

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 48142

**Title:** The Regulatory effect of the Chinese herbal medicine thorowax root, scutellaria root and white peony root on non-alcoholic fatty liver disease

**Reviewer's code:** 03388095

**Reviewer's country:** Reviewer\_Country

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-12 13:19

**Reviewer performed review:** 2019-04-16 12:31

**Review time:** 3 Days and 23 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 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

• The study used Pioglitazone hydrochloride (PH) as the “positive control” based on previous study. However, it never explicitly mention why it is necessary to have such control group, particularly to readers not very familiar with it. In my view, the PH group

serves no particular purpose. Instead, it should include a control group with rats on standard diet and CHM treatment to see any direct impact of CHM on rats. For example, one may argue that the inhibitory effect of CHM on NAFLD could be due to CHM effect on rat's food intake or other step rather than on lipid metabolism. • Were different groups samples treated or collected blindly? It was not mentioned in the methods. • For table 2, it's better to list both body weight and liver weight in addition to the liver coefficient. • For Oil Red O staining, the authors should also try to quantitate the amount of hepatic steatosis in different groups (please see Exp Biol Med, 2010, 235(11): 1282-1286), otherwise the conclusion of "markedly reduced lipid .... In PH and CHM" (result section under Oil Red O staining) become questionable (based on eyeballing?). • One of the important conclusion of this study is to elucidate the effect of CHM on NAFLD is through the so-called "intestine-liver axis", however, in the end of manuscript discussion section, it also said that "our results indicated that the effect of CHM on the regulation of the intestinal axis was not very effective". Please explain or revise. • One of critics with Chinese herb medication is a crude extract which the exact gradients may vary from different labs or lots number. Although traditional Chinese medicine has been proven very effective in some cases, efforts also should be made to isolate and purify the effective component. • The manuscript writing still has room to polish and make it easy to read.

## INITIAL REVIEW OF THE MANUSCRIPT

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- [ ] The same title
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## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 48142

**Title:** The Regulatory effect of the Chinese herbal medicine thorowax root, scutellaria root and white peony root on non-alcoholic fatty liver disease

**Reviewer's code:** 03647461

**Reviewer's country:** United States

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-12 13:13

**Reviewer performed review:** 2019-04-17 20:30

**Review time:** 5 Days and 7 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 type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input checked="" 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 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

The title, abstract and methodology sections need to be more refined and streamlined. The use of a comma in a title is unusual and must be discouraged. The authors could probably use one common phylogenetic or taxonomic name for all the three herbal roots

in the title description to avoid using the comma. A better title would be “The regulatory effect of Chinese herbal roots on Non-alcoholic Fatty Liver Disease”. The paper is a very interesting one for understanding the therapeutic effect of certain Chinese herbal roots for “soothing” NAFLD symptoms. However, I think there is a leap of faith when you conclude that the intestinal mucosa barrier is also regulated by the Chinese herbal medicine thorowax root, scutellaria root, and white peony root. Your experiment may have shown some regulation of lipid metabolism and some liver function. However, the herbs did not demonstrate their ability to regulate liver axis or show regulatory effect on the intestinal mucosal barrier. The use of the word “regulation” seems a little far-fetched. Your experimental protocols were straightforward and showed results that either upregulated inflammatory factors or down-regulated them, but the mechanistic studies of the regulations that the authors purport to have demonstrated is a little far-fetched. It would have also been appropriate to establish a cellular model of NAFLD by culturing HepG2 or other similar cells in a medium that contained a long chain fat emulsion. These cells could have been treated with serum-containing CHM group from the sacrificed rats. Besides the cytokines and other liver markers, after treatment, the levels of adenylate-activated protein kinase (AMPK)  $\alpha$  (AMPK $\alpha$ ), p-AMPK $\alpha$ , acetyl coenzyme A carboxylase (ACC)  $\alpha$  (ACC $\alpha$ ), pACC $\alpha$ , PPAR $\gamma$ , and SREBP-2 could have also been measured. The AMPK agonist could have served as a positive control compound. The effect of CHM or AICAR (especially the number of lipid droplets) could have been observed in the serum levels of TG, TC, LDL-C, AST, ALT, and insulin in NAFLD rats, and their serum HDL-C levels, their tissues and HepG2 cells. A corollary assessment of CHM, PH and AICAR effects on the levels of p-AMPK $\alpha$  and PPAR $\gamma$  in the NAFLD liver tissues and HepG2 cells could have the work more convincing and relatable. Although, this work was not about the contribution of the microbiome to NAFLD symptoms, the “liver axis” in liver disease is also influenced by the microbiota, which



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may have been affected by the Chinese herbs.

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##### *BPG Search:*

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- ☐ No

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 48142

**Title:** The Regulatory effect of the Chinese herbal medicine thorowax root, scutellaria root and white peony root on non-alcoholic fatty liver disease

**Reviewer's code:** 02860895

**Reviewer's country:** Japan

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-14 01:52

**Reviewer performed review:** 2019-04-22 14:35

**Review time:** 8 Days and 12 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 checked="" type="checkbox"/> Grade B: Very good	<input checked="" 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 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

This is an article that revealed a part of mechanisms of the efficacy of Chinese herbal medicine (CHM) on NAFLD. The authors tried to perform a theoretical approach through gut-liver axis concept, that may be a primary pathway of NAFLD development.



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While potential importance of this paper, I have a couple of concerns as follows; In both CHM and pioglitazine (PH) groups, the disease severity of NAFLD was successfully attenuated. Because effects of CHM on the intestinal factors were insufficient, the authors emphasized that the beneficial effects of CHM on NAFLD were results of direct action to liver (liver axis). However, since effects of CHM were overall weaker than those of PH, the negative results in intestine might be false-negative caused by a small sample size. The authors should re-examine a larger number of experimental animals, or should change their interpretation. As an issue of terminology, "axis" means a route connecting more than two factors. Hence, the term "liver axis" is nonsense because a single organ has no such connecting route "axis". The authors should revise the manuscript as considering sufficiently these points.

#### **INITIAL REVIEW OF THE MANUSCRIPT**

##### ***Google Search:***

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- ☐ No



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 48142

**Title:** The Regulatory effect of the Chinese herbal medicine thorowax root, scutellaria root and white peony root on non-alcoholic fatty liver disease

**Reviewer's code:** 01808881

**Reviewer's country:** United States

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-04-13 00:27

**Reviewer performed review:** 2019-04-22 19:55

**Review time:** 9 Days and 19 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 checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
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		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
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			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

The goal of this study was to determine the regulatory effect of the Chinese herbal medicine on NAFLD. The authors showed that the extract was able to treat many indices of fatty liver and also preserved the liver-gut axis. There were many concerns noted: 1)

The model for high fat high sucrose only generates fatty liver. Could the authors have gone longer to at least get some inflammation (NASH) in their model? 2) The authors should inform the calories percent of the fat and carbohydrates in the diet. 3) The authors have used abbreviations in the abstract without defining them the first time they were used. Please correct this deficiency in the abstract and the manuscript. 4) Reword the last sentence in the abstract for clarity. 5) In the methods section, were all group were gavaged daily with distilled water (control and the high-fat high sucrose group), PI or CHM, respectively for the last 4 weeks of the study. As written, it is not clear. 6) Please conduct liver triglyceride biochemical analysis. 7) Were TNF, TGF, NFkB, TLR4 done on the serum as denoted in the methods section or were these determinations done on liver tissues as shown in the results section? Which is correct? Further, if indeed these were done on liver tissues, are the ELISA kits purchased form NeoBiosciences, Shenzhen, China that were used compatible with the tissues? How were the tissues prepared for ELISA? 8) Give details on measuring SIgA in intestinal tissue. 9) Serum endotoxin levels should be measured. 10) The authors should comment on what would be an effective dose of CHM for human? The dose that the authors chose for their treatment group was 8.64g/Kg. This is not going to be a dose that can ever be used for an adult human.

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