

RE: No.: 88518

December 27, 2023,

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Dear Prof. Hariyanto

Thank you for your letter dated December 7, 2023, regarding our manuscript entitled “Rikkunshito increases peripheral incretin hormone levels in humans and rats”. submitted to *the World Journal of Methodology* (No. 81518). We were pleased that both the Editorial Board and the reviewer found our data interesting and we appreciate your helpful comments. We have addressed the concerns of the reviewer in the new version of our manuscript. Enclosed please find the revised manuscript and figures. The following is a point-by-point response to the suggestions and queries of the reviewer.

Thank you for the opportunity to incorporate your useful suggestions and those of the reviewers into the revision of this manuscript. We hope you now find this study suitable for publication in *the World Journal of Methodology*.

Sincerely

Hiroshi Kono

Science editor:

We were pleased that the editor found our manuscript merit and appreciate your useful comments.

General comments:

I. Comments for the main manuscript contents

(1) The editor pointed out that the rationale of the current study is rough and is not clearly provided in the Introduction section.

A) The reviewer asked what the unmet medical need of PPPD patients is. The editor suggested that the authors need to explain that they need rikkunshito ingestion. In patients undergoing pylorus-preserving pancreaticoduodenectomy (PpPD), postoperative oral food intake does not increase easily due to delayed gastric emptying (DGE). Therefore, it needs to dissolve DGE after PpPD. Alternatively, it was previously reported that rikkunshito (TJ-43) increases active ghrelin levels and oral food intake in an animal model. Therefore, first of all, this study was designed to address this issue. In addition, another unmet medical issue after PpPD is blood sugar control, since pancreatic surgery reduces the islet cells, suggesting that insulin secretion is reduced. Furthermore, one risk factor of pancreatic cancer is diabetes

mellitus. Therefore, in this study, the effects of TJ-43 on incretin hormones were also investigated (line 16 and page 6; line 15 and page 5).

B) The reviewer asked what the unsolved problem of TJ-43 in the past research was and suggested that the authors need to provide the rationale in the Introduction section. We agreed with the reviewer's comments. Indeed, it has been reported that TJ-43 increases active ghrelin levels; however, other effects have not been investigated yet. Therefore, measurement both of active ghrelin and incretin hormones were investigated this study is conducted (line 15 and page 5).

(2) The reviewer asked whether TJ-43 is a standard treatment for post-PPPD patients. The reviewer suggested that if not, this study should be a prospective study rather than a retrospective study. This is a very important issue. Indeed, in Japan, TJ-43 is treated frequently in a lot of patients after PpPD to improve the DGE. However, to show clear evidence of the effects of TJ-43 after pancreatic surgery, it could need to conduct a prospective study in further investigations (line 16 and page 6; line 15 and page 5).

(3) The reviewer asked when the subjects performed insulin-secreting tests and serum glucose tests for 3 weeks after TJ-43 treatment. Since, in Figure 2, serum incretin and GIP content exhibited a time-dependent increase in the TJ-43(+) group, which means

the time point of the insulin test and glucose test is critical. This is a thoughtful question. Indeed, Japanese herbal medicines are usually not effective immediately after administration and require a period of 2 to 3 weeks of treatment. Therefore, the glucose and insulin secretion tests were performed 3 weeks after treatment of TJ-43 in this study. In addition, for blood glucose and insulin measurements, animals fasted for 12 hours, and the OGTT and insulin secretin test started at 9 a.m. (line 17 and page 8).

- (4) The captions and legends of the figures are too rough to read, particularly, the figure caption, which explained nothing. We apologize for these problems and have revised them in the revised manuscript (please see the figures and legends in the revised manuscript). **OK done**

II. Table(s) and Figure(s):

The editor suggested that all 6 figures and 1 table should be improved as detailed suggestions for each are listed in the specific comments section. Accordingly, we have revised figures and a table in the revised manuscript (please see the revised figures and a table in the revised manuscript). **OK done**

III. References:

The editor pointed out that the references cited in the manuscript were not updated.

Accordingly, we have updated the references in the revised manuscript (please see the references in the revised manuscript.). **OK done**

IV. The English-language grammatical presentation:

The editor pointed out that there are many errors in grammar and format, throughout the entire manuscript. Therefore, the editor suggested that the English-language grammatical presentation needs to be improved to a certain extent. We fully apologize for these problems and have re-edited the revised manuscript by a native English speaker before re-submission.

Specific comments:

- (1) The editor requested to provide the figures cited in the original manuscript in the form of a PowerPoint file. We agreed with the editor's comments and have provided all figures formatted in the PowerPoint file **OK done**
- (2) The reviewer suggested that all figure legends are incorrectly formatted and require a general title and explanation for each figure. Accordingly, we have revised all figures

and figure legends in the revised manuscript (please see the revised figures in the revised manuscript). **OK done**

(3) The reviewer requested that the authors do not use any *, #, †, §, ‡, ¥, @....in the manuscript. Accordingly, we have revised all figures as the reviewer requested in the revised manuscript. **OK done**

(4) The editor suggested that the authors use superscript numbers for statistical significance. Accordingly, we have revised all figures as editor's requests in the revised manuscript. **OK done**

(5) The editor suggested that the authors add the Core tip section. Accordingly, we have added the Cor tip section in the revised manuscript (please see the Cor tip section in the revised manuscript).

(6) The editor pointed out that the "Article Highlights" section is missing. Accordingly, we have added the "Article Highlights" section at the end of the main text in the revised manuscript please see the Article Highlight in the revised manuscript. **OK done**

(7) The editor asked to provide the Informed consent statement for the World Journal of Methodology. Accordingly, we have provided it for revision. **OK done**

Company editor-in-chief:

We were pleased that the reviewer recommended the manuscript transfer to the World Journal of Methodology for publication.

We have supplemented and improved the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript for revision.

Reviewer #1:

We were pleased that the reviewer found our manuscript merit and appreciate your useful comments.

Major comments:

1. The reviewer pointed out the rationale of the current study is rough and is not clearly provided in the Introduction section. Furthermore, the reviewer asked what the unmet medical need of PpPD patients is, and the authors should explain the reason that they need TJ-43 ingestion. In patients undergoing pylorus-preserving pancreaticoduodenectomy (PpPD), postoperative oral food intake does not increase easily due to delayed gastric emptying (DGE). Since TJ-43 increases active ghrelin levels and oral food intake, TJ-43 often is administered in patients undergoing PpPD. In addition to food intake, control of blood glucose levels is also an important issue to dissolve in patients undergoing PpPD. To dissolve this issue, we investigated the effects of TJ-43 on incretin hormones which control blood sugar in this study (line 16 and page 6; line 15 and page 5) [please also see the answer for the science editor's comments: General concerns (1); A)].
2. The reviewer asked what the unsolved problem of TJ-43 in the past research was. The reviewer suggested that the authors need to provide this issue in the Introduction. Previously, it was reported that TJ-43 increases active ghrelin levels and oral food intake in an animal model and human study. However, it is not clarified the effects of TJ-43 on other gastrointestinal hormones (line 16 and page 6; line 15 and page 5) [please also see the answer for the science editor' comment: General concerns (1); B)].

3. The reviewer asked if TJ-43 is a standard treatment for post-PpPD patients. If not, the editor suggested that this trial should be a prospective trial rather than a retrospective study. Since it was reported that TJ-43 increases active ghrelin levels and oral food intake, TJ-43 often is administered in patients undergoing gastrointestinal surgery, including PpPD. In addition to food intake, control of blood glucose levels is also an important issue to dissolve in patients undergoing PpPD (line 16 and page 6; line 15 and page 5) [please also see the answer for the science editor' comment: General concerns (2)].
4. In Figure 2, serum incretin levels exhibited a time-dependent increase in the TJ-43 (+) group, which means the time point of the insulin test and glucose test is critical. Therefore, the reviewer asked when the subjects performed insulin-secreting and serum glucose tests. This is a thoughtful question. Indeed, animals were treated with TJ-43 for 3 weeks before these tests. They fasted for 12 hours and then, the OGTT and insulin secretin tests started at 9 a.m. (line 17 and page 8) [please also see the answer for the science editor' comment: General concerns (3)].
5. The captions and legends of the figures are too rough to read particularly, the figure caption, which explained nothing and suggested we rewrite them. We apologize for this issue and have revised them in the revised manuscript (please see the caption and legends of the figures [please also see the answer for the science editor' comment: General concerns (4)]. **OK done.**