



PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 53546 (50314)

Title: High omega-6: omega-3 ratios induces mitochondrial dysfunction and altered lipid metabolism

Reviewer's code: 03465463

Position: Editorial Board

Academic degree: FCPS, PhD

Professional title: Adjunct Professor, Professor

Reviewer's country: Taiwan

Author's country: United Kingdom

Reviewer chosen by: Ruo-Yu Ma

Reviewer accepted review: 2019-09-05 08:03

Reviewer performed review: 2019-09-06 10:11

Review time: 1 Day and 2 Hours

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 Grade E: Do not publish	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

SPECIFIC COMMENTS TO AUTHORS



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This submission is going to investigate the effect of increasing ratios of omega-6:3 fatty acids on mitochondrial function and lipid metabolism mediators. I like to give the following comments. 1. Application of arachidonic acid (AA) as omega-6 and docosahexaenoic acid (DHA) as omega-3 must introduce in clear or supply the reference(s) to support it. 2. Source of VL-17A cells and the XF Cell Mito Stress Test Kit must indicate in detail. 3. Incubation time seems not so important in the results. Why? 4. Expression of CB2 failed to promote as CB1 in this cell line. Why? 5. Limitation(s) of this report may assist the unclear concerns. 6. There is no doubt that high omega-6: omega-3 conditions contributed to NAFLD development. However, the potential mechanism(s) fail to conduct in this report. 7. Novelty of this report needs to indicate in the conclusion.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- The same title
- Duplicate publication
- Plagiarism
- No

BPG Search:

- The same title
- Duplicate publication
- Plagiarism
- No



PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 53546 (50314)

Title: High omega-6: omega-3 ratios induces mitochondrial dysfunction and altered lipid metabolism

Reviewer's code: 00053659

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Professor, Surgeon

Reviewer's country: Japan

Author's country: United Kingdom

Reviewer chosen by: Ruo-Yu Ma

Reviewer accepted review: 2019-10-21 03:40

Reviewer performed review: 2019-10-21 04:58

Review time: 1 Hour

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

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Ghazali et al. investigated a biological effect of the fatty acids on the cancer cells. They cultured cancer cells with normal (1:1, 4:1) and high (15:1, 25:1) ratios of omega-6: omega-3 fatty acids (arachidonic (AA): docosahexaenoic (DHA)) at various time points. They found that high AA:DHA ratio decreased mitochondrial activity and promoted intracellular triglyceride accumulation. Therefore, they concluded that a high AA:DHA ratio induced triglyceride accumulation, increased oxidative stress, and disrupted mitochondrial functions. The observation seems to be interesting, although it is unclear whether the cells would maintain lipid metabolism and high lipid concentration would be unsuitable to see physiological mechanisms. It could be just toxic rather than biological effect. The limitation of the study should be discussed. The entire format of the paper should follow the author guidelines.

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 53546 (50314)

Title: High omega-6: omega-3 ratios induces mitochondrial dysfunction and altered lipid metabolism

Reviewer's code: 00503536

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Doctor

Reviewer's country: Japan

Author's country: United Kingdom

Reviewer chosen by: Ruo-Yu Ma

Reviewer accepted review: 2019-10-27 11:46

Reviewer performed review: 2019-10-29 14:01

Review time: 2 Days and 2 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
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The manuscript written by Ghazali et al. describes high omega-6: omega-3 ratios induces mitochondrial dysfunction and altered lipid metabolism in the culture system with HepG2 cells. The data may represent the key events in the development of NAFLD, and thus important for the understanding of the disease. The experiments are well performed and interesting, but there are some concerns that need to be addressed. Major points 1. The effect of high AA:DHA ratios on intracellular triglyceride accumulation or ROS production seems transient. Other phenomena might also be transient, although the data are not shown. If so, it is unclear how these effects of high AA:DHA could contribute to the development of NAFLD. More statements are needed on the effect time. 2. The authors used HepG2 cells. Since the cells derived from hepatoblastoma, it is unclear if the same effects are seen in normal hepatocytes. The authors should discuss on that point.

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BPG Search:

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 53546 (50314)

Title: High omega-6: omega-3 ratios induces mitochondrial dysfunction and altered lipid metabolism

Reviewer's code: 02438768

Position: Editorial Board

Academic degree: MD

Professional title: Associate Professor

Reviewer's country: China

Author's country: United Kingdom

Reviewer chosen by: Ruo-Yu Ma

Reviewer accepted review: 2019-10-23 12:11

Reviewer performed review: 2019-10-31 03:11

Review time: 7 Days and 14 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
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Comments for ESPS Manuscript NO 50314 This study is interesting. The followings are my several major and minor concerns. Major concerns: 1.The omega-6 fatty acids/omega-3 fatty acids ratio plays a key role in health. This study may support a role for a high omega-6:omega-3 ratio in the the pathogenesis of non-alcoholic fatty liver disease (NAFLD). However, a recent study has shown that reducing the dietary omega-6 :omega-3 did not attenuate NAFLD progression [Enos RT, et al. "Lowering the dietary omega-6: omega-3 does not hinder nonalcoholic fatty-liver disease development in a murine model." Nutr Res. 2015 May;35(5):449-59]. Thus, the potential mechanisms of their roles could contribute to the development of NAFLD that should be conducted in this study. 2.The advantages and limitations of the study should be discussed. Minor concerns: The format of the paper does not meet the WJH's requirements.

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 53546 (50314)

Title: High omega-6: omega-3 ratios induces mitochondrial dysfunction and altered lipid metabolism

Reviewer's code: 04091933

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor, Senior Researcher

Reviewer's country: Russia

Author's country: United Kingdom

Reviewer chosen by: Ruo-Yu Ma

Reviewer accepted review: 2019-10-21 16:17

Reviewer performed review: 2019-11-02 13:35

Review time: 11 Days and 21 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
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<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
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The study is extremely important due to the high global frequency of NAFLD. The study results are clear and suggest that high AA:DHA ratio increased lipotoxicity, triglyceride accumulation, ROS and leads to mitochondrial dysfunction. Study design, presentation of results and discussion are correct. References are very relevant. One small but important point on my part. Arachidonic acid cannot be equated with all omega-6 acids, as well as docosahexaenoic acid cannot be equated with all omega-3 acids. Such identification and simplification can significantly distort study conclusions. For example, recent studies show a different (not always harmful/pro-inflammatory) role of other omega-6 acids (e.g. linoleic acid, eicosadienoic acid). Similarly, a cell model using human hepatoma cell line VL-17A cannot be extrapolated to normal hepatocytes. Therefore, I would recommend a more correct title of the article, for example, 'High AA/DHA ratio induces mitochondrial dysfunction and altered lipid metabolism in human hepatoma cell line'.

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