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315-321 Lockhart Road,  
Wan Chai, Hong Kong, China

## ESPS Peer-review Report

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

**ESPS Manuscript NO:** 6114

**Title:** PRIMARY BILIARY CIRRHOSIS. PATHOGENIC ROLE OF OXIDATIVE AND NITROSATIVE STRESS

**Reviewer code:** 02444852

**Science editor:** Qi, Yuan

**Date sent for review:** 2013-10-03 19:49

**Date reviewed:** 2013-10-07 13:02

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<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"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

The manuscript by Grattagliano et al. provides a survey review of the pathogenetic role of oxidative and nitrosative stress mechanisms in primary biliary cirrhosis. In separate chapters they focus on oxidative and nitrosative stress, interactions of both stress types and on the role of hepatic mitochondrial changes. Overall the authors present a well reasoned and designed review that places oxidative and nitrosative stress, and hepatic mitochondrial changes at the center of a discussion about the pathogenesis of primary biliary cirrhosis. Critical points: 1. The authors describe a lot of different mechanisms. Therefore, they should provide at least 2-3 figures explaining these mechanisms and concepts. This is especially necessary for the general readers. 2. For me is not clear why the authors present Table 1. Are the data from own investigations or from others? This is not explained in the text. 3. Also is not clear for me why they provide figures 1-4 with relatively specific data from selected studies in the review. In addition, the figures are not explained in the text!. As mentioned in 1. the review merits some figures explaining mechanisms and concepts.



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**ESPS Manuscript NO:** 6114

**Title:** PRIMARY BILIARY CIRRHOSIS. PATHOGENIC ROLE OF OXIDATIVE AND NITROSATIVE STRESS

**Reviewer code:** 00160357

**Science editor:** Qi, Yuan

**Date sent for review:** 2013-10-03 19:49

**Date reviewed:** 2013-10-09 19:08

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<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"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

Authors focused on the important mechanism of the liver damage during PBS, the oxidative and nitrosative stress. Although review manuscript present summarization of the current knowledge, several problems and questions raised with the respect to complex pathophysiology of the disease. Comments The primary point is that PBC is the inflammatory condition, thus the oxidative stress and NO production are automatically involved. However I miss such association in the manuscript. Detailed relationship to NF-kB, cytokine, immune cell response should be added in this context and thoroughly discussed - is the oxidative/nitrosative stress cause or it is rather accompanying issue of PBS? Manuscript is very difficult to read and stay oriented. Sometimes seems that information is split to different part of manuscript - e.g. thioredoxin- perhaps separate chapter/paragraph would improve understanding of its position - together with some figure summarizing its function. Better organization of each chapter such as: executive mechanism - regulation - modulation would be very helpful. I missed figures and schemes to integrate regulation pathways, and inter-relationships. There are only one table and few pictures in the manuscript presenting mainly data of unknown origin and methodological background. The relationships to other mechanism such apoptosis, necrosis, autophagy may improve the picture. Authors claimed that the pathways offer possible therapeutic approach. Could the authors present the summary (table etc) of current knowledge from preclinical but especially from clinical studies about efficacy of antioxidants or nitric oxide modulators in PBS therapy (or in corresponding animal models). Also, there are some current strategies to treat PBC such as UDCA, how they can modify presented pathophysiological mechanisms? Changes in bile flow, and involved transporters with the role of responsible nuclear



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receptors are completely omitted. At least note and citations should be added + relationship to regulatory cascade of oxidative stress and NO production should be addressed. In this place - the question about regulatory role of bile acids in these processes should be specified. Separate paragraph about current status of oxidative and nitrosative status detection in patients with PBC and possibilities of its interpretation should be specified. Summary tables of clinical studies is required, to support current knowledge about oxidative and nitrosative status and its importance for disease severity and progression - perhaps together with inflammatory markers. The final sentence of conclusion/manuscript is not very clear - did author mend that modulation of oxidative stress is superior to currently used strategy by UDCA or perspective FXR receptor modulators? Minor comment - Page 13 - problem with references 5 and 89, ...hepatocyte GMPc ?



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**ESPS Manuscript NO:** 6114

**Title:** PRIMARY BILIARY CIRRHOSIS. PATHOGENIC ROLE OF OXIDATIVE AND NITROSATIVE STRESS

**Reviewer code:** 00046378

**Science editor:** Qi, Yuan

**Date sent for review:** 2013-10-03 19:49

**Date reviewed:** 2013-11-13 02:46

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<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"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

Thank you for considering me in this revise. I suggest accepting with major revise and returning this manuscript to the author to revise and repair the following defects. 1- it seems as a pre-final draft that contains many editing errors 2- the authors missed to add the mentioned graphs 3- also, the authors mention unpublished data as references 4- the general view looks redundant and too long, I suggest to make an appropriate reduction in the text



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**ESPS Manuscript NO:** 6114

**Title:** PRIMARY BILIARY CIRRHOSIS. PATHOGENIC ROLE OF OXIDATIVE AND NITROSATIVE STRESS

**Reviewer code:** 02860712

**Science editor:** Qi, Yuan

**Date sent for review:** 2013-10-03 19:49

**Date reviewed:** 2013-12-26 22:33

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<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"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

Primary biliary cirrhosis (PBC) results from the breakdown of immune self tolerance, biliary epithelial cell (BEC) damage, and ductopenia. The ensuing cholestasis induces further damage, independently of the upstream inflammatory changes. This paper describes the molecular pathophysiology of oxidative and nitrosative stress related to cholestasis and reflects the commitment of the authors in this field. Major alterations include the reduced expression of aquaporin , decreased secretion of glutathion, and ultimately, changes in the redox state. As a consequence, protein sulphydrils in the reduced form decrease in cholestasis, leading to changes in cell membrane structure. These changes also implicate alterations in enterocyte mucosa and in hepatocyte mitochondria. Along with defects in the redox state, cholestasis leads to nitrosative stress. In my view, relevant points in this paper are the following: 1) Data reported in this review, such as the levels of thioredoxin and the inverse relationship between thioredoxin and nitrotyrosine suggest that oxidative/ nitrosative stress takes place in an early phase of the disease and plays a pathogenic role; 2) Markers of oxidative/nitrosative stress could be predictors of long term outcome 3) UDCA reduced the oxidative/nitrosative stress in 5 patients in stage 1 and in 13 patients in stage 2 of PBC. These findings need further confirmation, given that biochemical criteria at 1 year are not robust predictors of the long-term outcome of early PBC. By contrast, it was shown ( Poupon 1997) that long-term treatment with UDCA is most effective (by which mechanisms?) in advanced stages of the disease. This issues should be further addressed in the concluding remarks Minor changes: Abstract line 6 : thiols oxidations should be thiol oxidation Absstract line 11: some parameters?



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specify



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

**ESPS Manuscript NO:** 6114

**Title:** PRIMARY BILIARY CIRRHOSIS. PATHOGENIC ROLE OF OXIDATIVE AND NITROSATIVE STRESS

**Reviewer code:** 02860846

**Science editor:** Qi, Yuan

**Date sent for review:** 2013-10-03 19:49

**Date reviewed:** 2013-12-28 04:18

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

### COMMENTS TO AUTHORS

The manuscript by Grattagliano et al. described the role of oxidative and nitrosative stress in primary biliary cirrhosis . Authors highlighted the major points of these pathogenic stress and they well explained why it might use several derivatives as markers and to monitor disease progression. Moreover, the paper showed the interplay between antioxidant molecules and oxidative/nitrosative stress. Interestingly, they focused on the use of UDCA and its reduction of the oxidative/nitrosative stress in patients in early stage of PBC The data presented in this manuscript are coherent with the conclusions of the authors but there are multiple writing errors throughout the paper. An editing work is required.



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**ESPS Manuscript NO:** 6114

**Title:** PRIMARY BILIARY CIRRHOSIS. PATHOGENIC ROLE OF OXIDATIVE AND NITROSATIVE STRESS

**Reviewer code:** 02860653

**Science editor:** Qi, Yuan

**Date sent for review:** 2013-10-03 19:49

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input checked="" 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"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

However in spite the article is definitely recommended to be published, some considerations might be recommended to authors that may improve the paper. 1. Check for spelling - eg, p.19 'immunomodulatory properties'; 2. oxidative and nitrosative stress is closely linked with many cellular mechanisms that might be discussed, namely proteomic, gene damage, virus, induction, cancerogenesis issues, vascular mechanisms, etc. Extensive discussion of this options may contribute to integrative understanding of the problem and help to develop novel treatments.