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ANSWERING REVIEWERS

Name of journal: World Journal of Gastroenterology

Manuscript NO: 53151

Title:SILYMARIN, BOSWELLIC ACID AND CURCUMIN ENRICHED DIETETIC FORMULATION REDUCES THE GROWTH OF INHERITED INTESTINAL POLYPS IN AN ANIMAL MODEL

Reviewer's code: 03478148
Position: Editorial Board
Academic degree: DVM, DVSc
Professional title: Assistant Professor, Research Scientist
Reviewer's country: India
Author's country: Italy
Reviewer chosen by: Artificial Intelligence Technique
Reviewer accepted review: 2019-12-11 03:55
Reviewer performed review: 2019-12-18 05:51
Review time: 7 Days and 1 Hour

SPECIFIC COMMENTS TO AUTHORS

Comments: The study " SILYMARIN, BOSWELLIC ACID AND CURCUMIN ENRICHED DIETETIC FORMULATION REDUCES THE GROWTH OF INHERITED INTESTINAL POLYPS IN AN ANIMAL MODEL" is well designed and executed. However there are few points which need to be addressed:

• How the dose of the formulation was decided as 22.4 mg/kg BW and the level of the compounds decided for the enriched diet?

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The hypothesis of this study was that the combinations of phytochemicals may exert beneficial health effects beyond what provided by a single phytochemical due to the different mechanisms of action of the compounds. For this purpose, we previously compared *"in vitro"* the effect of each component of the nutritional combination with the complete formulation on cultured colonic cancer cell proliferation (reference no. 19). Moreover, the formulation was established taking into account bioavailability data obtained by the daily intake amount of the components achieving appropriate plasma concentrations and total intestinal absorption (reference no. 20). Successively, we estimated food intake (16.7 mg/100 g body weight) according to Italian Association for Laboratory Animal Science, November 2012 (reference no. 22). Based on these assumptions, the dose of the formulation reflected a daily intake/mouse of silymarin 0.892 mg, AKBA 0.672 mg and curcumin 0.448 mg. Finally, we emphasized that the dosage used for the individual nutritional components turned out to be lower than that used for the single substances for "*in vivo*" experiments on the same animal model (references no. 13, 39, 40).

• The gross lesion image (Fig 1B) is not clear. Provide clear image with higher magnification and closer view of the intestinal lesion.

Thank you for your comment. We have added in figure 1B boxes with higher magnification in order to better highlight the polypoid lesions arisen in mouse intestine.

• Fig 2 . Clarify the changes in the Microscopic image of intestine using arrows.

Thank you for your suggestion. We have added arrows and asterisk in order to emphasize cell crowding/pleomorphism and nuclear hyperchromatism in cancerous tissue.

• In Fig 3 only 48h image is presented. Provide the images for 72 and 96 hours to increase he clarity.

In figure 3, we have enclosed two further boxes (C and D), reporting the picture of BrdU

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expression at 72 and 92 hours, respectively, in the standard group. Since the immunofluorescent appearance at the same time points in the enriched diet group was similar without significant differences compared to the standard group, we did not add images of the enriched diet group. Indeed, the only significant difference between the two treatment arms took place at 48 hours, as reported and discussed in the text.

• No or minimal inflammation is observed. However, inflammation is the feature of cancerous tissue. Justify?

Inflammation evaluation was performed in non-dysplastic/neoplastic tissue, since our aim was to assess its role in carcinogenetic process. Therefore, we did not detect this parameter in pre-cancerous or cancerous lesions, where it is found as a consequence of necrosis.

• No effect ER beta receptor. Need more clarification and justification.

It is possible that the text of the first version of the paper has not been completely clear as regards the effect of dietary formula on ER beta. So we changed it in revised manuscript. Indeed, we found that ER beta protein was poorly expressed in polyps of both groups, while it was well expressed in normal mucosa of enriched and standard diet with a more marked signal in the first group, as clearly shown by Western blotting. The presence of high grade dysplasia and carcinoma in polypoid lesions may explain the poor expression of ER beta at this level, since ER beta is poorly expressed in high grade dysplasia and carcinoma (reference n.30). Moreover, ER beta protein was well expressed in normal mucosa of enriched and standard diet with a more marked signal in the first group. Therefore, a stimulation of ER beta by silymarin could have occurred at this level and played a role in anti-neoplastic effect of dietary treatment.

• Include most recent refernces in the manuscript and check for English editing.

In the revised manuscript, we have enclosed some recent references, as requested by the reviewer.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

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Reviewer's code: 02732495
Position: Peer Reviewer
Academic degree: MD
Professional title: Associate Professor
Reviewer's country: Turkey
Author's country: Italy

Reviewer chosen by: Artificial Intelligence Technique
Reviewer accepted review: 2019-12-19 18:34
Reviewer performed review: 2019-12-21 22:06
Review time: 2 Days and 3 Hours

SPECIFIC COMMENTS TO AUTHORS

In this interesting experimental study, the authors aimed to assess the effects of a nutritional formulation with anti-carcinogenetic properties consisting of silymarin, boswellic acid and curcumin on preventing inherited intestinal cancer. They concluded that these nutrients posed a chemo-preventive synergic effect in inherited intestinal cancer as they stated that this effect might be mediated by the reduction of epithelial proliferation, the increase of apoptosis and the acceleration of villous cell renewal due to dietary formulation intake. The study is well designed and the manuscript is

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appropriately written. I congratulate the authors for their successful work.

We thank very much the reviewer for the kind appreciation of our manuscript.

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