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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 28215
Title: Antioxidant and anti-inflammatory action of melatonin in an experimental model of secondary biliary cirrhosis induced by bile duct ligation
Reviewer's code: 03459537
Reviewer's country: Portugal
Science editor: Yuan Qi
Date sent for review: 2016-06-29 15:01
Date reviewed: 2016-07-27 20:47

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[Y] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This manuscript is a good research article. The study is interesting and appropriated because provide novel information about the beneficial effects of melatonin on a model of cirrhosis. The authors study the antioxidant and anti-inflammatory effects of a treatment with the indoleamine and evaluate the possible reversion of the structural changes induced in the liver by bile duct ligation. Minor comments: - Text needs to be read out to remove some typographical and grammar mistakes. For example, in page 12, line 7 (activities of GPx and GST were...); page 17, line 23 (the sentence "when administered to Mel in BLD+Mel group" should be revised) and page 18, line 23 (describe FR at first usage). - The abstract is appropriated but authors should describe the abbreviation "Mel" at first usage. - The introduction provides a reasonable background and rationale for the studies. Figures and legends are clear and well captured and the conclusions are, in general, well supported. Page 5, line 6. Authors should better indicate that melatonin secretion (not production) is inhibited by light. Page 5, 3rd paragraph. Please, include reference(s) about the investigations demonstrating the AOX potential of Mel, especially in this disease. Authors should also indicate that the study is devised to

analyze the effects of bile duct ligation on liver fibrosis, the redox and inflammatory systems and their possible attenuation by melatonin. - Material and methods section should include the protocols for tissue homogenization and plasma extraction. Authors must indicate the zeitgeber time of melatonin administration and detailed protocols for AST and ALT determinations (or a reference describing these protocols). In addition, authors should also indicate where the antioxidant enzymes and GSH have been measured (plasma or liver?) and better explain the protocol for gluthatione determination. Total glutathione and oxidized glutathione were also measured? In addition, the method for the development of immunohistochemistry (diaminobenzidine?) together with the catalogue numbers of the antibodies must be also mentioned. The uppercase letters identifying images are not correctly placed in figure 1. - In the results section, it is not clearly indicated whether the measurements of liver enzyme activities, lipid peroxidation and GSH levels were taken in plasma or liver. Pictures from figures 4 and 5 should be better described from a histological point of view. For example, in figure 5, the BDL image is difficult to interpret taking into an account the image shown in figure 4 showing hepatocyte cords and fibrosis. Hepatocytes are not easily distinguishable in the BDL group from figure 5. By adding asterisk and/or arrows to pictures, the most important features or changes (inflammatory infiltrations, fibrosis, etc.) would be easily identified making easier image interpretation. Authors must also describe the immunostaining observed in figures 6 and 7 that seems to be restricted to the fibrotic area when using an antibody against iNOS and to the hepatocytes in the BDL group when using an antibody against TNFalpha. Furthermore, magnification or scale bars must be included in figures 6 and 7. In figure 7, authors should explain why the BDL-Mel image seems to present lower staining than the CO group while the histogram show the opposite result. - In discussion section, authors should better discuss the opposed effects observed between both antioxidant systems (SOD, CAT vs. GPx, GSH) (page 19). Accordingly, since GPx activity uses reduced glutathione, authors should also explain the results in BDL group showing high GSH and GPx. Overall, this is a significant study, recommended for publication after minor revision.

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ESPS PEER-REVIEW REPORT

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[ ] Grade E: Poor		[Y] No	[ ] Major revision
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		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In this paper, the authors used animal models to study the protective effect of melatonin against secondary biliary cirrhosis induced by bile duct ligation. They provided experimental proofs for the protective effect by detecting liver enzyme levels and LPO and antioxidant enzyme concentrations. And the histological analysis also supported a positive effect of melatonin for treating secondary biliary cirrhosis. Totally, the research was well designed and the authors got good results as expected. The experimental results could provide strong support to their conclusion. In addition, the paper is well organized. My conclusion is accept.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
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		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In Abstract: - Write LPO in full In core tip: - I would remove the part on melatonin, and rather say "Melatonin provides hepatic-protection in the experimental model of bile duct ligation" or something similar to this. In the introduction: - Remove "is an organ that" - This part of the sentence "several vital functions, including direct synthesis and metabolism of many substances" is too vague (please rephrase) - Add "the" before "ability to synthesize" (in paragraph one) - Move the following paragraph "Cirrhosis of the liver represents the most advanced stage of fibrosis, in which there is evident loss of structure of the hepatic parenchyma. It is directly associated with development of septa and fibrotic nodules, changes in hepatic blood flow, and high risk of liver failure [4]" and place it after the sentence "Occurrence of these changes may lead to the development of liver fibrosis, which, in turn, can lead to secondary biliary cirrhosis [5]" - Insert references in the following places "As cirrhosis constitutes a major public health problem (REFERENCE)" and "Prolonged obstruction of the bile duct in rats is an experimental model for induction of secondary biliary cirrhosis (REFERENCE)" - Split the following sentence into two part, it's too long: See how I adapted the

sentence here "As cirrhosis constitutes a major public health problem, much research is being conducted to develop and test different substances that could be used in its treatment. The aims of such substances are to improve quality of life, increase survival, slow disease progression, and possibly, mitigate the damage caused by formation of free radicals (FRs) [7,8]" - Remove the part "and insulin resistance-related effects"; it is irrelevant for your paper. - Remove the abbreviation "AOX" from the whole manuscript please and write in full. - I would rewrite the following paragraph "Taking into account the high prevalence of this disease and the evidence for an AOX potential of Mel demonstrated in several investigations, the present study assessed the possible antioxidant effect of Mel in experimental cholestatic liver fibrosis induced by bile duct ligation in rats" and replace it with "There is an existing link between cirrhosis, inflammation and oxidative stress and treatments are required to protect the liver against damage. Therefore, this present study investigated whether melatonin (an anti-inflammatory agent and antioxidant) would afford hepatic-protection in a model of cirrhosis". In materials & methods: - "animal" instead of "animals" - Rewrite the following part so that it is the same as in your abstract "The sample comprised 32 male Wistar rats (mean weight 300 g), which were allocated across four groups: control (CO, n=8), Mel-treated control (CO+Mel, n=8), bile duct ligation (BDL, n=8), and Mel-treated bile duct ligation (BDL+Mel, n=8)" - "two knots made using 3.0 silk" - Under the heading: "Liver enzyme activity" – Your first sentence should start with "Activity" and not "levels". Also under this heading, you need references after the words "kinetic method" and "colorimetric method" - Under the heading: "Hepatosomatic and splenosomatic indices" do you mean "HSR = liver weight (g)"? Also, replace the words "mouse" with "rat" - Under the heading: Lipid peroxidation" to what temperature was the sample heated? 95 degrees Celsius? - Was your TBARS not perhaps expressed as "nmol malonic dealdehyde/mg protein"? - Under the heading: Histological analysis; with what was the 10% formalin buffered? In results section: - Under your results section and the heading "liver enzyme activities" – Please double those percentage increases/decreases in AST and ALT. It is not increased by 379%, but rather 337% and not 72% reduced but 308%. You have to double all of these percentages. In discussion section: - In the second paragraph, line 4: Start the sentence with "Our findings also demonstrated that administration of Mel to animals"