

## ESPS PEER-REVIEW REPORT

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

**ESPS manuscript NO:** 15154

**Title:** Altered distribution of regulatory lymphocytes by oral administration of soy-extracts exerts a hepatoprotective effect alleviating immune mediated liver injury, non-alcoholic steatohepatitis and insulin resistance

**Reviewer's code:** 02822399

**Reviewer's country:** United States

**Science editor:** Jing Yu

**Date sent for review:** 2014-11-12 15:38

**Date reviewed:** 2014-11-23 18:14

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	PubMed Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input checked="" type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

Khoury and colleagues tried to determine the immune-modulatory and the hepatoprotective effects of oral administration of two soy extracts in immune mediated liver injury and NASH. Oral administration of the combination of OS and M1 soy derived extracts exerted an adjuvant effect in the gut-immune system, altering the distribution of regulatory T cells, and alleviating immune mediated liver injury, hyperlipidemia and insulin resistance. They did good work. However, I have some comments: Major: 1- While I mad reading the manuscript specially the Materials & Methods, Results and Figures parts, I feel that I am reading three separate manuscripts without any connection between them. Try to connect them. 2- The beneficial effects of soy on ConA induced liver damage was discussed previously (see the papers with PMID: 18846580, 18602077, .....). In addition, the effects of soy on NASH was discussed in the following papers with PMID: 21333494, 17420940, .... What is the novelty of your work. 3- You discussion depends mainly on illustration of the previous work and the importance of soy without discussing the results of your current work. 4- This study



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heavily relied on biochemical markers for conA-induced hepatitis, such as serum ALT and AST levels. To make a solid conclusion, it is important for the authors to employ pathological changes as to show the H/E stained hepatic sections. Minor: 1- In the manuscript, you used both abbreviations: conA and con A. Please use one form. 2- In figures: - Too long figure legends. - No explanation for the abbreviations used in figure legends. - No explanation for the significant signs against what group. 3- IN figures 2E and 3C: the H/E images are not clear. Please improve the resolution of your images and discuss your findings and use arrows.

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**ESPS manuscript NO:** 15154

**Title:** Altered distribution of regulatory lymphocytes by oral administration of soy-extracts exerts a hepatoprotective effect alleviating immune mediated liver injury, non-alcoholic steatohepatitis and insulin resistance

**Reviewer's code:** 01806455

**Reviewer's country:** United States

**Science editor:** Jing Yu

**Date sent for review:** 2014-11-12 15:38

**Date reviewed:** 2014-11-26 06:06

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	PubMed Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input checked="" type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

In the manuscript entitled "Altered distribution of regulatory lymphocytes by oral administration of soy-extracts exerts a hepatoprotective effect alleviating immune mediated liver injury, non-alcoholic steatohepatitis and insulin resistance", Khoury et al present evidence for the idea that soy extracts are hepatoprotective and immuno-modulatory in several different assays for both liver damage (ConA, HFD, MCD) and altered immune response. Overall, the evidence that there is something in the two extracts that ameliorates liver damage and alters the immune response is strong. The assays, however, bring us no clearer to understanding why or how. What is(are) the active compound(s)? Why combine the two extracts? Major concerns: 1) It is difficult to know exactly what is mediating the effects of these soy extracts. They are mystery combinations of many possible active compounds. There is little information on how or why these two mixtures should work well together. 2) There is also little evidence that there is any interbatch consistency in the extracts. I suspect that some of this may explain why the assays don't quite tell a consistent story. For example, it is hard to make much



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sense of the serum cholesterol and triglyceride level measurements. In one setting one drug-mixture dose/combination worked well at only one timepoint but when the other drug-mixture was added this efficacy was lost, and yet still if you then cut the doses tenfold and include both drug mixtures, that gave the best results (Fig 2A). It is hard to know what the ideal concentration (and combination) is based on most of the presented data. What is the best drug combination and why is there no consistency in it between assays. 0.3/3/6/9/30 ug??? Minor points: "Compared with the dexamethasone treatment, 30 micrograms of OS and M, lowered the pro-inflammatory cytokines TNF-(alpha) and INF-(gamma)" is not actually true as far as this reviewer can assess based on the data. Dexamethasone appeared to be the MOST effective in lowering cytokine levels. Perhaps this was a misstatement and should have been compared with control.

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**ESPS manuscript NO:** 15154

**Title:** Altered distribution of regulatory lymphocytes by oral administration of soy-extracts exerts a hepatoprotective effect alleviating immune mediated liver injury, non-alcoholic steatohepatitis and insulin resistance

**Reviewer's code:** 03022462

**Reviewer's country:** Germany

**Science editor:** Jing Yu

**Date sent for review:** 2014-11-12 15:38

**Date reviewed:** 2015-01-02 02:23

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	PubMed Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input checked="" type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

The present manuscript submitted by Khoury et al. deals with the effects of soy extracts in the progression of NAFLD/NASH in 3 mouse models inducing an autoimmune hepatitis and NAFLD. Despite some very interesting associations shown by the authors some issues should be further clarified: 1. The effects on liver transaminases shown in Figure 1 (especially on the more liver specific ALT) are moderate and do not show a dose-dependency. Therefore the authors should rephrase their description of the results and mention the moderate effects observed and the absence of dose dependency. 2. Which dose of dexamethasone was used in the experiments? 3. Data on BMI as well as mean biochemical values (fasting glucose, cholesterol, triglycerides, transaminases) of the mice of every group should be illustrated in a separate table. 4. How do the authors explain the observed effects of the soy extracts when given in combination but not of each soy extract alone? Since b-glucosylceramide is considered as the effector second messenger mediating the immunomodulatory effects the authors should mention if GC is contained both in M1 and OS. Could



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this be a potentiall explanation of the observation of the synergistic effects despite an ineffective monotherapy? 5. Figure 2F shows very moderate effects. 6. Figure 2A: how do the authors explain the observed effect with a dose of 0.3+0.3 but not with 3+3? 7. Which is the reason for the evaluation of spleen lymphocytes and not of serum lymphocytes via FACS-analysis? I believe the latter should be more representative for the alteration in the liver tissue and the whole organism. Minor comments: "hepatic stellate cells" in the introduction, it is not common to show asterisks with variable P-values in each figure.