



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 41772

Title: Glutathione depleting drugs, antioxidants and intestinal calcium absorption

Reviewer's code: 00609371

Reviewer's country: United States

Science editor: Xue-Jiao Wang

Date sent for review: 2018-09-03

Date reviewed: 2018-09-04

Review time: 18 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 checked="" 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
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors discussed the glutathione depleting drugs, antioxidants and intestinal calcium absorption in this review. This is an interesting topic, since abnormal intestinal calcium absorption has broad implications for highly impact disorders, such as diabetes, osteoporosis and aging. However, the major concerns are: 1) The underlying



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mechanism of abnormal intestinal calcium absorption could be very complex, and many different factors, including Glutathione (GSH), might co-regulate the intestinal calcium absorption. 2) One key question, at least for me, is that: in the real clinical contexts, what proportion of clinical observed abnormal intestinal calcium absorption is directly caused by GSH dysregulation? The reason I ask this question is that most investigators are still focusing on calcitriol, which is thought to be one of the most important molecules in the area. Is the importance of GSH and 1,25(OH)₂D₃ (calcitriol) comparable in anyway? Or GSH might only be the trivial contributor of the abnormal intestinal calcium absorption. 3) Another concern is that this same group has published a similar review one year ago in the same journal (i.e., Diaz de Barboza G, Guizzardi S, Moine L, Tolosa de Talamoni N. Oxidative stress, antioxidants and intestinal calcium absorption. World J Gastroenterol. 2017 Apr 28;23(16):2841-2853). I am wondering whether this is justifiable to have another update in the same area in such a short time frame. 4) I am wondering whether it is possible that correcting the abnormal intestinal calcium absorption through manipulating GSH might lead to untended backfire in the stress response, Since GSH metabolism is a very important mechanism of body to deal with the stress response.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 41772

Title: Glutathione depleting drugs, antioxidants and intestinal calcium absorption

Reviewer's code: 03552376

Reviewer's country: China

Science editor: Xue-Jiao Wang

Date sent for review: 2018-09-03

Date reviewed: 2018-09-20

Review time: 17 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input checked="" type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" 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
		<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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SPECIFIC COMMENTS TO AUTHORS

none

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 41772

Title: Glutathione depleting drugs, antioxidants and intestinal calcium absorption

Reviewer's code: 00506564

Reviewer's country: Spain

Science editor: Xue-Jiao Wang

Date sent for review: 2018-08-28

Date reviewed: 2018-09-22

Review time: 24 Days

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 checked="" 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
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			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors present a well-written and detailed review. However, several points should be addressed: Introduction is quite long and should be shortened. Also, it should be focused in offering a summary of the problem instead of offering so many details about Ca absorption. This is an overstatement since the same could be said for sodium, iron,



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aminoacids... and every other nutrient “Ca²⁺ absorption is one of the most important intestinal functions since the intestine is the only entrance gate of the cation into the body.” Are there many other entrance gates for many nutrients? So, authors should just say that “Ca²⁺ absorption is relevant since...” This sentence should be rephrased since it is not clear “A reduction in more than 70% in the active intestinal Ca²⁺ absorption, 55% in CB D9k expression and 90% in TRPV6 expression was observed in VDR null mice[19].” Tables should be shortened by removing the column “references” since they could be included as numbered citations. Authors should clearly state which studies have been performed in humans, in vivo or in animal models. They could also consider to divide the information in subheadings according to this. For instance: “The first approaches to revert or prevent the inhibition of intestinal Ca²⁺ absorption caused by GSH depletion consisted in the use of GSH monoester in order to replenish the intestine with the tripeptide[21]. In fact, this treatment leads to the normalization of the intestinal Ca²⁺ absorption. In addition, other strategies were also assayed because the intestinal GSH depletion could be generated not only by drugs but also by pathological conditions such as cholestasis and metabolic syndrome[63,58].” We have little idea in which model was the GSH monoester or “other strategies” used. Other example: “We did not find that QT alone ameliorates the Ca²⁺ transport in the intestine, but we demonstrated that QT blocks the inhibition of the intestinal Ca²⁺ absorption caused by MEN via GSH depletion. Similarly, QT by itself does not change the intestinal GSH content, but it prevents the GSH depletion produced by the quinone[52].” Authors could further discuss the potential role of glutathione in experimental colitis and/or inflammatory bowel disease. See, for instance:
<https://www.nature.com/articles/3780077.pdf?origin=ppub>
<https://www.sciencedirect.com/science/article/pii/S2213231715001573>
<https://www.ncbi.nlm.nih.gov/pubmed/9616308>



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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 41772

Title: Glutathione depleting drugs, antioxidants and intestinal calcium absorption

Reviewer's code: 02629138

Reviewer's country: Russia

Science editor: Xue-Jiao Wang

Date sent for review: 2018-08-28

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Review time: 26 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
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			Conflicts-of-Interest:
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SPECIFIC COMMENTS TO AUTHORS

This is very interesting and review in which the authors have analyzed comprehensively the role of glutathione (GSH) in the intestine, the molecular mechanisms by which GSH depleting drugs inhibit the intestinal Ca²⁺ absorption and the prevention or restoration of these effects by drugs that act through normalization of intestinal GSH content. The



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review covers the following aspects such as a) GSH synthesis and its physiological role in the intestine, b) GSH depletion and the intestinal calcium absorption, c) Reversion/prevention of the inhibition of intestinal calcium absorption caused by GSH depletion. In my knowledge, this is the first paper which reviews these aspects so deeply. Moreover, the paper is well written in English. I think the paper is acceptable for publication, but I have only one recommendation for the paper which may improve its quality. It would be interesting for readership of the journal to see an overview of environmental factors (chemicals, not drugs) which are known to be responsible for GSH depletion in the gastrointestinal tract and may have a role in the development of human diseases.

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