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Wan Chai, Hong Kong, China

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 3730
Title: NRF2 AND SNAIL-1 IN THE PREVENTION OF EXPERIMENTAL LIVER CIRRHOSIS BY CAFFEINE
Reviewer code: 02444854
Science editor: Gou, Su-Xin
Date sent for review: 2013-05-17 12:28
Date reviewed: 2013-05-17 23:29

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[Y] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

The present manuscript provides a detailed study on the effect of caffeine on experimental liver fibrosis in rats. Using two independent fibrosis models (bile-duct ligation and TAA administration) the authors demonstrate that caffeine strongly protects from liver fibrosis, which was most prominent in the TAA model and somewhat lower in bile duct-ligated rats. The authors provide convincing evidence that caffeine reduces the expression of pro-inflammatory and pro-fibrotic genes and especially activates the anti-oxidant factor Nrf2 and down-regulate the potential pro-fibrotic transcription factor Snail-1. Overall, this is a very interesting paper. The presented data is throughout of very good quality and the conclusions drawn are supported by sufficient data. The only weakness of the study is that the anti-fibrotic effects of caffeine in rats and hepatitis patients have been already published in several studies. However the manuscript also contains several new additional findings/approaches as specified below: - Two independent models are used - Besides TGF? (already published) several other pro-fibrotic factors are investigated - An interesting role of Nrf2 and Snail-1 for progression of liver fibrosis is postulated. Minor points: - the target cell of anti-fibrotic caffeine effects remains to be identified. Caffein could act protective directly on hepatocytes. In this case reduced HSC activation would be an indirect effect due to reduced hepatocyte injury which triggers HSC activation. Alternatively, caffeine could act anti-fibrotic by directly inhibiting HSC activation e.g. by down-regulation of pro-fibrotic genes specifically in HSC. However, this would not explain decreased ALT values in caffeine treated mice. Authors should discuss potential target cells on the basis of current literature - Heading for 3.8: correct Snai1 by Snail-1 - the English needs some minor improvement

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Title: NRF2 AND SNAIL-1 IN THE PREVENTION OF EXPERIMENTAL LIVER CIRRHOSIS BY CAFFEINE
Reviewer code: 00070577
Science editor: Gou, Su-Xin
Date sent for review: 2013-05-17 12:28
Date reviewed: 2013-05-19 21:45

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
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COMMENTS TO AUTHORS

The authors reported about the effect of caffeine using two rat models (intraperitoneal thioacetamide or bile duct ligation). Preventive effect of caffeine for liver cirrhosis is understandable, and the result of this paper itself is interesting. However there are some important problems must be resolved or explained. Major; 1) The authors mentioned in the manuscript that CFA dosed groups had less hepatocellular damage in 3.2. Because this group had less hepatocellular damage, it is natural in this group to have less activation of HSC and less fibrosis. Thus it is possible that all the results (such as less fibrosis) are due to less hepatocellular damage. The authors mentioned in the discussion that our results suggest that CFA displays beneficial effects and could prevent HSC activation and perpetuation. It is unclear HSC are affected by caffeine directly or indirectly (secondary)? 2) To expain NRF2 and Snail-1 in the prevention of liver cirrhosis the authors should confirm which types of cells are expressing NRF2 and Snail-1. Minor; 1) In table1, authors only checked the body weight. I think authors should check liver weight/body weight as most of the manuscript has done. 2) In table2, authors only checked the serum levels of AST and ALT. Authors should check other markers such as ALP, bilirubin etc. 3) In figure 1, to show the activation of stellate cells, α-SMA should be added.

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ESPS Manuscript NO: 3730
Title: NRF2 AND SNAIL-1 IN THE PREVENTION OF EXPERIMENTAL LIVER CIRRHOSIS BY CAFFEINE
Reviewer code: 01810523
Science editor: Gou, Su-Xin
Date sent for review: 2013-05-17 12:28
Date reviewed: 2013-05-20 04:25

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
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COMMENTS TO AUTHORS

In this study, Daniela and colleagues reported the protective effect of caffeine on liver inflammation and fibrogenesis in rat models of TAA an BDL. They observed increased NRF2 and decreased SNAIL-1 protein levels in caffeine treated rats, which correlated with increased mRNA expression of antioxidant enzymes SOD and CAT. The authors concluded that NRF2 and SNAIL-1 mediated protective effects of caffeine through induction of antioxidative activity and downregulating fibrogenic gene expression. The protective effect of caffeine on liver injury has been reported in both human and experimental animals. Although NRF2 and SNAIL-1 story was interesting, this manuscript was poorly written. As such, it made the results less comprehensible. Major concerns: 1. Was the objective of this study to investigate caffeine effects on liver fibrosis or cirrhosis? These two stages of liver disease have distinct pathology and should have been carefully defined and specifically characterized. Based on the manuscript, it seems TAA and BDL inducing fibrosis rather than cirrhosis in the present study. 2. The authors suggest that caffeine upregulates NRF2 and downregulates SNAIL-1 as potential mechanisms to prevent HSC activation and the consequent fibrogenesis. However, there is no evidence that the altered NRF2 and SNAIL-1 protein levels are HSC specific. 3. Furthermore, the SOD and CAT activities correlate well with their mRNA levels only in the BDL model, suggesting the protective effect of caffeine, at least in the TAA model, could be independent of NRF2 pathway. This should be further studied and discussed. 4. Liver weight, liver to body weight ratio, and the food intake should be reported, in addition to the body weight. Minor concerns: 1. Aim: needs to be rephrased. If you don't know "whether" caffeine prevents cirrhosis, how do you study the mechanisms? 2. Please use the lower case for gene names,

e.g. use Tnf-a instead of TNF-a. 3. Please avoid redundant use of sentences. For example, in the abstract, "Caffeine increased SOD and CAT expression presenting a strong correlation between mRNA and activity" means the same as "Expression of SOD and CAT was greater in animals treated with caffeine ($p<0.05$) founding a strong correlation between mRNA expression and enzyme activity."

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Reviewer code: 01489939
Science editor: Gou, Su-Xin
Date sent for review: 2013-05-17 12:28
Date reviewed: 2013-05-21 04:42

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[Y] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
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		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS
It is a well written and conducted study. There are some typographical errors.