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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 5438
Title: Sopnocarpine attenuates liver fibrosis in rats through inhibiting TLCui, Xue-Mei signaling pathway
Reviewer code: 00003652
Science editor: Cui, Xue-Mei
Date sent for review: 2013-09-09 16:20
Date reviewed: 2013-09-10 14:36

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] 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
[Y] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
This study examines the anti-fibrotic effects of a plant alkaloid sophocarpine in two models of hepatic fibrosis induced by bile duct ligation or dimethylnotrosamine injection. The authors report decreased hepatic stellate cell activation with reduced extracellular matrix deposition upon sophocarpine administration in both models. This was associated with a decrease in the inflammatory mediators IL6 and TGFbeta1. In vitro exposure to sophocarpine decreased HSC activation, cytokine production and TLR4-related signalling pathways. The authors conclude that the observed amelioration of hepatic fibrosis by sophocarpine is mediated via the TLR4 signalling pathway. While this paper postulates sophocarpine as a potentially useful therapeutic anti-fibrotic agent, several issues need to be addressed in order to ensure that the data provide robust basis for the authors' speculation : 1) The Methods section notes that for both models there were 12 animals in each of the treatment and control groups. Yet only 6 animals per group were assessed for IHC and histology. Why were the livers of all animals not examined? Furthermore, were the liver lesions in both models diffuse or focal? If the latter, selection of only 3 fields per section will not be representative of the whole section. Could the authors comment? 2) For expression of inflammatory mediators, morphometric analysis of immunostained sections (Fig 3) is essential before any quantitative comparisons can be made between groups. 3) Cytokines are not only produced by HSCs but also by inflammatory cells infiltrating the injured liver. It would be of interest to determine whether inflammatory cell infiltration was reduced in sophocarpine treated livers. 4) How do the doses of sophocarpine used in vitro relate to the dose used in vivo? 5) For the in vitro data (Figs 4 and 5) no statistical analysis has been provided. What was the n and p value for the different comparisons? The mRNA data

would be strengthened if western blotting was performed to assess whether changes at the transcriptional level were translated into changes at the protein level for the ECM proteins and inflammatory cytokines. 6) Was TLR4 expression in HSCs induced in LPS incubated cells? This is not apparent from Fig 4c since only relative mRNA expression has been provided. Fig 4d requires labels for various lanes of the immunoblot. Densitometry analysis of immunoblots is essential. 7) The PCNA western blot is entirely unconvincing. Densitometry data should be provided. 8) In general, while there may be some associated changes in TLR4 signalling in HSCs incubated with sophocarpine, this reviewer is not convinced that the effect of the compound is mediated via this pathway alone. It would be of interest to assess the effects of sophocarpine on oxidant stress and apoptotic pathways. 9) Minor : Grammar and spelling need attention. The title itself has a spelling mistake "Sopnocarpine" should be "Sophocarpine"

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Title: Sopnocarpine attenuates liver fibrosis in rats through inhibiting TLCui, Xue-Mei signaling pathway
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
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[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[Y] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
This article evaluates the effect of sophocarpine, a substance derivated from a plant, as a antifibrotic agent. Authors performed the study with two animal model of hepatic fibrosis (chemical induction and bile duct ligation). Author's findings consist after administratation of sohocarpine to animal models - Decrease in IL-6 and TGF beta 1, inflammation cytokines. - Decrease hepatic stellate cells activation in vitro - Decrease TLR-4-related cytokine production - Reduce extracellular matrix deposition. Comment to authors: - Title: spelling error in "sophocarpine" (no sopnocarpine) - Summary: correct. There are some abbreviations not explained. - Methods and results: o Sample size is small, so it is difficult to asses these findings. Besides, there were 12 animals. Why only analyzed a half?. Technician is blinded, so they try to correct bias. o They do not analyze all the samples. Why? Sometimes, as in human, liver damage it is not homogeneous. o They analyzed different cytokines. But cytokines could be synthesized by other cells different from HSC. They did not control this. o Why only LPS is used to stimulate and induce cytokine production? o Sophocarpine administration in different dosage for 72 h. Did they try nother timing? Why 72 h? o And sophocarpine dosage was the same in vivo than in vitro? o Western blot is inespecific. - Discussion: authors could comment a little bit more about possible bias and limitation of the study. Besides, the downregualtion of cytokines could involved other signalling pathways.

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
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COMMENTS TO AUTHORS

The article entitled: Sopnocarpine attenuates liver fibrosis in rats through inhibiting TLR4 signaling pathway describe the protective effects of Sopnocarpine alkaloids against two models of fibrosis in rats. The manuscript is well organized and the results are clear. However, some points should be discussed as follow: 1. Title: should indicate clearly that this study carried out in Rats. 2. Abstract: Abbreviations appear first in abstract before text without explanation (e.g. ECM, HSCS). 3. Materials and methods: Fibrosis model induced by dimethylnitrosamine (DMN) should be discussed briefly in the text. 4. Materials and methods : Why there was a difference between the number of rats in control (n=7) and treated group (n=12), statistically this will give wrong results 5. Materials and methods: What are the doses used for DMN and Sopnocarpine in the two models. 6. Materials and methods: Why the animals were sacrificed 3 weeks after BDL or 4 weeks after DMN administration. 7. Materials and methods: The author mention that three fields were selected randomly from each of two sections, and six rats from each group were examined. What is the relationship between the selected sections and rats in this paragraph? 8. When ANOVA test is used it should be followed by multiple comparison test. 9. Results: Fig.2 there is no statistical data provided in the text although there is symbol (*) on some figures. 10. Where are the scale bars for photos in fig. 3 11. Discussion: the authors did not explain why they used two models for fibrosis and what is difference in mechanism of protection of Sopnocarpine for each model. 12. Discussion: the author did not explain why the levels of liver parameters (ALT, AST……) are much higher in BDL model than in DMN model.