

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47784

Title: Lingguizhugan decoction attenuates diet-induced obesity and hepatosteatosis via gut microbiota

Reviewer's code: 03699916

Reviewer's country: Denmark

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-03-27 07:25

Reviewer performed review: 2019-04-02 06:39

Review time: 5 Days and 23 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

General comment: Present study authors investigate Lingguizhugan decoction (LZD) combined with caloric restriction (CR) treatment to improve metabolic parameters by modulating gut microbiota. This study demonstrated that CR together with LZD lowers

body weight and blood glucose levels in mice with normal diet. Fecal microbiota transplantation (FMT) attenuates diet-induced obesity and hepatic steatosis, promotes FA oxidation and suppresses hepatic lipid biosynthesis, and alters high fat diet (HFD)-induced changes in gut microbiota. The present study provides a new aspect in understanding the pharmacological effects of herbal plants in modulating gut microbiota, therefore it is important for publish such important research data in WJG. It is also relevant for the gastroenterologist, patients with gastrointestinal diseases and readership in WJG. This is well-designed study with well English writing. The figures are also well to present the result the design and results of the study. Minor comments: 1, The result section in the abstract is needed to provide the results in little bit detail, for example the P values should be shown to see if the effect is significant. 2, Some parts in the Result section should belong to Introduction or Discussion, it is suggested to move it to the Introduction or discussion. For example: 1) Previous studies have reported that CR in combination with LZD can improve metabolic parameters in MetS patients [7], yet the exact mechanism is not clear. Recent findings have revealed an import role of gut microbiota in modulating overall metabolism, and onset of metabolic diseases such as obesity, diabetes and hyperlipidemia [10]. We thus wondered whether CR in combination with LZD exerted its effects by modulating gut microbiota. To explore this, we first tested if CR combined with LZD affected energy and lipid metabolism in mice without any disturbance in metabolism, that is, mice fed with ND. (Belong to Introduction) 2) We speculated whether FMT from CR + LZD-treated mice would provide beneficial effects against diet-induced obesity in C57BL/6 mice. We collected feces from ND-fed mice receiving control treatment or CR +LZD treatment, and transplanted the gut microbiota by oral gavage of fecal homogenates. (Belong to Introduction) 3) SREBP1-c is a membrane-bound transcription factor that plays an important role in regulating lipogenic gene expression [20]. PPAR γ plays an important

role in HFD-induced upregulation of lipogenic gene expression and hepatic lipid biosynthesis [21, 22]. ACC catalyzes acetyl-CoA to form malonyl-CoA, an essential substrate for synthesizing FA and an inhibitor of FA oxidation [23]. Thus, ACC levels are crucial in determining lipid metabolism and overall energy metabolism [24]. FASN is a large multi-peptide enzyme whose major function is synthesizing palmitate, a long-chain saturated FA [25]. SCD1 is a key enzyme in catalyzing the synthesis of unsaturated FA oleic acid. Thus, increased expression of these lipogenic genes explains the increases in lipid deposition in the liver and adipose tissues. (Belong to Discussion) 3, The repetition should be avoided. For example, the description of "We previously reported that LZD, a traditional Chinese herbal medicine, in combination with CR, lowers plasma TC and TG levels in patients with MetS [7]. Similarly, LZD in combination with CR also attenuates HFD-induced obesity and hyperlipidemia in rats [28]. Yet, the underlying mechanism is not clear." repeats three times in Introduction, Result and Discussion. Please make cross-check to see if there are repetition of description throughout the manuscript. The repetition should be avoided in the scientific paper. 4, Normally, the references should not be cited in the Result section. There are several places in the result section have cited references, please check.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

BPG Search:



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
<https://www.wjgnet.com>

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47784

Title: Lingguizhugan decoction attenuates diet-induced obesity and hepatosteatosis via gut microbiota

Reviewer's code: 03811054

Reviewer's country: Egypt

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-09 12:33

Reviewer performed review: 2019-05-09 16:16

Review time: 3 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Minor revision 1. What are the LD50 of LZD and CR? 2. Authors collected blood samples from tail vain of mice at 0, 15, 30, 60 and 120 min after glucose injection... What is the amount of blood that was taken each time in the experiment? 3. H&E staining and



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Oil Red O staining ... Is there a reference to this method?

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

BPG Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47784

Title: Lingguizhugan decoction attenuates diet-induced obesity and hepatosteatosis via gut microbiota

Reviewer's code: 00597793

Reviewer's country: United States

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-12 12:00

Reviewer performed review: 2019-05-12 14:56

Review time: 2 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input checked="" type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input checked="" type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This is a well done and exhaustive study showing that a Chinese traditional medicine is of help for treating / preventing metabolic disorders. I have one question: Why did you not examine the effect of LZD on the flora of the rodents and see if it directly

changed the GI microbiome and metabolic / weight factors? You could then do all of the studies reported here to confirm your results and to study the mechanism of effect? Small issues: METHODS - what is MQ? OCT? METHODS, Immunoblotting - explain to the reader why you chose these genes? You do so later in the DISCUSSION section. I suggest you move the section from the DISCUSSION to here. RESULTS - remove the first few lines of the RESULTS. You have said it already. Begin with "We first tested..." RESULTS - chart 2 E - the 2 bars appear to me to be equal, not different? RESULTS - Figure 3. Put a color scheme above as you do in Fig 2 DISCUSSION - please discuss weight loss with the LZD.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

BPG Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 47784

Title: Lingguizhugan decoction attenuates diet-induced obesity and hepatosteatosis via gut microbiota

Reviewer's code: 00053493

Reviewer's country: Mexico

Science editor: Jia-Ping Yan

Reviewer accepted review: 2019-05-09 12:35

Reviewer performed review: 2019-05-13 15:59

Review time: 4 Days and 3 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Title: Lingguizhugan decoction attenuates diet-induced obesity and hepatosteatosis via gut microbiota. Authors aimed to investigate the role of gut microbiota in metabolic parameters and the effect of probiotics and Lingguizhugan decoction on these effects.



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

They utilized water-soluble components out of the raw materials and dried as Lingguizhugan decoction (LZD) extracts and administered the extract to mice for 16 weeks. They found that caloric restriction (CR) together with LZD lower body weight and blood glucose levels in mice with normal diet. In addition, fecal microbiota transplantation (FMT) attenuated diet-induced obesity and hepatic steatosis and promoted FA oxidation and suppressed hepatic lipid biosynthesis. FMT alters high fat diet-induced changes in gut microbiota. In conclusion, the results point toward that CR + LZD improve metabolic parameters via modulating gut microbiota. Major comments:

- 1.- What is the composition of LZD? What are the properties of these compounds? Are they antioxidants, antiinflammatory? Why not utilizing a pure compound instead of an extract?
- 2.- Did you characterized the composition of FMT? Please insert a table with the probiotics of FMT. Why not utilizing a well-characterized preparation of probiotics?
- 3.- In your model. Did you find inflammation or fibrosis?
- 4.- Explain the molecular mechanism by which FMT decreased lipogenic factors in livers.
- 5.- Does a leaky gut was involved in the pathogenesis? was it a mechanism?
- 6.- Did you make any attempt to measure Inflammation (TRLs, NF-kappaB, TNF-alpha, Il-1)?
- 7.- The way in which results are presented is confusing (at least to me) because groups are missing in histograms and histologies. I cannot see the control (NORMAL) group, for instance, in histologies, a slice showing the normal parenchyma or normal biochemical values to compare with are missing. Other controls are needed, for example FMT control, LZD control, vehicle control, normal diet control, etc.
- 8.- Medicinal plants or LZD may act as prebiotics?

Minor comments: Despite that the manuscript was edited, it contains some typos, please see the introduction section “has recently been show “ Please use abbreviations through the manuscript after defining once.

INITIAL REVIEW OF THE MANUSCRIPT



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
<https://www.wjgnet.com>

Google Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

BPG Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No