

ANSWERING REVIEWERS

January 25, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format.

Title: Hepatoprotective effect of silymarin. A current review

Author: Nancy Vargas-Mendoza, Eduardo Madrigal-Santillán, Ángel Morales-González, Jaime Esquivel-Soto, Cesar Esquivel-Chirino, Manuel García-Luna y González-Rubio, Juan A. Gayosso de Lucio and José A. Morales-González

Name of Journal: World Journal of Hepatology

ESPS Manuscript NO: 7092

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

Answer: The format was updated with comments from reviewers

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1. Authors introduce the effect of silymarin in hepatic disease related with oxidative stress, such as alcoholism. Introducing the hepatic effect of silymarin to the readers of World J of Hepatology is meaningful in a sense of attenuating hepatic disease. However it is very difficult to understand this manuscript due to lots of mistakes in English usage and in construction of the sentences. For example, I can find the content of "CHARACTERIZATION OF SILYMARIN" in "SILYMARIN". That confuses understanding this manuscript. "SILYMARIN" and "CHARACTERIZATION OF SILYMARIN" have to be written with one subtitle instead of two. And I cannot understand this sentence in Abstract, "Sly diminishes Kupffer cell activity and the production of glutathione, also inhibiting its oxidation." Because glutathione is an antioxidant, Sly will stimulate the production of glutathione instead of diminishing the production of glutathione.

Answer: We corrected the aspects of the manuscript requested by the reviewer, including the English language concerns. We clarified the confusion in the text concerning glutathione levels. In addition, we used a single subtitle under the silymarin heading.

Reviewer 2. Silymarin extracts from a traditional herb, Milk thistle, the authors reviewed the features and possible mechanism of hepatoprotection of silymarin. Comments 1. As a review, it should introduce the novel, comprehensive progress of Silymarin on treatment of human liver diseases. 2. Some content repeated in different sessions, which can be integrated. 3. The names of Author and their Institutions should be in English, not in Spanish. 3. The use of abbreviation is not normative. Such as, (1)some abbreviations (e.g.

Et-OH, CCl₄, LPO) should be deleted from Abstract, because they appear one time only; (2) the first letter of word is in capital when it is given a abbreviation; (3) the abbr. of Sly should be given when the word of silymarin first appear (Page 5, Line 9), not second (Page 5, Line 10), and the silymarin should be replaced by Sly in next text; (4) the abbr. of Milk thistle (Mt) appear 2 times (Page 4, Line 28; Page 5, Line 13). 4. The hepatic disease may be one of the primary causes of morbimortality throughout the world (Page 4, Line 11-12). 5. The references should be re-prepare according to the WJH-Instructions to authors.

Answer: We added new information on silymarin to the manuscript and corrected the authors' affiliations and the abbreviations. In addition, we addressed and corrected the English language issues in the manuscript. We also added information on the mortality data and corrected the references according to the format requested by the journal. Similarly, we corrected silymarin and used *Cardo mariano* without abbreviations.

Reviewer 3. The paper entitled " Hepatoprotective effect of silymarin. A current review " by Vargas-Mendoza and collaborators briefly describes the role of Silymarin as hepatic protector. This work is short but well-constructed but some problems should be solved: 1) Authors should better describe the mechanisms underlying Sly effect on cancer which are only hinted. 2) Authors should carefully read the whole text since several repetition are present. 3) Paper should be carefully amended by a mother tongue colleague, in fact some sentences are not completely understandable.

Answer: We added information on the mechanisms of the protective effect of silymarin in cancer, corrected the English, and removed repeated information.

Reviewer 4. Manuscript No: 7092 Title: Hepatoprotective effect of silymarin. A current review. Authors: Morales-González et al. This minireview presents a summary of data concerning the use of the plant extract silymarin in the treatment of hepatic disease. The manuscript pays especial attention to the antioxidant properties of the drug, but a more detailed comparison with other antioxidants would be desired. Overall, the review seems superficial and will benefit from the inclusion of additional information and figures. In addition, a careful review of the English is recommended, as some sentences lack verbs or became too long to understand the rationale followed by the authors. Most of the Greek symbols are lost in the text, please use the "insert symbol" tool. Specific comments: 1- The Authors contributions statement is written in Spanish. Please, translate. 2- Abstract, the use of abbreviations in this section should be avoided. 3- Abstract, line 11. It is stated that "Sly diminishes Kupffer cell activity and the production of glutathione", please clarify whether the decreased production of glutathione refers to the whole tissue or jus Kupffer cells. 4- Introduction, line 4. "is transported to liver" should be "is transported to the liver". 5- Introduction, line 7. What is the reason to differentiate between drugs and pharmaceuticals? 6- Introduction, line 8. "A great part of the population is afflicted.." could you please be more specific? Is there a percentage estimated by the World Health Organization, for example? In this same sentence " cirrhosis due to the consumption or not of ethanol" could be better expressed simply as "cirrhosis", since it is independent of its origin. 7- Silymarin, line 2. The description of flavonoid structure and its oxidation to several families of flavonoids should be complemented with a figure including the most relevant examples. Such a scheme would help the reader in understanding the chemical

modifications involved in the oxidation process. 8- Silymarin, paragraph 2. The information contained in this paragraph is repeated in other parts of the text. Please, avoid repetition of the information unless determinant to understand the meaning. 9- Silymarin, page 5, 2nd paragraph. Again, in my opinion, the text would benefit from a scheme/figure of the group silymarin components. 10- Silymarin, page 5, 3rd paragraph, line 5. It is mentioned that Sly exerts its protective effects by "increasing glutathione tissue levels" whereas in the Abstract it was stated that "Sly diminishes Kupffer cell activity and the production of glutathione". Please, clarify these contradictory statements. This problem appears again in page 9, 1st line. 11- Silymarin, page 5, 4th paragraph, line 3. Please, give some examples of cell cycle regulators and apoptotic proteins whose expression is affected by Sly. 12- Silymarin, page 5, 4th paragraph, last line. "Isosilybin B showed the most potent activity. The isolation.." This part of the text would benefit from the addition of specific data, for example percentages against control groups, etc.. 13- Page 6, last paragraph. Again a scheme of the modification mentioned to improve solubility would be helpful. 14- Page 7, 2nd paragraph, line 1. What do you mean by "formal studies"? 15- Page 7, 2nd paragraph, line 9. What do you mean by "hepatocyte synthesis"? 16- Page 7, 3rd paragraph, 1st sentence. The meaning of this sentence is obscure. Concepts as "struct esteroidea" are unintelligible. 17- Page 7, 3rd paragraph, line 7. What do you mean by "it exerts an influence on intracellular glutathione"? 18- Page 7, 3rd line from the bottom, "...because these have diminished infection due to the virus..", I suppose you mean that cell lines (which?) treated with the mentioned compounds are more resistant to HCV infection than control cells. Please, modify this confusing sentence to explain the effects reported. 19- Page 8, last p

Answer. We performed changes in the manuscript according to the observations of the reviewer such as adding Greek symbols, including the authors' contributions in English, and removing the abbreviations in the Abstract. We also clarified the confusion on glutathione levels in the text. In the Introduction section, the following phrase "...such as Ethanol (Et-OH), drugs, pharmaceuticals, and toxins,..." refers to drugs as products that cause harm and pharmaceuticals (medicaments) refers to pharmaceutical products. We added information about the population affected with cirrhosis, added a figure with the components of silymarin, and removed repeated information. We added the cell cycle regulators that affect silymarin, and the apoptotic proteins,. We also corrected the matter on formal studies, modified obscure phrases, and addressed each of the valuable suggestions provided by the reviewer.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Hepatology*.

Sincerely yours,

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