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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 51410

Title: Irisin attenuates intestinal injury, oxidative and ER stress in mice with L-arginine - induced acute pancreatitis

Reviewer's code: 00505440
Position: Editorial Board
Academic degree: MBBS, MD, PhD
Professional title: Doctor, Senior Lecturer
Reviewer's country: Australia
Author's country: China
Reviewer chosen by: Artificial Intelligence Technique
Reviewer accepted review: 2019-09-17 08:43
Reviewer performed review: 2019-09-18 06:40
Review time: 21 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[Y] Accept (General priority)	[ ] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[Y] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

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This is a nice study and well written manuscript

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 51410

Title: Irisin attenuates intestinal injury, oxidative and ER stress in mice with L-arginine - induced acute pancreatitis

Reviewer's code: 03735398
Position: Peer Reviewer
Academic degree: PhD

Professional title: Research Assistant Professor

Reviewer's country: Poland

Author's country: China

Reviewer chosen by: Artificial Intelligence Technique

Reviewer accepted review: 2019-09-18 20:54

Reviewer performed review: 2019-10-01 08:15

Review time: 12 Days and 11 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

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The manuscript no 51410 is focused on the possible effects of irisin administration on intestinal injury in experimental model of acute pancreatitis. The MS is appropriately written and well-organized. The data is presented cleary. However, there are some critical comments related to the description of methdodology. Also, I would like to recommend to revise the manuscript (at least the discussion) following comments pointed-out below. However, there are few major and minor points below: - please, provide the appropriate reference (in „Materials and Methods" section) to the experimental model implemented in this study - please, provide the information about the total number of mice included in the study and within each experimental group - I would recommend to include details regarding „scoring criteria" to „Materials and Methods" section (histological evaluation) - please, provide the information about the ALL chemicals and drugs used in the study - what was the post-hoc test used for statistical analysis? - what was the dilution of each antibody used in the study? - Few studies were published recently showing that the beneficial or harmful effect of exercise (possibly followed by the moderate or intensive increase in irisin release) within gastrointestinal tract also associated with ROS generation depends on its intensity (e.g. doi: 10.3390/nu11051127; doi: 10.1371/journal.pbio.2006159; doi: 10.26402/jpp.2018.1.13.; doi: 10.1093/ecco-jcc/jjy026). Therefore, it would be interesting to consider by Authors to test the effect of even higher dose of irisin in the experimental model included in this manuscript or at least to discuss the possible limitation of the study.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 51410

Title: Irisin attenuates intestinal injury, oxidative and ER stress in mice with L-arginine - induced acute pancreatitis

Reviewer's code: 00073640
Position: Editorial Board
Academic degree: PhD

Professional title: Associate Research Scientist

Reviewer's country: Slovenia

Author's country: China

Reviewer chosen by: Jin-Zhou Tang

Reviewer accepted review: 2019-10-11 15:25

Reviewer performed review: 2019-10-22 14:07

Review time: 10 Days and 22 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[Y] Grade D: Fair	[ ] Grade D: Rejection	[Y] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

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The manuscript evaluated effect of irisin on intestinal mucosa of mice. The aim was to evaluate oxidative and endoplasmic reticulum stress. However, since oxidative status of an organism is significantly affected by numerous factors, and authors did not provide much information about it, there is serious doubt about the validity of the study and results. My major comments are as follows. Authors wrote: »ARRIVE guidelines statement: All of our experiments follow ARRIVE guidelines.« – From that statement it is clear that authors do not know what ARRIVE guidelines are. ARRIVE guidelines are instructions which information should be stated in the manuscript when experiment is performed on animals. Authors did not provided necessary information about animal experiment and therefore it is not possible to evaluate the quaility and validity of the results. Authors wrote: »All experimental procedures were consistent with international guidelines for the care and use of laboratory animals…«. Which international guidelines? There are many guidelines but international? Authors wrote: »all animals were housed for one week under standard conditions…« What are standard conditions?!!!! Standard conditions does not exsist therefore ARRIVE guidelines were published to help authors what information they should provide when animals are used. I strongly suggest that authors read and follow ARRIVE guidelines and provide the necessary data in their manuscript. Important data about experimental design that should be stated in the manuscript are: - Authors stated that animal fasted for 12 hours before experiment – WHY? were animals in metabolic cages i.e. without bedding, enrichment etc.. - How many animals were in one cage (singly housed or in groups – how many animals per cage?), bedding material, diet (type and manufacturer), water (tap, autoclaved, sterilized, acidified…) - Microbiological state – health monitoring report – microbiological state can significantly affect results Housing conditions (temperature, humidity etc), light/dark period etc. All above mentioned factors (which are also stated in ARRIVE guidelines) are very important factors that significantly affect oxidative enzymes and consequently

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validity of the results. In addition, the protocol is very purly explained: - It is not clear why animals received »2 hourly intraperitoneal injections of L-arginine (4.0 g/kg L-arginine, A5006, Sigma-Aldrich, Shanghai, China).« Authors did not provide the volume injected and the reason why such protocol was used. - It is not clear why only one application of irisin was used, and why the dose was used. Again, authors did not provide the injected volume. - It is not clear why authors killed mice 69 hours after irisin treatment and why not 7 or 14 day or 30 day after (time that is recommended to get valid results). Histologic evaluation section: authors wrote: »Three sections were randomly selected for each group, two fields were randomly photographed for each section...«. 6 mice per group were used, suffered and then only 3 sections for each group were used? This is not ethical!!! Authors should macroscopically and histologically evaluate all animals used in experiment according to good laboratory standard procedures. Statistics section. Authors wrote: »One-way ANOVA was used to analyze the differences between groups ». Since the authors have 4 groups, MANOVA with post hock test should be used and because of small samples mean +/- SEM (and not standard deviation) shoul be used. There is serious doubth regarding the protocol and ethical justification of animal use. - Mice received intraperitoneal injection every 2 hours in 72 hours, which is 36 intraperitoneal injections in 3 days. Why they did not use minipumps instead 36 intraperitoneal injections in 3 days!!! This is very painful and stressful for the animals (mice need time to rest-day and time to activity-night – so if they were disturbed every two hours at night the mice did not have dark period, which affects the melatonin production and oxidative stress etc) and therefore the results are questionable, specially because the authors investigated oxidative stress – shuch protocol is not appropriate and significantly affects not only animal welfare but most importantly the results.

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