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E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 19163
Title: Oxidative stress modulation in hepatitis C virus infected cells
Reviewer's code: 02996776
Reviewer's country: Japan
Science editor: Jing Yu
Date sent for review: 2015-05-08 09:12
Date reviewed: 2015-07-23 18:46

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

COMMENTS TO AUTHORS

This paper is a review where Lozano-Sepulveda et al. try to answer some questions about the relationship between viral and cellular proteins and the resulting regulation of oxidative stress in case of HCV infection. Authors describe molecular mechanisms of HCV-induced oxidative stress, while highlighting the effect of some molecules that modify the levels of cellular oxidative stress in HCV infected cells. It's worth to discuss data about the usefulness and the interaction of antioxidant therapy in case of HCV infection.

The objective of this review was explicitly stated, and through the text, the authors tried to answer the question with a kind of scientific rigour, by citing some of the important references to explain the regulation of Redox-system in normal and infectious situations. Figures and table are quite

explaining the flow of idea and the conception of the review. The manuscript is concise, clear and comprehensive.

However, some minor issues should be considered prior to the publication

Minor issues:

- In the introduction, the authors give a whole statistical review of liver diseases in USA. Is there any interest behind this? This is not explained, because HCV infection and associated liver diseases are major health problem worldwide, and there are even countries with higher prevalences. Furthermore, even the authors are not from USA to say that they are dealing with the problematic in their country!! So, please reconsider this paragraph.
- Please provide keywords
- Please review the text, there are many spelling mistakes.
- In abstract section, you need not to abbreviate HCV, twice (lines 3).
- There are many recent references on the field, please refresh your literature (please take a look following examples).
- Please number pages and lines
- There are more recent data about the mechanisms of HCV proteins like core, E2 and NS5A in oxidative stress. Please update HCV and oxidative stress- section.

Ivanov AV, Smirnova OA, Petrushanko IY, Ivanova ON, Karpenko IL, Alekseeva E, Sominskaya I, Makarov AA, Bartosch B, Kochetkov SN, Isaguliants MG. HCV core protein uses multiple mechanisms to induce oxidative stress in human hepatoma huh7 cells. Viruses. 2015 May 29;7(6):2745-70.

Seo YL, Heo S, Jang KL. Hepatitis C virus core protein overcomes H2O2-induced apoptosis by downregulating p14 expression via DNA methylation.J Gen Virol. 2015 Apr;96(Pt 4):822-32.

Ivanov AV, Smirnova OA, Ivanova ON, Masalova OV, Kochetkov SN, Isaguliants MG. Hepatitis C virus proteins activate NRF2/ARE pathway by distinct ROS-dependent and independent mechanisms in HUH7 cells. PLoS One. 2011;6(9):e24957.

Ming-Ju H, Yih-Shou H, Tzy-Yen C, Hui-Ling C. Hepatitis C virus E2 protein induce reactive oxygen species (ROS)-related fibrogenesis in the HSC-T6 hepatic stellate cell line.J Cell Biochem. 2011

Jan;112(1):233-43.

Dionisio N, Garcia-Mediavilla MV, Sanchez-Campos S, Majano PL, Benedicto I, Rosado JA, Salido GM, Gonzalez-Gallego J. Hepatitis C virus NS5A and core proteins induce oxidative stress-mediated calcium signalling alterations in hepatocytes. J Hepatol. 2009 May;50(5):872-82.

- Ivanov AV, Smirnova OA, Ivanova ON, Masalova OV, Kochetkov SN, Isaguliants MG. Hepatitis C virus proteins activate NRF2/ARE pathway by distinct ROS-dependent and independent mechanisms in HUH7 cells. PLoS One. 2011;6(9):e24957.

-In "antioxidant therapy" section

There are recent data regarding antioxidant therapy against HCV. Also, it has been recently reported a protective role of amantadine in mitochondrial dysfunction and oxidative stress mediated by HCV. It should be better to report current information about the role of antioxidant therapy.

Hsiang CY, Lin LJ, Kao ST, Lo HY, Chou ST, Ho TY. Glycyrrhizin, silymarin, and ursodeoxycholic acid regulate a common hepatoprotective pathway in HepG2 cells.
Phytomedicine. 2015 Jul 15;22(7-8):768-77.

Morgan TR, Osann K, Bottiglieri T, Pimstone N, Hoefs JC, Hu KQ, Hassanein T, Boyer T, Kong L, Chen WP, Richmond E, Gonzalez R, Rodriguez LM, Meyskens FL. A phase II, randomized, controlled trial of S-adenosylmethionine in reducing serum alpha-fetoprotein (AFP) in patients with hepatitis C cirrhosis and elevated AFP. Cancer Prev Res (Phila). 2015

Bunchorntavakul C, Wootthananont T, Atsawarungruangkit A. Effects of vitamin E on chronic hepatitis C genotype 3: a randomized, double-blind, placebo-controlled study.
J Med Assoc Thai. 2014

Quarato G, Scrima R, Ripoli M, Agriesti F, Moradpour D, Capitanio N, Piccoli C. Protective role of amantadine in mitochondrial dysfunction and oxidative stress mediated by hepatitis C virus protein expression. Biochem Pharmacol. 2014 Jun 15;89(4):545-56.

Yang M, Li N, Li F, Zhu Q, Liu X, Han Q, Wang Y, Chen Y, Zeng X, Lv Y, Zhang P, Yang C, Liu Z. Xanthohumol, a main prenylated chalcone from hops, reduces liver damage and modulates oxidative reaction and apoptosis in hepatitis C virus infected Tupaia belangeri. Int Immunopharmacol. 2013 Aug;16(4):466-74.

Farias MS, Budni P, Ribeiro CM, Parisotto EB, Santos CE, Dias JF, Dalmarco EM, Fröde TS, Pedrosa

RC, Wilhelm Filho D. Antioxidant supplementation attenuates oxidative stress in chronic hepatitis C patients. Gastroenterol Hepatol. 2012,35(6):386-94.

- References section
Reference 5: please give volume number and page numbers.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 19163
Title: Oxidative stress modulation in hepatitis C virus infected cells
Reviewer's code: 00071702
Reviewer's country: India
Science editor: Jing Yu
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
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		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Major concern: Oxidative stress imposed either directly by the virus or by the host immune response is considered an important pathogenic mechanism in HCV infection. Moreover, HCV is potentially lymphotropic, invading and propagating in cells of the immune system. It is known that synthesis and maturation of HCV proteins occur at the level of the ER but HCV proteins accumulate at the point of contact between the mitochondrial outer membrane and the ER. By transient fusion of the membranous sub-compartments, the viral proteins migrate from the ER to the mitochondria. Therefore, a direct interaction of HCV proteins with the mitochondrial machinery in hepatic and extra-hepatic sites is strongly posited. Impairment of mitochondria-nuclear cross talk through involvement of PI3 kinases has been recently demonstrated by Bhargava et al., 2011. This and other such recent advances with regard to redox signalling and HCV infection need to be included to provide a holistic understanding of the subject. This is certainly lacking in the current form of the manuscript. Minor concerns: Abstract: The authors must avoid generalized statements in the abstract (first 2-3). Major implication on patho-physiology, drugs in pre- and clinical trials and potential leads in clinical translation must be highlighted. Core tip: Immune perturbation following

the infection and subsequent implications must be included. Introduction: There is a lack of continuum in epidemiological details discussed in the 1st paragraph and available therapeutic options discussed in the 2nd. Include 2-3 sentences with regard to disease severity, prevalence and endemicity in beginning of the 2nd paragraph followed by why is it necessary to design newer molecules and therapies. HCV and oxidative stress: In this segment the authors must provide a complete understanding without invoking ER at the first place. Thrust on implication of redox-stress in both hepatic-extra hepatic sites must be categorically discussed, this will help the readers. Table: Inclusion of a table delineating various anti-oxidant therapies so far considered along with their mode of action, target, possible implication and failure must be included. References: Try and include more recent references.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
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Title: Oxidative stress modulation in hepatitis C virus infected cells
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Reviewer's country: Germany
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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COMMENTS TO AUTHORS

This review describes interaction of oxidative stress with HCV infection and discusses treatment options. It lists several substances considered as (more or less effective) antioxidants in hepatitis C, and tries to elucidate pathophysiological mechanisms. From a clinical point of view, antioxidants could be interesting in resource-limited settings as an alternative to the costly Directly Acting Antivirals (DAAs) to reduce inflammatory activity. Unfortunately, most of the data cited are quite old and need to be updated. I recommend to shorten the introduction. It seems advisable to focus the epidemiology data on poor-resource regions since patients in most industrialized countries will receive DAAs. The conclusion should weigh the substances, and the authors should state which one might be most interesting and might be worthwhile further research, either in combination with DAAs or alone. Table 1 should include the literature. It seems difficult to mix in vitro data together with clinical trial results in one table. The style is acceptable, but there are several mistakes in spelling and punctuation. The title is not optimal since "therapy" of HCV is not in the focus of the review. I would suggest "Oxidative stress modulation in HCV infected patients" as the main title.