the last column. 6. Figure 2. Numbers in the x-axis signature (exp. n=24) are unclear. Are there a numeric of patients? Why isn't it the same? If n=24, does that mean 6 people dropped out of the study? The text of the Materials and Methods section does not contain this information. 7. Figure 3. This figure does not represent real data on diversity. The real increase in diversity is determined at the level of lower taxa -

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genera or phylotypes. Taking into account the obtained difference between groups at different times of sampling, shown in Figure 5, it is necessary to change Figure 3. It is necessary to present diversity at the level of genera or phylotypes, including the top 25 or 50 most represented phylotypes in the analysis. This will allow you to more clearly show the differences between patients. 8. Figure 4. It is desirable to add a confidence score. It may be appropriate to provide other indices, such as Chao or the observed units (ASV or OTU). 9. References: It is necessary to carefully review the links provided by the list for their correctness, for example, pages are not indicated in ref. 3, 12, 18, 48, 49.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03887097

Position: Editorial Board

Academic degree: MBBS, MSc

Professional title: Doctor

Reviewer's Country/Territory: Singapore

Author's Country/Territory: Austria

Manuscript submission date: 2022-06-27

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-07-28 14:55

Reviewer performed review: 2022-08-09 03:35

Review time: 11 Days and 12 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] 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

1. The pathophysiology of IBS is poorly understood and is currently thought to represent a complex interplay among the gut microbiota, mucosal immune system, impaired mucosal barrier function, visceral hypersensitivity, gut motility, and alterations in the gut-brain axis. In addition to ref [4] and [5], suggest authors cite a relevant and recent review on the topic (citation: pubmed.ncbi.nlm.nih.gov/30288077). 2. "Glock Health, Science and Research GmbH acted as sponsor of this multicenter study" - more details are required to ascertain the roles and responsibilities of the sponsor, whether the sponsor was directly or indirectly involved in the design and conduct of clinical trial. 3. "44 patients were screened" - try not to start a sentence with a number. 4. The information provided in Table 1 is rather vague and hard to interpret, what exactly are "Allergies/Hypersensitivity", "Metabolism and nutrition disorders", "Psychiatric disorders" and "Gastrointestinal disorders"? These are extremely vague and broad headings, suggest zooming in to more granular and clinically meaningful conditions, e.g. lactose intolerance, which is exceedingly common in IBS-D patients. 5. How was study attrition and dropout handled? This was not apparent to readers. 6. Please change "microbial architecture" to "gut microbiome". 7. Purified Clinoptilolite-Tuff has been shown to be an effective sorbent for gluten derived from food sources (citation: pubmed.ncbi.nlm.nih.gov/35563533). This could be a reason for its supposed benefit. 8. ".. present trail" - misspelled. It should be 'trial'. 9. "In a recent meta-analysis of established traditional therapies in IBS, tricyclic antidepressants are recommended for treatment of abdominal pain, but careful dosing is warranted based on the side-effect profile46,47" - authors should also mention that other supplements such as Vitamin D

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has only showed very modest effects (citation: pubmed.ncbi.nlm.nih.gov/35396764). 10. "... the clinical benefit of PCT could be demonstrated in various clinical meaningful endpoints" and "In this randomized, placebo-controlled study, the purified clinoptilolite tuff product G-PUR® demonstrated safety and clinical benefit in patients with IBS-D, representing a promising novel treatment option for these patients" - given the limitations of the present trial and the fact that G-PUR did not actually perform statistically (or clinically) superior to placebo, I would suggest authors temper the study conclusions. 11. Table 2 should include 95% confidence intervals and estimates.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 78405

Title: Safety and efficacy of purified clinoptilolite-tuff treatment in patients with irritable bowel syndrome with diarrhea: Randomized controlled trial

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03887097

Position: Editorial Board

Academic degree: MBBS, MSc

Professional title: Doctor

Reviewer's Country/Territory: Singapore

Author's Country/Territory: Austria

Manuscript submission date: 2022-06-27

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2022-09-09 04:12

Reviewer performed review: 2022-09-09 05:18

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

Thank you for the revisions.